Clinical Investigations

Modulation of Ventilatory Reflex Control by Cardiac Resynchronization Therapy

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ABSTRACT

Background: Heart failure (HF) is characterized by heightened sensitivities of the CO_2 chemoreflex and the ergoreflex which promote increased ventilatory drive manifested as increased minute ventilation per volume of expired CO_2 (V_E/VCO_2). The aims of this study were to evaluate the effects of cardiac resynchronization therapy (CRT) on carbon dioxide (CO_2) chemosensitivity and the arterial CO_2 setpoint.

Methods and Results: Consecutive HF patients (n = 35) who underwent clinically indicated CRT were investigated by means of cardiopulmonary exercise testing and CO_2 chemosensitivity evaluation with the use of a rebreathe method before and 4-6 months after CRT. Pre- and post-CRT measures were compared with the use of either paired *t* test or Wilcoxon test. Decreased peak V_E/VCO_2 (44 ± 10 vs 40 ± 8; $P < .01$), CO_2 chemosensitivity (2.2 ± 1.1 vs 1.7 ± 0.8 L min^{-1} mm Hg^{-1}; $P = .04$), and increased peak end-tidal CO_2 (29 ± 5 vs 31 ± 5 mm Hg; $P < .01$) were also observed after CRT. Multivariate analysis adjusted for age and sex showed the decrease of peak V_E/VCO_2 from before to after CRT to be most strongly associated with the increase of peak end-tidal CO_2 ($\beta = -0.84$; $F = 21.5$; $P < .0001$).

Conclusions: Decrease of V_E/VCO_2 after CRT is associated with decreased CO_2 chemosensitivity and increase of the arterial CO_2 setpoint, which is consistent with decreased activation of both the CO_2 chemoreflex and the ergoreflex. (*J Cardiac Fail 2015;21:367−373*)

Key Words: Heart failure, cardiopulmonary exercise testing, chemosensitivity, pacing.

For patients with advanced heart failure (HF) and left ventricular dyssynchrony prospective, randomized, controlled studies have demonstrated that cardiac resynchronization therapy (CRT) improves life quality, functional status, and exercise capacity,[1,2] reverses left ventricular remodeling,[3] and decreases mortality.[4] Current guidelines for CRT include left ventricular ejection fraction (LVEF) ≤35%, New York Heart Association (NYHA) functional class III or IV symptoms, and QRS duration ≥120 ms in HF patients receiving optimized pharmacotherapy.[1] Despite substantial evidence supporting the benefit of CRT for patients with advanced HF and ventricular dyssynchrony,[5] the effects of this management on ventilatory control have not been completely characterized.

Regulation of breathing is frequently abnormal in patients with advanced HF and often manifests as hyperventilation[6] associated with worse functional capacity[7] and increased mortality.[8] The pathogenesis of hyperventilation may include activation of pulmonary J receptors owing to congestion, activation of atrial stretch receptors, and ventilation-perfusion mismatch, as well as increased activation of central and peripheral chemoreflexes and the ergoreflex.[7,9−12] Disordered ventilatory control may be identified by cardiopulmonary exercise testing (CPET),

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including measurement of ventilatory efficiency (V_E/VCO_2) and end-tidal carbon dioxide ($P_{ET}CO_2$). Quantification of V_E/VCO_2 and $P_{ET}CO_2$ identifies the magnitude of hyperventilation and has also proven useful for prognostication.[8]

V_E/VCO_2 is related inversely to the partial pressure of arterial carbon dioxide ($PaCO_2$) and positively to the ratio of ventilatory dead space to tidal volume (V_D/V_T) by the alveolar gas equation:

$$V_E/VCO_2 = 863/(PaCO_2 \times [1 - (V_D/V_T)])$$

Decrease of V_E/VCO_2 subsequent to CRT has been previously reported.[13–15] However, the contribution of the components of the alveolar gas equation to the observed decline of V_E/VCO_2 after CRT has not been previously described. We hypothesized that CRT promotes decreased V_E/VCO_2 by an increase of the arterial carbon dioxide (CO_2) setpoint and reduction of CO_2 chemosensitivity. Therefore, the aims of the present study were to evaluate V_E/VCO_2 and $P_{ET}CO_2$ by CPET, as well as directly measure and compare CO_2 chemosensitivity before and 4-6 months after clinically indicated CRT.

Materials and Methods

Subject Selection

Subjects were consecutive ambulatory outpatients who underwent clinically indicated CRT. All subjects met standard criteria for CRT, including NYHA class III–IV symptoms, QRS duration ≥120 ms, and LVEF ≤35%. All subjects were on optimal pharmacotherapy for ≥3 months before CRT. Subjects who could not perform CPET or did not return for follow-up evaluation at 4-6 months after CRT were excluded. Every participant gave written informed consent after being provided a description of study requirements. This study was conducted in accordance with the Declaration of Helsinki and approved by the Mayo Clinic Institutional Review Board. All procedures followed institutional and Health Insurance Portability and Accountability Act guidelines.

Post-CRT Assessment

Assessment of subject functional status and quality of life were performed before CRT and 4-6 months after CRT. The NYHA functional class at baseline and at follow-up was assessed independently by a physician directly involved with patient care. Submaximal exercise performance was measured by means of the 6-minute walk distance. HF-related quality of life was assessed by means of the Minnesota Living With Heart Failure Questionnaire, which assesses the impact of HF and its treatment on the physical, emotional, social, and mental dimensions of quality of life.

Exercise Testing

Exercise capacity was assessed by means of CPET to volitional fatigue after instrumentation for the measurement of heart rate, metabolic gas exchange, and oxygen saturation. The protocol used an initial treadmill speed and grade of 2.0 miles per hour and 0, respectively, with speed and grade increased every 2 minutes to yield ~2 metabolic equivalent increase per work level to a rating of perceived exertion of 18–20 on the Borg scale. Exercise ventilation and gas exchange were assessed by means of metabolic cart (Medical Graphics, St Paul, Minnesota) during CPET. Measures included oxygen consumption, CO_2 output, tidal volume, minute ventilation, breathing frequency, and $P_{ET}CO_2$. These data were collected continuously and reported as averages obtained over the final 30 seconds of each workload. Derived measures included the V_E/VCO_2 ratio, and respiratory exchange ratio, defined as the ratio of CO_2 output and oxygen consumption. The V_E/VCO_2 ratio has been shown to strongly correlate with the V_E/VCO_2 slope[7] and may be used to describe ventilatory efficiency at different stages of exercise as well as at rest.

CO_2 Chemosensitivity

CO_2 chemosensitivity was measured by means of a modified rebreathe technique as previously described.[16] Subjects breathed from a mouthpiece connected to a 6-liter rebreathing bag. The bag included 5% CO_2 and balance oxygen at study initiation. End-tidal oxygen and $P_{ET}CO_2$ were monitored by mass spectroscopy as were breath-by-breath changes of minute ventilation. As subjects rebreathe, the inspired CO_2 in the rebreathe bag increases and oxygen falls. Over the course of the study, inspired oxygen levels did not fall below 500 mm Hg (~70% oxygen). Rebreathing was allowed to continue in all subjects until the $P_{ET}CO_2$ reached 50–55 mm Hg (~8% CO_2, requiring 4 min). The slope of the plot of the change of minute ventilation versus the change of $P_{ET}CO_2$ was used as an index of CO_2 chemosensitivity. Three runs were performed for each subject and values reported as the mean.

Spirometry, Arterial Blood Gases, B-Type Natriuretic Peptide, and Echocardiography

Spirometry including measurement of forced vital capacity and forced expiratory volume at 1 second was performed before and after CRT according to American Thoracic Society standards.[17] Arterial blood for measurement of pH, partial pressure of CO_2, partial pressure of oxygen, base excess, bicarbonate, and venous blood for measurement of B-type natriuretic peptide (BNP) were collected at rest before CRT and at follow-up. BNP concentrations were measured by means of the commercially available Shionogi immunoradiometric assay (Shionogi and Co, Osaka, Japan). Echocardiography measurements were performed before and after CRT with focus on cardiac chamber dimension, LVEF, stroke volume index, and right heart pressures.

Estimation of Dead Space Ventilation

The alveolar gas equation enables estimation of the ratio of V_D/V_T.[9] This was performed at rest with the use of $PaCO_2$ (directly measured by arterial blood gases) and V_E/VCO_2 (measured by means of metabolic cart). By substitution of $P_{ET}CO_2$ as a surrogate for $PaCO_2$ these same parameters were estimated during exercise.

Statistical Analysis

For the evaluation of normally distributed data, the Shapiro-Wilk test was used. Pre- to post-treatment comparisons were made by means of the Student *t* test or the Wilcoxon test. Linear regression was performed to evaluate changes (from before to after CRT) of the relationship between $P_{ET}CO_2$ or V_D/V_T and V_E/VCO_2. Correlation between the change of $P_{ET}CO_2$ during exercise and CO_2 chemosensitivity was calculated by means of Spearman rank correlation coefficient. Differences in proportions were tested by means of 2-tailed Fisher exact test. Multiple regression adjusted for age and sex was performed to evaluate which