Effect of Cardiac Resynchronization Therapy on Pulmonary Function in Patients With Heart Failure

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Pulmonary congestion due to heart failure causes abnormal lung function. Cardiac resynchronization therapy (CRT) is a proven effective treatment for heart failure. The aim of this study was to test the hypothesis that CRT promotes increased lung volumes, bronchial conductance, and gas diffusion. Forty-four consecutive patients with heart failure were prospectively investigated before and after CRT. Spirometry, gas diffusion (diffusing capacity for carbon monoxide), cardiopulmonary exercise testing, New York Heart Association class, brain natriuretic peptide, the left ventricular ejection fraction, left atrial volume, and right ventricular systolic pressure were assessed before and 4 to 6 months after CRT. Pre- and post-CRT measures were compared using either paired Student's *t* tests or Wilcoxon's matched-pair test; p values <0.05 were considered significant. Improved New York Heart Association class, left ventricular ejection fraction, left atrial volume, right ventricular systolic pressure, and brain natriuretic peptide were observed after CRT (p <0.05 for all). Spirometry after CRT demonstrated increased percentage predicted total lung capacity (90 ± 17% vs 96 ± 15%, p <0.01) and percentage predicted forced vital capacity (80 ± 19% vs 90 ± 19%, p <0.01). Increased percentage predicted total lung capacity was significantly correlated with increased peak exercise end-tidal carbon dioxide ($r = 0.43$, $p = 0.05$). Increased percentage predicted forced vital capacity was significantly correlated with decreased right ventricular systolic pressure ($r = -0.30$, $p = 0.05$), body mass index ($r = -0.35$, $p = 0.02$) and creatinine ($r = -0.49$, $p = 0.02$), consistent with an association of improved bronchial conductance and decreased congestion. Diffusing capacity for carbon monoxide did not significantly change. In conclusion, increased lung volumes and bronchial conductance due to decreased pulmonary congestion and increased intrathoracic space contribute to an improved breathing pattern and decreased hyperventilation after CRT. Persistent alveolar-capillary membrane remodeling may account for unchanged diffusing capacity for carbon monoxide. **(Am J Cardiol 2013;112:838−842)**

Previous studies regarding the effects of cardiac resynchronization therapy (CRT) on pulmonary function have been limited.[1] The hallmark of symptom alleviation subsequent to heart failure (HF) therapy is decreased dyspnea. We hypothesized that CRT promotes increased lung volumes, bronchial conductance, and gas diffusion. Accordingly, the aim of this study was to quantify pulmonary function in patients with HF before and after clinically indicated CRT.

Methods

Patients referred for clinically indicated CRT were screened for recruitment. All subjects met established clinical criteria for CRT, including QRS duration ≥130 ms, New York Heart Association class II to IV HF, and a left ventricular ejection fraction ≤35% despite optimal pharmacotherapy[2] for ≥3 months. All participants gave written informed consent after being provided a description of study requirements. This study was approved by the Mayo Clinic Institutional Review Board.

Pulmonary function testing measurements were performed at baseline 1 to 2 days before CRT implantation and at clinically indicated follow-up 4 to 6 months after CRT. Pulmonary function measurements included total lung capacity, vital capacity, residual volume, alveolar volume, forced vital capacity (FVC), forced expiratory volume at 1 second, maximal forced expiratory flow (FEF), FEF at 25% to 75% of vital capacity (FEF 25%−75%), and single-breath diffusing capacity for carbon monoxide. Spirometric and diffusing capacity for carbon monoxide data were collected in accordance with American Thoracic Society standards.[3]

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See page 841 for disclosure information.

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Table 1
Clinical responses to cardiac resynchronization therapy (n = 44)

Parameter	Pre-CRT	Post-CRT	p Value
BMI (kg/m^2)	28 ± 5	28 ± 4	0.45
New York Heart Association class	3 ± 0.3	2 ± 0.8	<0.01
Left ventricular ejection fraction (%)	24 ± 7	32 ± 13	<0.01
Left atrial volume (n = 41) (cm^3)	123 ± 52	110 ± 50	0.02
Left ventricular diastolic diameter (mm)	67 ± 10	64 ± 12	<0.01
Right ventricular systolic pressure (n = 42) (mm Hg)	46 ± 13	40 ± 12	<0.01
Brain natriuretic peptide (n = 40) (pg/ml)	2,216 ± 7,093	977 ± 1,616	<0.01
Creatinine (mg/dl)	1.3 ± 0.4	1.2 ± 0.4	0.10
Medications			
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers	41 (93%)	40 (91%)	0.99
Digoxin	21 (48%)	24 (55%)	0.67
β blockers	42 (95%)	42 (95%)	1.00
Diuretics	35 (80%)	36 (82%)	1.00

Data are expressed as mean ± SD or number (percentage).

Table 2
Pulmonary function tests (absolute values) (n = 44)

Parameter	Pre-CRT	Post-CRT	p Value
Total lung capacity (n = 40) (L)	5.7 ± 1.3	6.0 ± 1.2	<0.01
Residual volume (n = 40) (L)	2.5 ± 0.8	2.7 ± 0.9	<0.01
Vital capacity (L)	3.3 ± 0.9	3.4 ± 0.8	0.10
Alveolar volume (L)	4.8 ± 1.0	4.9 ± 1.0	0.04
FVC (L)	3.2 ± 0.8	3.2 ± 0.8	0.76
Forced expiratory volume at 1 second (L)	2.3 ± 0.7	2.4 ± 0.7	0.11
FEF 25%−75% (L/s)	1.7 ± 0.9	1.8 ± 1.1	0.04
Maximal FEF (L/s)	7.4 ± 1.9	7.6 ± 2.0	0.08
Diffusing capacity for carbon monoxide (ml/min/mm Hg)	18 ± 7	17 ± 5	0.18

Data are expressed as mean ± SD.

Exercise ventilation and gas exchange were assessed by metabolic cart (Medical Graphics, St. Paul, Minnesota) during cardiopulmonary exercise testing. Measures included peak oxygen consumption, carbon dioxide output, end-tidal carbon dioxide, tidal volume, minute ventilation, and breathing frequency. Derived measures included ventilatory efficiency, defined as minute ventilation/carbon dioxide output. Tidal volume and minute ventilation were also normalized to vital capacity to evaluate changes of breathing pattern during exercise in patients before and after CRT.

For statistical analysis, the Shapiro-Wilk test, paired Student's *t* test or Wilcoxon's test, Mann-Whitney U test or unpaired Student's *t* test, 2-tailed Fisher's exact test, and Pearson's or Spearman's rank correlation were used. Data are summarized as mean ± SD; p values <0.05 were considered statistically significant. Statistical analysis was performed using Statistica version 10.0 (StatSoft Inc., Prague, Czech Republic) and SAS (SAS Institute Inc., Cary, North Carolina).

Table 3
Pulmonary function tests (percentage predicted values) (n = 44)

Parameter	Pre-CRT	Post-CRT	p Value
Total lung capacity (%) (n = 40)	90 ± 17	96 ± 15	<0.01
Residual volume (%) (n=40)	113 ± 31	121 ± 31	<0.01
Vital capacity (%)	81 ± 18	82 ± 18	0.17
Alveolar volume (%)	79 ± 15	81 ± 14	0.08
FVC (%)	80 ± 19	90 ± 19	<0.01
Forced expiratory volume at 1 second (%)	73 ± 19	75 ± 20	0.15
FEF 25%−75% (%)	59 ± 29	65 ± 36	0.04
Maximal FEF (%)	98 ± 23	101 ± 23	0.24
Diffusing capacity for carbon monoxide (%)	69 ± 16	68 ± 15	0.21

Data are expressed as mean ± SD.

Results

The mean age of the pre-CRT subjects (n = 44) was 66 ± 12 years. They were predominantly men (75%) in New York Heart Association class III (89%), with low left ventricular ejection fractions (24 ± 7%), markedly decreased peak oxygen consumption (13 ± 3 ml/kg), and elevated brain natriuretic peptide (2,216 ± 7,093 pg/ml). The cause of HF was ischemic in 49%. Changes after 4 to 6 months are listed in Table 1. There were no changes in HF medications (Table 1), including mean furosemide dose, after CRT (51 ± 46 vs 55 ± 50 mg/day, p = 0.33). New York Heart Association class improved by ≥1 functional class in 66% of patients, which is similar to the response rates previously published in larger studies.[4,5]

Pulmonary function testing after CRT showed improvements in static and dynamic parameters for absolute and percentage predicted values (Tables 2 and 3). Mean expiratory maximal flow-volume loops after CRT demonstrated decreased pulmonary restriction and increased bronchial conductance (Figure 1). The improvement of static and dynamic pulmonary function parameters after CRT was significantly correlated with the changes in several exercise parameters, body mass index (BMI), creatinine concentration, and right ventricular systolic pressure (Table 4).

Subjects after CRT had improved breathing patterns (higher tidal volume and lower breathing frequency; Figure 2), breathed more efficiently (lower minute ventilation/carbon dioxide output), and had less hyperventilation (higher end-tidal carbon dioxide) and higher oxygen consumption (Table 5).

The improvement in FVC was inversely correlated with the changes in BMI and creatinine, and FEF 25%−75% was also inversely correlated with the change in BMI. In the subgroup of subjects who improved both dynamic parameters (n = 21), creatinine significantly decreased (1.3 ± 0.4 vs 1.2 ± 0.4 mg/dl, p <0.01), as did BMI (30 ± 4 vs 29 ± 4 kg/m^2, p = 0.03). Conversely, in the remaining subjects (n = 23) who did not improve dynamic parameters, creatinine remained unchanged (1.2 ± 0.4 vs 1.2 ± 0.4, p = 0.97), while BMI significantly increased (27 ± 5 vs 28 ± 5 kg/m^2, p <0.01) after CRT.

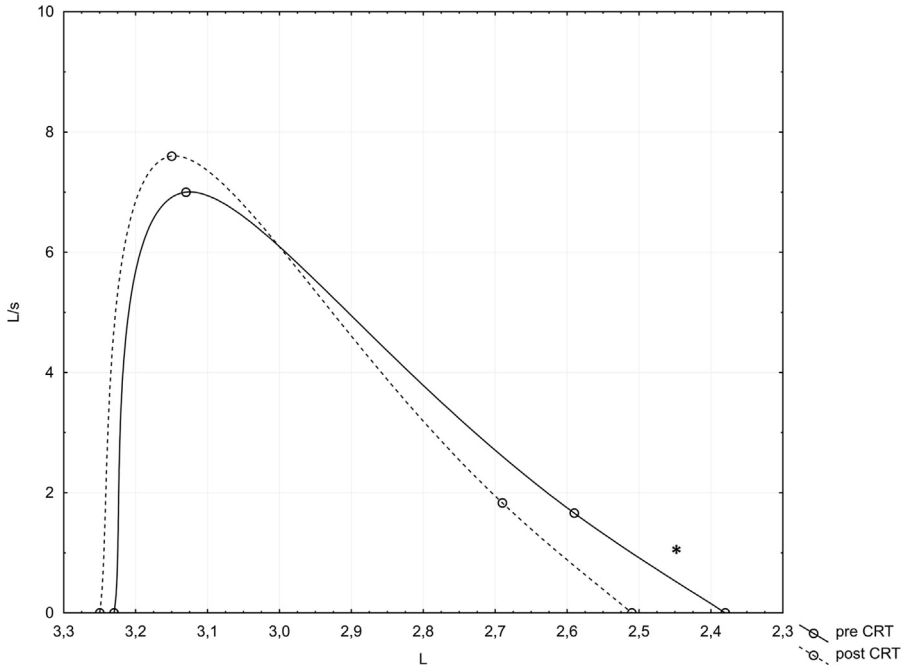

Figure 1. Mean expiratory maximal flow-volume loops. Comparison between baseline and follow-up after CRT for the entire study group (n = 44). The post-CRT loop demonstrates significantly higher residual volume (RV) ($p < 0.01$) and a tendency for increase peak expiratory flow ($p = 0.08$).

Table 4
Significant associations between parameter changes (before to after cardiac resynchronization therapy)

Parameter (Δ)	r	p
Static parameters		
Total lung capacity		
Rest breathing frequency	−0.35	0.04
Peak partial pressure of end-tidal carbon dioxide	0.35	0.05
Total lung capacity (%)		
Peak partial pressure of end-tidal carbon dioxide	0.43	0.05
Residual volume		
Peak partial pressure of end-tidal carbon dioxide	0.43	0.05
Residual volume (%)		
Peak ventilatory efficiency	−0.35	0.05
Alveolar volume		
Rest breathing frequency	−0.35	0.03
Dynamic parameters		
FVC (%)		
BMI	−0.35	0.02
Creatinine	−0.49	0.02
Right ventricular systolic pressure	−0.30	0.05
FEF 25%−75%		
BMI	−0.53	<0.01
FEF 25%−75% (%)		
BMI	−0.51	<0.01

Discussion

The novel findings of this study were that CRT promoted improved static (total lung capacity, residual volume, and alveolar volume) and dynamic (FEF 25%−75% and FVC) pulmonary function, consistent with increased lung volumes and increased bronchial conductance, while diffusing capacity for carbon monoxide remained unchanged. In addition, pulmonary function improvement was significantly correlated with improved ventilatory efficiency and breathing pattern at rest and during exercise.

HF is characterized by pulmonary restriction and obstruction.[6] Restrictive lung function has been shown to be a consequence of congestion and increased heart size.[6,7] In addition, pulmonary hypertension and bronchial congestion may contribute to small airway obstruction.[6−10] Although CRT has been shown to decrease pulmonary congestion,[11] Laveneziana et al[1] recently reported no apparent relation of CRT to pulmonary function. However, their observations may have been due to an underpowered sample size (n = 7). In contrast, in our subjects (n = 44), static (total lung capacity, residual volume, and alveolar volume) and dynamic (FEF 25%−75% and FVC) pulmonary function test parameters significantly improved after CRT.

In our study, the increase in lung volume after CRT was significantly correlated with improved ventilatory efficiency, a less tachypneic breathing pattern, and higher end-tidal carbon dioxide. These findings are consistent with previous investigations demonstrating a rapid shallow breathing pattern with hypocapnia in patients with restrictive lung function during exercise.[12−14] Furthermore, Olson et al[15] recently demonstrated a relation between the severity of HF, heart size, intrathoracic volume, and lung restriction. In our subjects, CRT was associated with significant decreases in left atrial volume and left ventricular diastolic diameter, which may have promoted an increase of intrathoracic space available for expansion of lung volume.

The improvement of dynamic pulmonary function (FEF 25%−75% and FVC) after CRT was significantly correlated with decreased right ventricular systolic pressure, as well as decreased creatinine and BMI. Meyer et al[10] and others[16−18] have previously shown that pulmonary hypertension may

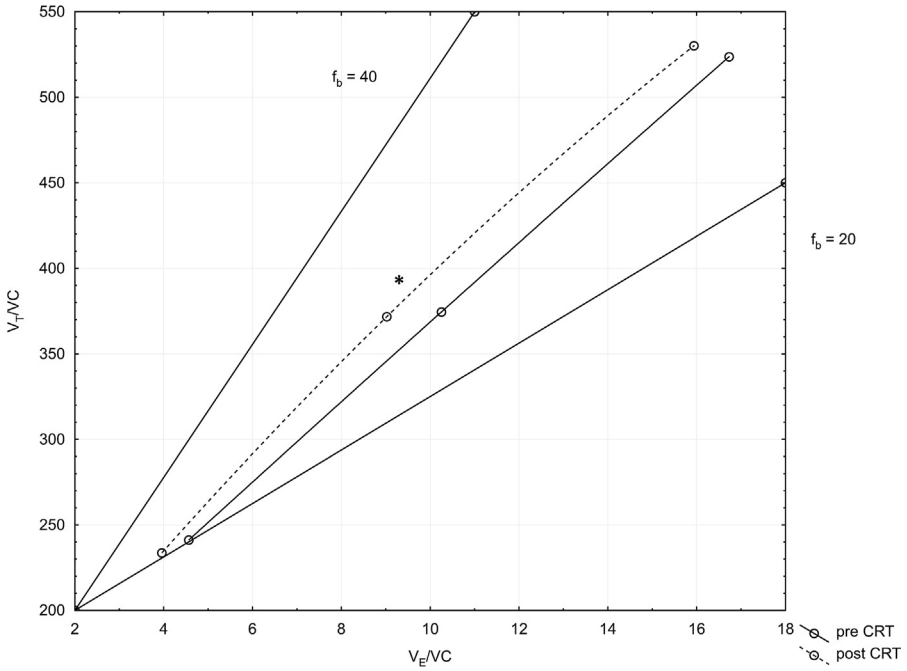

Figure 2. Change of breathing pattern during exercise in patients before and after CRT. Minute ventilation ($\dot{V}_E$) normalized for subject vital capacity (VC) ($\dot{V}_E/VC$). Proportion of VC used for tidal breath (V_T/VC). *Straight lines* represent isopleths of respiratory rate (20 and 40 breaths/min). Subjects before CRT had a more tachypneic breathing pattern than subjects after CRT. Exercise $\dot{V}_E/VC$ was significantly higher before CRT (*p = 0.04), and rest $\dot{V}_E/VC$ tended to be higher before CRT (p = 0.07). Subjects after CRT breathed with lower breathing frequency (f_b) and higher V_T consistent, with increased lung compliance after CRT.

Table 5
Ventilatory changes at rest and peak exercise (n = 36)

Parameter	Pre-CRT	Post-CRT	p Value
Rest			
Tidal volume (ml)	761 ± 291	747 ± 293	0.41
Breathing frequency (breaths/min)	19 ± 6	18 ± 5	0.05
Partial pressure of end-tidal carbon dioxide (mm Hg)	32 ± 4	33 ± 4	0.18
Ventilatory efficiency	44 ± 9	42 ± 8	0.04
Dead-space volume/tidal volume	0.22 ± 0.06	0.21 ± 0.06	0.46
Peak exercise			
Oxygen consumption (ml/kg)	13 ± 3	14 ± 3	0.04
Tidal volume (ml)	1,671 ± 492	1,723 ± 547	0.21
Breathing frequency (breaths/min)	35 ± 7	33 ± 6	0.02
Partial pressure of end-tidal carbon dioxide (mm Hg)	28 ± 5	31 ± 5	<0.01
Ventilatory efficiency	44 ± 10	39 ± 7	<0.01
Dead-space volume/tidal volume ratio	0.22 ± 0.06	0.21 ± 0.06	0.08
Respiratory exchange ratio	1.14 ± 0.13	1.16 ± 0.11	0.51

Data are expressed as mean ± SD.

promote bronchial obstruction. Increased pulmonary artery pressure is frequent in patients with HF[19] and has been previously shown to be reduced by CRT.[20,21] Dang et al[22] showed that intervention by left ventricular assist device implantation caused increased renal perfusion and consequently decreased edema with reduced BMI. Similarly, in our subjects, a decrease in creatinine was significantly correlated with a decrease in BMI (r = 0.40, p <0.01), suggesting that improved renal perfusion with enhanced diuresis after CRT promoted decreased edema and BMI. Pulmonary edema has been shown to increase bronchial obstruction, and dynamic pulmonary function test parameters have been shown to improve with diuresis in patients with HF.[23] Boerrigter et al[24] demonstrated that glomerular filtration rate is increased after CRT. These observations suggest that CRT promotes improved renal perfusion in a subset of our subjects, with decreased pulmonary vascular congestion and edema, which promoted increased bronchial conductance. Finally, in our study, no change in diffusing capacity for carbon monoxide was observed, suggesting that remodeling of the alveolar-capillary membrane associated with HF may persist, as has been previously reported.[25,26]

Eight subjects did not undergo complete, paired pre- and post-CRT cardiopulmonary exercise testing. However, these 8 subjects did not differ significantly from the remainder of the cohort with regard to age, gender, clinical (BMI, brain natriuretic peptide, left ventricular ejection fraction, and New York Heart Association class), and pulmonary function test parameters.

Disclosures

Dr. Somers is a consultant for ResMed, San Diego, California; Cardiac Concepts, Minneapolis, Minnesota; GlaxoSmithKline, London, United Kingdom; Sepracor, Marlborough, Massachusetts; Deshum; Respicardia, Minnetonka, Minnesota; and Medtronic Inc., Minneapolis, Minnesota. Grants were funded by the Respironics Foundation, the ResMed Foundation, and the Sorin Corporation.

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