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Modulation of Ventilatory Reflex Control by Cardiac Resynchronization Therapy

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Abstract

Background—Heart failure (HF) is characterized by heightened sensitivity of the CO₂ chemoreflex and the ergoreflex which promote increased ventilatory drive manifest as increased minute ventilation per volume of expired CO₂ (V_E/VCO_2). The aims of this study were to evaluate the effects of cardiac resynchronization therapy (CRT) on carbon dioxide (CO₂) chemosensitivity and the arterial CO₂ setpoint.

Methods and results—Consecutive HF patients (n=35) who underwent clinically-indicated CRT were investigated by cardiopulmonary exercise testing and CO₂ chemosensitivity by a rebreathe method before and 4-6 months post-CRT. Pre- and post-CRT measures were compared by either paired t-test or Wilcoxon test. Decreased peak V_E/VCO_2 (44 ± 10 vs. 40 ± 8 ; $p < 0.01$), CO₂ chemosensitivity (2.2 ± 1.1 vs. 1.7 ± 0.8 L/min/mmHg; $p = 0.04$) and increased peak end-tidal CO₂ (29 ± 5 vs. 31 ± 5 mmHg; $p < 0.01$) were also observed post-CRT. Multivariate analysis adjusted for age and gender showed the decrease of peak V_E/VCO_2 from pre- to post-CRT was most strongly associated with the increase of peak end-tidal CO₂ ($b = -0.84$; $F = 21.5$; $p < 0.0001$).

Conclusion—Decrease of V_E/VCO_2 post-CRT is associated with decreased CO₂ chemosensitivity and increase of the arterial CO₂ setpoint consistent with decreased activation of both the CO₂ chemoreflex and the ergoreflex.

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Keywords

heart failure; cardiopulmonary exercise testing; chemosensitivity; pacing

Introduction

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 remodelling (3) and decreases mortality (4). Current guidelines for CRT include left ventricular ejection fraction (LVEF) $\leq 35\%$, NYHA class III or IV symptoms and QRS duration $\geq 120\text{ms}$ 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 due 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), including measurement of ventilatory efficiency ($\dot{V}_E/\dot{V}_{CO_2}$) and end-tidal carbon dioxide ($P_{ET}CO_2$). Quantification of $\dot{V}_E/\dot{V}_{CO_2}$ and $P_{ET}CO_2$ identifies the magnitude of hyperventilation and has also proven useful for prognostication (8).

$\dot{V}_E/\dot{V}_{CO_2}$ is inversely related to the partial pressure of arterial carbon dioxide (P_aCO_2) and positively to the ratio of ventilatory dead space to tidal volume (V_D/V_T) by the alveolar gas equation

$$\dot{V}_E/\dot{V}_{CO_2} = \frac{863}{P_aCO_2 \times (1 - V_D/V_T)}.$$

Decrease of $\dot{V}_E/\dot{V}_{CO_2}$ 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 $\dot{V}_E/\dot{V}_{CO_2}$ post-CRT has not been previously described. We hypothesized that CRT promotes decreased $\dot{V}_E/\dot{V}_{CO_2}$ by an increase of the arterial carbon dioxide (CO_2) setpoint and reduction of CO_2 chemosensitivity. Hence, the aims of this study were to evaluate $\dot{V}_E/\dot{V}_{CO_2}$ 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.

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 $\leq 35\%$. All subjects were on optimal pharmacotherapy for at least 3 months prior to CRT. Subjects who could not perform CPET or did not return for follow-up evaluation at 4-6 months post-CRT were excluded. All participants 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 prior to CRT and 4-6 months post-CRT. The NYHA class at baseline and at follow-up was assessed independently by a physician directly involved with patient care. Submaximal exercise performance was measured by the 6 minute walk distance. Heart failure-related quality of life was assessed by 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 CPET to volitional fatigue following 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 an approximate 2 metabolic equivalent increase per work level to a rating of perceived exertion of 18 to 20 on the Borg scale. Exercise ventilation and gas exchange were assessed by metabolic cart (Medical Graphics; St. Paul, MN) during CPET. Measures included oxygen consumption, CO_2 output, tidal volume, minute ventilation, breathing frequency and $\text{P}_{\text{ET}}\text{CO}_2$. These data were collected continuously and reported as averages obtained over the final 30s of each workload. Derived measures included $\text{V}_\text{E}/\text{VCO}_2$ defined as the $\text{V}_\text{E}/\text{VCO}_2$ ratio, and respiratory exchange ratio, defined as the ratio of CO_2 output and oxygen consumption. The $\text{V}_\text{E}/\text{VCO}_2$ ratio has been shown to strongly correlate to the $\text{V}_\text{E}/\text{VCO}_2$ 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 a modified re-breathe 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 $\text{P}_{\text{ET}}\text{CO}_2$ 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 mmHg ($\sim 70\%$ oxygen). Rebreathing was allowed to continue in all subjects until the $\text{P}_{\text{ET}}\text{CO}_2$ reached 50-55 mmHg (about 8% CO_2 requiring 4 minutes). 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, BNP and echocardiography

Spirometry including measurement of forced vital capacity and forced expiratory volume at one second was performed pre- and post-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 brain natriuretic peptide (BNP) were collected at rest *pre-CRT* and at follow-up. BNP concentrations were measured by the commercially available Shionogi immunoradiometric assay (Shionogi & Co, Ltd; Osaka, Japan). Echocardiography measurements were performed pre- and post-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 using $PaCO_2$ (directly measured by arterial blood gases) and $\dot{V}_E/\dot{V}CO_2$ measured by 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-post treatment comparisons were made by the Student t-test or Wilcoxon test. Linear regression was performed to evaluate changes (from pre- to post-CRT) of the relationship between $P_{ET}CO_2$ or V_D/V_T and $\dot{V}_E/\dot{V}CO_2$. Correlation between the change of $P_{ET}CO_2$ during exercise and CO_2 chemosensitivity was calculated by Spearman's rank correlation coefficient. Differences in proportions were tested by two-tailed Fisher exact test. Multiple regression adjusted for age and gender was performed to evaluate which parameter changes were most strongly associated with the change of $P_{ET}CO_2$ and results expressed as the regression coefficient, F ratio and p value. Data is summarized as mean $\pm$ SD or median (inter-quartile range) with p values <0.05 considered statistically significant. Statistical analysis was performed using Statistica 10.0 (StatSoft, Prague, Czech Republic) or the Statistical Analysis System (SAS Institute Inc., North Carolina).

Results

Baseline Characteristics

Thirty-five HF subjects were studied pre- and post-CRT. *Six subjects did not report for the follow-up and were excluded. These excluded subjects were not different in baseline clinical or exercise characteristics.* Baseline pre-CRT characteristics are summarized in Table 1. Prior to CRT the majority of subjects were NYHA class III (97%); one subject was class IV. Mean LVEF was $24 \pm 8\%$, median BNP 657 (377-1547) ng/L and mean peak exercise oxygen consumption 13.4 ± 3.5 mL/min/kg. The etiology of HF was ischemic in 17 (49%) subjects.

Clinical changes post-CRT—For the entire subject group, CRT significantly improved NYHA class, LVEF, stroke volume index, *BNP concentration*, 6 minute walk distance and Minnesota Living with Heart Failure Questionnaire score (Table 2).

Rest and Exercise Ventilation

Rest and exercise ventilatory measures are shown in Table 3 and are consistent with decreased ventilatory drive post-CRT. At rest, post-CRT subjects had significantly lower $\dot{V}_E/\dot{V}_{CO_2}$ and decreased breathing frequency. Similarly, at 50% peak exercise, post-CRT subjects had significantly lower $\dot{V}_E/\dot{V}_{CO_2}$, lower breathing frequency and higher $P_{ET}CO_2$. At peak exercise, post-CRT subjects also had significantly lower $\dot{V}_E/\dot{V}_{CO_2}$ and higher $P_{ET}CO_2$ as well as significantly increased tidal volume. Breathing frequency was lower at peak exercise, though this difference was not significant. Notably, end-tidal CO_2 decreased significantly during exercise both pre-CRT (32 ± 4 vs. 29 ± 5 mmHg; $p < 0.01$) and post-CRT (33 ± 5 vs. 31 ± 5 mmHg; $p = 0.01$). However, the magnitude of the decline of $P_{ET}CO_2$ during exercise was significantly less post-CRT compared to pre-CRT (-3.1 ± 3.8 vs. -1.6 ± 3.5 mmHg; $p = 0.04$). In addition, the magnitude of the decline of $P_{ET}CO_2$ during exercise pre-CRT was significantly inversely correlated to CO_2 chemosensitivity ($r = -0.57$; $p < 0.001$). However, post-CRT, at which time CO_2 chemosensitivity had decreased, this relationship was no longer significant ($r = -0.16$; $p = 0.38$). For the entire group, there was no significant change of peak exercise oxygen consumption post-CRT.

Change of Ventilatory Efficiency

As expected per the alveolar gas equation, a correlation between $\dot{V}_E/\dot{V}_{CO_2}$ and V_D/V_T was observed with exercise ($r = 0.45$; $p < 0.01$ pre-CRT and $r = 0.57$; $p < 0.001$ post-CRT); however, a significant shift ($p < 0.001$) of the slope of this relationship occurred from pre- to post-CRT (Figure 1). A strong correlation was also observed for $\dot{V}_E/\dot{V}_{CO_2}$ and $P_{ET}CO_2$ with exercise ($r = -0.95$; $p < 0.0001$ pre-CRT and $r = -0.91$; $p < 0.0001$ post-CRT), though no shift of slope ($p = 0.84$) was observed from pre- to post-CRT (Figure 2). The observed shift of slope for the $\dot{V}_E/\dot{V}_{CO_2}$ versus V_D/V_T relationship is consistent with the observed increase of $P_{ET}CO_2$ and decreased CO_2 chemosensitivity observed post-CRT. By contrast, the slope of the relationship of $\dot{V}_E/\dot{V}_{CO_2}$ versus $P_{ET}CO_2$ did not shift post-CRT consistent with no change of the estimated V_D/V_T ratio. Multivariate analysis adjusted for age and gender showed the decrease of peak $\dot{V}_E/\dot{V}_{CO_2}$ was most strongly associated with the increase of peak $P_{ET}CO_2$ ($b = -0.84$; $F = 21.5$; $p < 0.0001$) and the increase of peak oxygen consumption ($b = -0.70$; $F = 10.1$; $p < 0.00001$). Furthermore, the increase of peak $P_{ET}CO_2$ was positively associated with the increase of peak oxygen consumption ($b = 0.69$; $F = 11.5$; $p < 0.00001$).

CO_2 chemosensitivity, spirometry and arterial blood gases

Post-CRT, subjects had significantly lower CO_2 chemosensitivity at rest. Forced vital capacity also improved significantly post-CRT while arterial blood gas analysis at rest demonstrated no significant differences pre- versus post-CRT (Table 4).

Discussion

The novel findings of this study were that CRT promotes decrease of $\dot{V}_E/\dot{V}CO_2$ via an increase of the arterial CO_2 setpoint and decreased CO_2 chemosensitivity. By contrast, the estimated V_D/V_T ratio did not change post-CRT and did not contribute to the decrease of $\dot{V}_E/\dot{V}CO_2$. We also showed an independent association of the pre- to post-CRT increase of $P_{ET}CO_2$ and the increase of peak oxygen consumption. These observations are consistent with decreased ventilatory drive subsequent to CRT attributable to decreased CO_2 chemoreflex activation and increase of the CO_2 setpoint, possibly mediated by decreased activation of the ergoreflex.

Effect of CRT on Ventilatory Drive

Advanced HF is associated with increased ventilatory drive which may manifest as increased $\dot{V}_E/\dot{V}CO_2$ and decreased $P_{ET}CO_2$ (8). In our study, $\dot{V}_E/\dot{V}CO_2$ significantly decreased post-CRT as has been previously reported (13–15). However, the contributions of the components of the alveolar gas equation to the observed decline of $\dot{V}_E/\dot{V}CO_2$ have not been previously shown. Moreover, understanding of the relative contributions of ventilatory dead space and the arterial CO_2 set point to the decline of $\dot{V}_E/\dot{V}CO_2$ post-CRT may provide insight regarding the effects of CRT on ventilatory control and symptom benefit in HF patients.

We observed a shift of slope for the $\dot{V}_E/\dot{V}CO_2$ versus V_D/V_T relationship consistent with the significant increase of $P_{ET}CO_2$ observed post-CRT and as predicted by the alveolar gas equation. By contrast, the slope of the relationship of $\dot{V}_E/\dot{V}CO_2$ versus $P_{ET}CO_2$ did not shift post-CRT consistent with no change of the V_D/V_T ratio. These findings suggest that *the decrease of ventilatory drive in our subjects was not due to the change of ventilation-perfusion matching in the lungs but was more likely due to modulation of central and peripheral ventilatory reflexes post-CRT.*

Previous studies have suggested that heightened sensitivity of the CO_2 chemoreflex (18) and ergoreflex (12) account for the exaggerated ventilatory response to exercise in HF patients. Increased CO_2 chemosensitivity has also been recently shown to be a powerful and independent predictor of mortality and proposed as a potential therapeutic target (19). In our subjects CO_2 chemosensitivity significantly decreased and was associated with a diminished ventilatory response during exercise post-CRT. However, increased CO_2 chemosensitivity alone cannot promote hyperventilation without a corresponding and simultaneous reduction of the arterial CO_2 setpoint (7). For HF patients, it has been proposed that a decrease of the CO_2 setpoint occurs due to either increased ergoreflex activation or a rise of sympathetic activity with exercise (7).

In our study, the setpoint at which $PaCO_2$ was maintained during exercise post-CRT appeared increased as $P_{ET}CO_2$ was significantly increased, consistent with diminished ergoreflex activation. Heightened ergoreflex activation in HF patients has been considered to be caused primarily by muscle hypoperfusion (20). Previous reports have suggested that CRT may decrease ergoreflex activation by improvement of muscle perfusion (13). In our subjects, the *increase* of peak exercise $P_{ET}CO_2$ post-CRT was significantly associated with

increase of peak oxygen consumption suggesting that improved exercise cardiac output and muscle perfusion promoted decreased ventilation by decreased activation of the ergoreflex.

Breathing Pattern

Patients with HF have altered ventilatory function due to multiple mechanisms including ventilation-perfusion mismatch, increased ventilatory drive (7) and altered lung mechanics (21). Lung congestion (11) and stiffness (22) promote changes of breathing pattern characterized by tachypnea and decreased tidal volume (23). In our subjects, the breathing pattern post-CRT compared to pre-CRT was characterized at rest and submaximal exercise by decreased breathing frequency, though tidal volume post-CRT at rest and during the first half of exercise was unchanged. A potential explanation for unchanged tidal volume at rest and submaximal exercise in post-CRT subjects may have been persistent increased lung stiffness due to congestion. However, post-CRT our subjects had a significant increase of tidal volume at peak exercise and an increase of rest forced vital capacity consistent with a previous study showing that CRT decreased lung stiffness (24). Hence, in our subjects it seems more likely the decrease of breathing frequency post-CRT was not due to increased tidal volume, but instead due to decreased ventilatory drive.

Limitations

The primary limitation of this study was the use of $P_{ET}CO_2$ as a surrogate for $PaCO_2$ during exercise which may lead to underestimation of V_D (30). In mitigation, to justify use of $P_{ET}CO_2$ as a surrogate for $PaCO_2$ the alveolar-arterial CO_2 difference should be low. Accordingly, we compared the alveolar-arterial CO_2 difference at rest pre- and post-CRT and observed no significant difference (6.6 ± 4.8 vs. 5.2 ± 3.8 mmHg; $p=0.14$). During exercise, the estimated V_D/V_T ratio significantly declined both pre-CRT (0.37 ± 0.07 vs. 0.28 ± 0.04 ; $p<0.01$) and post-CRT (0.35 ± 0.07 vs. 0.28 ± 0.05 ; $p<0.01$), suggesting an improvement of ventilation-perfusion matching and lowering of the alveolar-arterial CO_2 difference, supporting the concept that $P_{ET}CO_2$ was an appropriate surrogate for $PaCO_2$. Moreover, the alveolar-arterial CO_2 difference has been shown to decline with exercise further justifying the use of $P_{ET}CO_2$ as a surrogate for $PaCO_2$ (25). Finally, the relation of $P_{ET}CO_2$ and $PaCO_2$ has been studied under conditions of varying V_D/V_T and good correlation has been observed (26).

Conclusion

Decrease of $V_E/\dot{V}CO_2$ post-CRT is associated with decreased CO_2 chemosensitivity and increase of the CO_2 setpoint, consistent with decreased activation of both the CO_2 chemoreflex and the ergoreflex *with reduced ventilatory drive*.

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- Aim of this study was to evaluate CRT effect on V_E/V_{CO_2} and its components
- CRT increases arterial CO_2 setpoint and decreases CO_2 chemosensitivity
- CRT does not change the V_D/V_T ratio

Figure 1. Relation of $\dot{V}_E/\dot{V}_{CO_2}$ and V_D/V_T pre- and post-CRT. Slopes of ventilatory efficiency ($\dot{V}_E/\dot{V}_{CO_2}$) and ratio of tidal volume to dead space (V_D/V_T) at 50% peak exercise are compared pre- and post-CRT. The shift of the slope of this relationship from pre- to post-CRT is consistent with observed decreased CO_2 chemosensitivity, increased $P_{ET}CO_2$ and reduced ventilatory drive.

Figure 2.

Relation of V_E/V_{CO_2} and $P_{ET}CO_2$ pre- and post-CRT. Slopes of ventilatory efficiency (V_E/V_{CO_2}) to end-tidal carbon dioxide pressure ($P_{ET}CO_2$) at 50% peak exercise are compared pre- and post-CRT. The lack of change of the slope of this relationship from pre- to post-CRT is consistent with no change of the V_D/V_T ratio and no change of ventilation-perfusion matching.

Table 1
Baseline subject characteristics (n=35)

Age (years)	64 ± 12
Men No. (%)	26 (74%)
BMI	28 ± 5
NYHA III/IV No. (%)	34 (97%)/1 (3%)
LVEF (%)	24 ± 8
Sinus rhythm No. (%)	24 (69%)
QRS duration (ms)	164 ± 31
BNP (ng/L) *	657 (377-1547)
Ischemic etiology HF No. (%)	17 (49%)
peak exercise $\dot{V}O_2$ (mL/min/kg)	13.4 ± 3.5

*
 median (inter-quartile range)

BMI = body mass index; BNP = brain natriuretic peptide; HF = heart failure; kg = kilogram; L = litre; LVEF = left ventricle ejection fraction; min = minute; mL = millilitre; ms = millisecond; ng = nanogram; NYHA = New York Heart Association; $\dot{V}O_2$ = oxygen consumption

Table 2

Clinical Outcomes with CRT (n=35)

Parameter	Pre-CRT		Post-CRT		P
	Mean	SD	Mean	SD	
NYHA Class	3	0.2	2	0.8	<0.01
MLWHF (n=33)	46	25	33	27	0.01
6MWD (m) (n=30)	381	107	421	96	<0.01
LVEF (%)	24	8	34	15	<0.01
SVI (mL/m ²)	37	11	42	12	0.03
BNP (ng/L) (n=33) *	657	(377-1547)	436	(242-860)	<0.01
Medication	n(%)		n(%)		
ACE-I or ARB n(%)	34 (97)		34 (97)		1.00
Digoxin n(%)	16 (46)		19 (54)		0.63
Beta blocker n(%)	33 (94)		34 (97)		0.99
Diuretics n(%)	26 (74)		30 (86)		0.37

* median (inter-quartile range)

6MWD = 6 minutes walking distance; ACE-I = angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blockers; BNP = brain natriuretic peptide; L = litre; LVEF = left ventricle ejection fraction; m = meter; m² = square meter; min = minute; mL = millilitre; MLWHF = Minnesota Living with Heart Failure score; ng = nanogram; NYHA = New York Heart Association; SVI = stroke volume index

Table 3

Pre vs. post CRT: Resting and Exercise Ventilation (n=35)

Parameter	Pre-CRT		Post-CRT		p
	Mean	SD	Mean	SD	
rest					
$\dot{V}_E$ (L/min)	14	6	13	5	0.10
V_T (mL) *	784	(540-890)	701	(577-877)	0.78
V_D/V_T	0.37	0.08	0.35	0.07	0.10
f_b (bpm)	20	6	17	5	<0.01
$P_{ET}CO_2$ (mmHg)	32	4	33	5	0.21
$\dot{V}_E/\dot{V}CO_2$	45	10	42	8	<0.01
50% exercise					
$\dot{V}_E$ (L/min)	31	9	28	8	0.16
V_T (mL)	1172	379	1190	462	0.35
V_D/V_T	0.3	0.05	0.3	0.06	0.67
f_b (bpm)	28	7	25	6	<0.01
$P_{ET}CO_2$ (mmHg)	31	6	33	6	<0.01
$\dot{V}_E/\dot{V}CO_2$	41	9	38	8	0.03
100% exercise					
$\dot{V}O_2$ (mL/min/kg)	13.4	3.5	14.2	3.4	0.12
$\dot{V}CO_2$ (mL/min)	1281	433	1386	462	0.06
$\dot{V}_E$ (L/min)	52	15	52	15	0.60
V_T (mL)	1445	(1215-1861)	1530	(1234-1866)	0.05
V_D/V_T	0.28	0.05	0.28	0.05	0.33
f_b (bpm)	36	7	33	6	0.06
$P_{ET}CO_2$ (mmHg)	29	5	31	5	<0.01

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Parameter	Pre-CRT		Post-CRT		p
	Mean	SD	Mean	SD	
$\dot{V}_E/\dot{V}_{CO_2}$	44	10	40	8	0.01
RER	1.14	0.1	1.14	0.1	0.80

* median (inter-quartile range)

bpm = breaths per minute; CSA = central sleep apnea; f_b = breathing frequency; kg = kilogram; L = litre; min = minute; mL = millilitre; mmHg = millimetres of mercury; $P_{ET}CO_2$ = partial pressure of end-tidal carbon dioxide; RER = respiratory exchange ratio; $\dot{V}_{CO_2}$ = carbon dioxide production; $\dot{V}_D/\dot{V}_T$ = death space/tidal volume ratio; $\dot{V}_E$ = minute ventilation; $\dot{V}_E/\dot{V}_{CO_2}$ = ventilatory efficiency; $\dot{V}O_2$ = oxygen consumption; V_T = tidal volume

Table 4
Comparison of Chemosensitivity, Spirometry and Arterial Blood Gases

Parameter	Pre-CRT		Post-CRT		P
	Mean	SD	Mean	SD	
$V_E / P_{ET}CO_2$ (L/min/mmHg) (n=30)	2.2	1.14	1.7	0.8	0.04
FEV ₁ (%) (n=33)	76	18	79	18	0.30
FVC (%) (n=33)	80	17	88	18	<0.01
DLCO (mL/min/mmHg) (n=33)	19	8	18	5	0.11
pH (n=34)	7.42	0.07	7.43	0.05	0.70
pO ₂ (mmHg) (n=34) *	84	(79-90)	88	(79-93)	0.12
pCO ₂ (mmHg) (n=34)	39	4	39	7	0.70
HCO ₃ (mmol/L) (n=34)	25	3	25	3	0.79
BE (mmol/L) (n=34) *	1	(0-3)	2	(0-2)	0.75

* median (inter-quartile range)

$V_E / P_{ET}CO_2$ = central carbon dioxide chemosensitivity; BE = base excess; DLCO = pulmonary diffusing capacity of carbon; FEV₁ = forced expiratory volume at one second; FVC = forced vital capacity; HCO₃ = bicarbonate; L = litre; monoxide; min = minute; mL = millilitre; mmHg = millimetres of mercury; mmol = millimol; pCO₂ = partial pressure of carbon dioxide; pO₂ = partial pressure of oxygen