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VENTILATORY GAS EXCHANGE AND EARLY RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY

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Abstract

Background—Cardiac resynchronization therapy (CRT) is an accepted intervention for chronic heart failure (HF), though approximately 30% of patients are non-responders. The purpose of this study was to determine if exercise respiratory gas exchange obtained prior to CRT implantation predicts early response to CRT.

Methods—Prior to CRT implantation, patients were assigned to either a mild-moderate group (Mod G, n=33, age= 67±10yrs) or a moderate-severe group (Sev G, n=31, age=67±10yrs) based on abnormalities in exercise gas exchange. Severity of impaired gas exchange was based on a score from the measures of V_E/V_{CO_2} slope, resting $P_{ET}CO_2$ and change of $P_{ET}CO_2$ from resting to peak. All measurements were performed pre- and 3~4 months post CRT implantation.

Results—While the Mod G did not improve gas exchange ($p>0.05$), the Sev G improved significantly ($p<0.05$) post-CRT. In addition, the Mod G did not improve right ventricular systolic pressure (RVSP) (pre vs. post: 37±14 vs. 36±11 mmHg, $p>0.05$), while the Sev G significantly improved RVSP by 23% (50±14 vs. 42±12 mmHg, $p<0.05$). Both groups improved LVEF ($p<0.05$), New York Heart Association ($p<0.05$) and quality of life ($p<0.05$), but no significant differences were observed between groups ($p>0.05$). No significant changes were observed in brain natriuretic peptide (BNP) in either group post CRT.

Conclusion—Based on pre CRT implantation ventilatory gas exchange, subjects with the most impaired values appeared to have more improvement post CRT possibly associated with a decrease in RVSP.

Keywords

Heart failure; ventilatory efficiency; exercise; pulmonary hypertension

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DISCLOSURES

The authors for this manuscript have nothing to disclose.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has become an essential treatment for selected patients with heart failure (HF). Patients often demonstrate benefits with CRT such as improved cardiac function, improved exercise ventilatory efficiency as well as exercise capacity.¹ However, 25 to 30% of patients do not respond to CRT,²⁻⁴ and the outcomes vary according to disease severity and patient characteristics. A number of previous studies investigated the echocardiographic, functional and exercise responses to CRT, however, the results have not been consistent. This may be due to different criteria for responders and non-responders and the timing of post CRT measurement. Therefore, an additional approach to predict favorable or non-response to CRT is needed.

The lungs and heart essentially function as an interdependent organ system. They are hemodynamically and neuro-mechanically linked. Moreover, light intensity exercise augments the interaction between the heart and lungs. Ventilatory responses to exercise as a prognostic tool to predict the severity of HF are well established.⁵⁻⁸ In addition, abnormalities in exercise capacity and gas exchanges are closely associated with morbidity and mortality.⁹⁻¹¹ The purpose of the present study was to determine if exercise gas exchange obtained prior to CRT implantation may predict early response based on LV ejection fraction, 6-minute walk distance, New York Heart Association (NYHA) classification, quality of life (QOL), brain natriuretic peptide (BNP) and change in right ventricular systolic pressure (RVSP).

METHODS

Subjects

Sixty four patients with advanced HF who were scheduled for CRT implantation were enrolled for the study. Subject recruitment criteria included NYHA Class II-IV, left ventricle ejection fraction (LVEF) $\geq$ 35% and QRS duration $>$ 120ms. Medication doses (beta-blockers, angiotensin-converting enzyme inhibitors, diuretics or angiotensin receptor blockers) remained stable from pre to post CRT implantation. Patients who had significant orthopedic limitations were excluded. The present study was approved by Mayo Clinic Institutional Review Board, and informed consent form was obtained from each subject before participation in the study.

Experimental Protocol

Prior to CRT implantation, subjects underwent assessments including left ventricular ejection fraction (LVEF) and right ventricular systolic pressure (RVSP) via echocardiography, NYHA, QOL (Minnesota living with heart failure questionnaire), N-terminal pro hormone brain natriuretic peptide (NT-Pro-BNP) and 6-min walking test (6MWT). In addition, subjects performed incremental exercise testing, and noninvasive respiratory gas exchange was measured via research based breath by breath metabolic cart (Medgraphics, Saint Paul, MN).

The exercise protocol was a submaximal incremental treadmill walking test. After 2 min walking at 1.0 mph for warm-up, the experimental test began at 1.0mph. The intensity was

increased by 1.0 mph and 0.5 grade every 2min based on exercise tolerance with the goal of obtaining approximately 1.0 of respiratory exchange ratio (RER). Gas exchange was continuously measured during exercise and the last 1minute of gas exchange values at each stage was averaged and VE/VCO_2 slope and the delta from baseline to the highest values were calculated for the analysis. Based on severity of impaired gas exchange, subjects were assigned to either a mild to moderately impaired gas exchange group (Mod G, n=33) or a moderate to severely impaired gas exchange group (Sev G, n=31). Subjects re-visited the laboratory 3–4 month post CRT implantation for post-testing.

Gas exchange variables and scoring system—For the present study, 3 key gas exchange variables including ventilatory equivalents for carbon dioxide (V_E/VCO_2) slope or ventilatory efficiency slope, resting end-tidal CO_2 ($P_{ET}CO_2$) and the change in $P_{ET}CO_2$ with exercise, were obtained to determine the severity of disease.^{6, 12, 13} These variables are closely related to prognosis and disease severity in HF. Ventilatory equivalent for carbon dioxide increase as disease severity worsens.^{6, 7} End-tidal CO_2 ($P_{ET}CO_2$) is also commonly utilized to track disease status and responses to therapy in HF. End-tidal CO_2 is often reduced with exercise in HF and represents abnormalities in gas exchange.^{5, 8}

For quantitative assessment of gas exchange, a simple multiple variable index (MVI) was developed based on a severity score (0=normal, 4=severely impaired gas exchange). The score was obtained for each key gas exchange variable and averaged for the total score was averaged. The population was divided by 2 groups based on this scoring system. Table 1 illustrates the MVI scoring system.¹³ For the present study, subjects who demonstrated the score lower than 2.5 were assigned to Mod G while those who showed the score higher than 2.5 were assigned to Sev G.

Statistical Analysis

The present study was a between subjects design. To compare the responses to CRT between groups, a group $\times$ treatment repeated measures analysis of variance was conducted. Subsequently a paired sample t-test and non-parametric t-test (Mann-Whitney U test) was conducted to compare the specific differences between pre and post and between groups respectively. Significance was set a priori at $p<0.05$.

RESULTS

All subjects completed experimental procedures. At baseline, when groups were separated based on exercise gas exchange data, the distribution of QRS in each group are illustrated in table 2. In addition, the Mod G differed from the Sev G on all clinical measures of disease severity except NT-pro BNP and NYHA classification (table 3).

At 3–4 months post CRT implantation, the Mod G had no significant change in the gas exchange score (MVI) ($p>0.05$) while the Sev G demonstrated significant improvement ($p<0.05$, figure 1). Both the Mod G and the Sev G improved LVEF after CRT implantation ($p<0.01$), but there was no significant difference between groups (figure 2, $p>0.05$). Furthermore, both groups showed improvements in NYHA and QOL (table 4, $p<0.05$), but no significant improvement in NT pro BNP was observed (table 4, $p=0.079$). There was a

trend toward significant difference in 6MWT between groups ($p=0.053$), and subsequent analysis demonstrated that the Mod G did not improve (table 4, $p>0.05$), while the Sev G improved (table 4, $p<0.05$).

For RVSP post CRT implantation, the Mod G improved by 7% but was not significant ($p>0.05$). The Sev G significantly improved by 23% ($p<0.01$). Figure 3 illustrates the changes in RVSP between groups post CRT implantation.

DICUSSION

Summary of findings

The purpose of the present study was to determine if using noninvasive exercise gas exchange to categorize HF patients prior to CRT implantation would predict early response to treatment. We found that groups with mild-moderate or moderate-severe exercise gas exchange abnormalities both demonstrated benefit based on NYHA, LVEF, and QOL. However, the group with more severe baseline abnormalities appeared to receive greater benefit than the less-severe group. Interestingly, the more severe group had the most improved exercise gas exchange possibly related to a significant reduction in RVSP.

Exercise gas exchange in heart failure

The lungs and heart not only compete for intrathoracic space but are also hemodynamically linked to supply adequate oxygen to tissues. A change in function of one organ directly influences the other and this relationship is more apparent in the dynamic state of exercise. Hence, pulmonary gas exchange during exercise is often utilized to track disease severity in HF. However, cardiopulmonary gas exchange parameters are often complicated to understand for many clinical settings. In the present experiment, we utilized submaximal exercise gas exchange instead of maximal exercise (VO_2 peak). In some cases, submaximal variables are less variable than maximal variables, and/or are sensitive and more reproducible because they are effort-dependent.^{14, 15} Our attempt in the present experiment was to simply merge several important gas exchange variables from lower intensity exercise that are known to be altered by the heart failure disease syndrome and to essentially avoid using peak VO_2 as a sole representation of disease severity.

The V_E/VCO_2 slope has been shown to be elevated in HF. This phenomenon is closely related to increased dead space ventilation, which results from increased ventilation during exercise, increasing with severity of disease state as well as a change in breathing pattern.^{6, 7, 16} End-tidal CO_2 (P_{ETCO_2}) at rest is typically low in patients with HF. This may be due to increased ventilation and decreased cardiac output, which results in ventilation-perfusion (V/Q) inhomogeneities.^{5, 6, 8, 12, 17} In addition, P_{ETCO_2} is shown to be lower during exercise, a possible result of augmented V/Q inhomogeneities due to low cardiac output.^{5, 12} Consequently, the changes in P_{ETCO_2} and V_E/VCO_2 during exercise in HF often demonstrate an inverse relationship.¹⁸

In the present experiment, prior to CRT implantation, patients with HF were classified into two groups (mild-moderately impaired and moderate-severely impaired groups) based on exercise gas exchange abnormalities. Overall, the Mod G had better overall clinical

measures related to disease severity (i.e., LVEF, NYHA, QOL, etc) than the Sev G at baselinets consistent with previous studies that have linked exercise gas exchange to disease severity in patients with HF.

Responses to cardiac resynchronization therapy

Cardiac resynchronization therapy is generally applied to patients who have stable optimal medical treatment, sinus rhythm, LVEF $\geq 35\%$, QRS $> 120\text{ms}$ and NYHA class III and IV. Despite these specific criteria, the response to CRT varies and a number of recipients still do not respond.²⁻⁴ The response to CRT are largely categorized based on the clinical measures of NYHA, QOL and 6MWT, exercise capacity (i.e., peak VO_2) and echocardiographic based measures (i.e., LVEF, LV end systolic volume, etc). A previous study by Yu et al. (2003) found that responders (improved LV reverse remodeling) and non-responders improved NYHA and QOL via CRT, but only responders improved LVEF, peak VO_2 and 6MWT.⁴ Another study by Bleeker et al. (2006) reported that 26% of CRT recipients did not improve LVEF and NYHA in their experiment, and 30% of whom improved NYHA did not improve LVEF.³ Accordingly, the responses to CRT and relationships between these parameters are not clearly understood. In addition, there are still approximately 40–50 % of CRT recipients (non-responders based on LV end systolic volume) who did not improve exercise capacity with no change in ventilatory efficiency.^{4, 19, 20} However, in the present experiment, we observed that the group who had more severe baseline gas exchange abnormalities demonstrated greater improvement with CRT than the less severe group. This result is accordant with a previous study illustrating that the group who demonstrated more depressed metabolic and ventilation parameters may benefit most from CRT.¹

Pulmonary congestion and gas exchange in HF

Left ventricular ejection fraction, exercise capacity and gas exchange have been important parameters to determine prognosis of HF. However, there are limited numbers of studies which have investigated the relationship between LVEF and exercise gas exchange following CRT implantation. Previous studies demonstrated that echocardiographic responders to CRT (i.e., LVEF, LV end systolic volume and etc) also improved exercise capacity and ventilatory efficiency.^{1, 4, 19, 20} However, it does not necessarily mean that changes in LVEF are directly related to exercise gas exchange. In the present experiment, while the Mod G improved LVEF without significant change in exercise gas exchange, the Sev G improved both parameters. Therefore it seems that improved gas exchange was independent of increased LVEF. This lack of congruence between resting measures of cardiac function and exercise gas exchange is further supported by a previous study by Piepoli et al. (2008) reporting that LVEF was improved 6 month-post CRT, but peak VO_2 and ventilatory efficiency did not.²¹ In addition, other studies demonstrated that peak VO_2 was not associated with LVEF and/or LV end diastolic volume.²²⁻²⁴ Therefore, the changes in LVEF following CRT may not be closely related to exercise capacity and gas exchange.

Interestingly, we observed that the Sev G with improved exercise gas exchange also improved RVSP. In HF, secondary (or passive) pulmonary hypertension refers to the condition of increased pulmonary vascular pressures, consequent to a rise in left ventricular filling pressures, which may eventually cause a rise in right ventricular pressure. This

pressure-overload in pulmonary vasculature and the right ventricle are an important issue in HF because it may eventually cause of right ventricular dysfunction.^{25, 26} Patients with HF generally demonstrate impaired gas exchange^{5, 6, 27} and diffusing capacity.^{28, 29} Although the mechanism is not still clearly understood, it is speculated that an elevated pressure in the pulmonary vasculature due to insufficient circulation plays a major role. This hypothesis is supported by previous studies using phosphodiesterase-5 (PDE-5) inhibitor, which has vasodilatory effect on the pulmonary vasculature. A study by Lepore et al. (2005) observed that administration of PDE-5 inhibitor with nitric oxide improved cardiac index with decreased pulmonary arterial pressure and pulmonary vascular pressure in HF with pulmonary hypertension.³⁰ Furthermore, other studies found that PDE-5 inhibitor improved exercise capacity³¹, ventilatory efficiency and dyspnea.³² Moreover, a study by Taylor et al. (2013) found that gas exchange can track pulmonary vascular response to exercise in HF.³³ In addition, in several of our previous studies, we have found the $P_{ET}CO_2$ tracks most closely with the degree of pulmonary hypertension in patients with HF.^{6, 34} Based on these findings, we hypothesize that improvements in RVSP and exercise gas exchange in the Sev G are consequences of reduced pulmonary vascular congestion and right heart hemodynamics in concert with lowered LV filling pressure via ventricular re-synchrony.^{35–37} In addition, the lack of improvement in RVSP in the Mod G may be due to lower baseline values. Compared to the Sev G, the Mod G had a significant lower RVSP pre CRT and this value is also lower than the clinical cutoff value of RVSP (~45mmHg) for pulmonary hypertension.³⁸ This may indicate that the Mod G did not have significant limitation from the pulmonary vasculature and thus had a smaller margin for improvement. However, further assessments are needed to support this assertion.

Limitations

In the present experiment, the mild-moderate group did not improve RVSP and gas exchange even though LVEF improved. The present experiment investigated early responses (3–6month) to CRT and thus follow-up tests are needed to determine the long-term effect of CRT. Indeed, a study by Piepoli (2008) observed that ventilator efficiency did not improve while LVEF improved.¹⁹ However, it eventually improved at 12month post CRT. Therefore, it is possible that the mild-moderate group required a longer period for adaptation. Another possible reason is that the mild-moderate group had less elevated RVSP at baseline, thus leaving less margins for improvement. In addition, the present experiment did not assess subjects' exercise training program and/or other treatment program post CRT.

Conclusions

Noninvasive exercise pulmonary gas exchange is a significant predictor of prognosis in patients with HF and tracks disease severity. The data in the present study suggest that patients with more severe baseline gas exchange abnormalities may demonstrate greater benefits from CRT implantation and this improvement in gas exchange may be associated with a decrease in RV pressure. However, further studies are needed to determine clear mechanisms for improvement of gas exchange via ventricular resynchrony with CRT and its' long-term effects.

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Figure 1.

The changes in MVI scores from pre to post CRT implantation in the Mod G and the Sev G groups. The Mod G (mild to moderately impaired group), the Sev G (moderate to severely impaired group). * denotes a significant group $\times$ time interaction ($p < 0.05$).

Figure 2.
The changes in LVEF (%) from pre to post CRT implantation in the Mod G and the Sev G groups. The Mod G (mild to moderately impaired group), the Sev G (moderate to severely impaired group), LVEF (left ventricle ejection fraction).

Figure 3.

The changes in RVSP (mmHg) from pre to post CRT implantation in the Mod G and the Sev G groups. The Mod G (mild to moderately impaired group), the Sev G (moderate to severely impaired group), RVSP (right ventricle systolic pressure). * denotes a significant group $\times$ time interaction ($p<0.05$).

Table 1

Multi-variable index scoring system.

	Resting $P_{ET}CO_2$	in $P_{ET}CO_2$	V_E/VCO_2	
Normal value	40	3.6	26	
Delta value	5	1.8	7	
Normal: 0	40	3.6	26	0.00/0/00
Normal to mild: 1	35	1.8	33	3.00/1.00
Mild to moderate: 2	30	0	40	6.00/2.00
Moderate to severe: 3	25	-1.8	47	9.00/3.00
Severe to very severe: 4	20	-3.6	54	12.00/4.00

Total score from 3 variables was divided by 3 for an average score. The score range is from 0 (normal) to 4 (severe).

Table 2

QRS width at baseline

	QRS		
	<130ms	130ms and <150ms	150ms
Mod G (n=33)	1	5	27
Sev G (n=30)	4	5	21

The distribution of baseline QRS width in the moderate group (n=33) and the severe group (n=30).

Table 3

Baseline measurements in the Mod G and the Sev G.

Groups			
	The Mod G (n=33)	The Sev G (n=31)	p-value
Age	67±10	67±10	
Gender (female/male)	6 / 27	7 / 24	
BMI (kg/m ²)	29.1±4.9	28.9±4.4	
Hypertension (%)	38%	52%	
NT Pro BNP (pmol/l)	1468±2251	1361±1178	p>0.05
NYHA	2.86±0.44	3.00±0.28	p=0.06
QOL	38.4±28.3	51.2±20.1	p=0.05
6MWT (m)	439±85	365±120	p<0.05
LVEF (%)	28±7	21±5	p<0.05
RVSP (mmHg)	37.3±14	50.4± 14	p<0.05
V _E /VCO ₂ slope	30.7±7.4	46.8±7.4	p<0.05
Resting P _{ET} CO ₂ (mmHg)	34.4±3.4	31.9±3.4	p<0.05
in P _{ET} CO ₂ (mmHg)	1.5±3.1	-4.1±2.5	p<0.05
MVI score	1.43±0.7	3.06±0.3	p<0.05
ACE inhibitor (%)	72.7	93.6	
Beta blocker (%)	87.9	96.8	
Diuretic (%)	78.8	90.3	

The Mod G (mild to moderate impaired gas exchange group), the Sev G (moderate to severe impaired gas exchange group), NT Pro BNP (N-terminal pro hormone brain natriuretic peptide), NYHA (New York heart association class), QOL (Minnesota quality of life questionnaire), 6MWT (6 minute walking test), LVEF (left ventricle ejection fraction), RVSP (right ventricle systolic pressure), V_E/VCO₂ slope (breathing efficiency: ventilatory equivalent for carbon dioxide), P_{ET}CO₂ (end-tidal carbon dioxide). MVI (multi-variable index score), MVI score range is 0 (normal) to 4 (severe). ACE inhibitor (angiotensin converting enzyme inhibitor).

Table 4

The outcomes pre and post CRT between the Mod G and the Sev G

	Mod G		Sev G	
	pre CRT	post CRT	pre CRT	post CRT
MVI	1.43 ± 0.7	1.53 ± 0.7	3.1 ± 0.3	2.5 ± 0.8*
LVEF (%)	28±7	41±13*	21±5	29±9*
NYHA	2.9±0.4	2.3±0.8*	3.0±0.3	2.1±0.8*
QOL	38.4±28	23.9±24*	51.2±20	31.0±25*
BNP (pg/ml)	1468±2251	1124±1678	1361±1178	881±906
6MWT (m)	439±85	402±79	365±120	413±133*
RVSP (mmHg)	37.3±13.8	35.5±10.8	50.4±14.4	42.1±12.3*
HR slope	11.3	9.73	8.76	9.88

MVI (multi-variable index score), LVEF (left ventricular ejection fraction), NYHA (New York heart association classification), QOL (Minnesota living with heart failure questionnaire), BNP (N-terminal pro hormone brain natriuretic peptide), 6MWT (6 minute walking test), RVSP (right ventricular systolic pressure), HR (heart rate) slope.

* denotes a significant difference between pre and post CRT.