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THE EFFECTS OF ATRIOVENTRICULAR AND INTER-VENTRICULAR DELAYS ON GAS EXCHANGE DURING EXERCISE IN PATIENTS WITH HEART FAILURE

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Abstract

BACKGROUND—Cardiac resynchronization therapy (CRT) has been an important treatment for heart failure. However, whether an individualized approach to altering AV and VV timing intervals would improve outcomes has been controversial. Changes in respiratory patterns and gas exchange are dynamic and may be influenced by timing delays. Light exercise enhances the heart and lung interactions. Thus, the present study investigated changes in non-invasive gas exchange by altering AV and VV timing intervals during light exercise.

METHODS—Patients (n=20, age=66±9yr) performed 2 walking tests post implantation. The protocol evaluated AV delays (100, 120, 140, 160, 180msec), followed by VV delays (0, −20, −40msec) while gas exchange was assessed.

RESULTS—There was no consistent group pattern of change in gas exchange variables across AV and VV delays (p>0.05). However, there were modest changes in these variables on an individual basis with variations in V_E/VCO_2 averaging 10%, O_2 pulse 11% and $P_{ET}CO_2$ 5% across AV delays, and 4%, 8% and 2% respectively across VV delays. Delays that resulted in the most improved gas exchange differed from nominal in 17/20 subjects.

CONCLUSION—Gas exchange measures can be improved by optimization of AV and VV delays and thus could be used to individualize the approach to CRT optimization.

Keywords

CRT; ventilation; resynchronization; cardio-pulmonary; exercise

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Disclosures

The authors for this manuscript have nothing to disclose.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has been an important treatment for heart failure (HF) patients. The rate of CRT device implantation has increased gradually since being introduced.^{1, 2} However, 25–30% of CRT recipients do not demonstrate improvements in symptoms and/or left ventricular function after implantation. This may be due to several issues, including the fact that atrioventricular (AV) and interventricular (VV) intervals of the CRT device are usually set at a standard, non-individualized nominal setting or are optimized during the resting state. Currently, most clinical attempts to optimize CRT are resting echo-based techniques.¹ However, a recent study by Chung et al.³ illustrated that no echo-based technique lead to improved outcomes with CRT. Hence, there is a need for new approaches for CRT optimization and individualization.

Cardiac resynchronization therapy is designed to improve pump function of the heart with resynchronization of ventricular activation via controlling AV and VV timing intervals. The lungs are intimately linked with cardiac function, and influenced by acute changes in left heart pressure.⁴ Therefore changes in cardiopulmonary gas exchange, e.g., end tidal CO₂ (P_{ET}CO₂), ventilatory efficiency (V_E/VCO₂) and oxygen pulse (O₂pulse), are dynamic as they reflect changes in cardiac function and thus may be influenced by AV and VV timing delays. Mild cardiac load with increased venous return via low intensity exercise enhances the interaction between the heart and lungs,⁵ and exercise testing is clinically used to determine disease severity and prognosis in HF.^{6–8} In addition, in HF submaximal exercise provides similar prognostic value and measures are more easily obtainable and less variable than at or near peak exercise.^{9, 10} Therefore, alterations in P_{ET}CO₂, V_E/VCO₂ and O₂ pulse via AV and VV interval modifications during submaximal exercise may reflect dynamic changes in cardiac function. The purpose of the present study was to investigate if changes in AV and VV timing intervals during low intensity exercise influence non-invasive gas exchange measures and if these measures in turn could be used as a possible method for optimization CRT timing intervals.

METHODS

Subjects

Subject recruitment criteria included patients with advanced HF, 30 to 80 years, New York Heart Association (NYHA) class II–IV, QRS duration > 120ms and left ventricle ejection fraction (LVEF) < 35%. For the current study 20 HF patients (17 males and 3 females, 66±9 yr) who were scheduled for CRT implantation participated. Sample size was estimated to determine a group effect via a calculation of 10% change in one of the gas exchange variables with n=20, 80% power and alpha=0.05. Patients were on stable doses of optimized medication (beta-blockers, angiotensin-converting enzyme inhibitors, diuretics or angiotensin receptor blockers) before and after implantation. They were able to perform light steady state submaximal exercise without significant orthopedic limitations. The study was approved by Mayo Clinic Institutional Review Board, and informed consent form was obtained from each patient prior to participation.

Experimental Procedure

Prior to CRT implantation, patients visited our cardiopulmonary laboratory for measurements of height, weight and classical outcome measures (LVEF, NYHA and QOL-Minnesota quality of life questionnaire). Then, patients re-visited within 1 to 4 weeks post implantation for assessment of classical outcome measures and submaximal walking tests. At that time, all patients underwent 2 separate low intensity walking tests (submaximal gas exchange tests with AV and VV delay modifications) on a treadmill. Breathing pattern and

gas exchange were measured via a research based system integrated with a Perkin Elmer MGA-1100 mass spectrometer (Pamona, CA). The protocol evaluated AV delay settings first followed by VV delay settings.

Protocol—Given the limited exercise tolerance of the HF population, the need for steady state exercise (to avoid a drift in gas exchange measures) but at the same time the need to complete a 10 min time window, we chose a very low level of exercise for the testing. This appeared adequate in preliminary testing to enhance heart and lung interactions and increase the signal relative to noise or variation for our key gas exchange measures. Therefore, steady state and very low intensity exercise (increase in HR by approximately 10 bpm), which resulted in a small increase in demand, venous return and cardiac load, was applied and all subjects exercised on a motor driven treadmill at 1.5mph/1.0% grade during the trials. The timing delays were evaluated after 2 min of rest and 3 min of steady state walking (warm-up). For AV delay modification, there were 5 discrete settings 20 msec apart using AV interval sequences of 100, 120, 140, 160 and 180 msec, while there were 3 settings, 0, -20 and -40ms, for VV intervals. Each setting was 2 min in duration and data obtained during the second min were averaged for the analysis. Optimum intervals were determined based on a simple gas exchange scoring system. In order to provide a quantitative assessment of the optimal choice of AV and VV delays and increase sensitivity, a ranking algorithm was used at the completion of each exercise test. For the scoring system 3 key gas exchange variables (ventilatory efficiency - V_E/VCO_2 , end tidal CO_2 - $P_{ET}CO_2$ and oxygen uptake per heartbeat- O_2 pulse) were applied, primarily since they had previously been most closely associated with HF disease severity, prognosis and cardiac function.^{7, 11-13}

In the literatures, V_E/VCO_2 and $P_{ET}CO_2$ are the most recognized parameters which closely track with disease severity in HF. An elevated V_E/VCO_2 is related to high dead space ventilation, which is linked primarily to increased breathing frequency in HF, which increases as disease severity worsens.^{13, 14} $P_{ET}CO_2$ typically decreases in patients with HF due to an increase in ventilation, a decrease in cardiac output and ventilation and perfusion (V/Q) inhomogeneities in the lungs.¹³⁻¹⁶ The decrease in $P_{ET}CO_2$ is typically inversely related to V_E/VCO_2 and therefore it is expected that $P_{ET}CO_2$ and V_E/VCO_2 show similar patterns in which $P_{ET}CO_2$ decreases when V_E/VCO_2 increases. Therefore we primarily applied these two parameters with 90% of total available score (45% for $P_{ET}CO_2$ and 45% for V_E/VCO_2). O_2 pulse (VO_2/HR) has also been associated with stroke volume during exercise and it appears to track relatively well in a variety of populations.^{7, 17, 18} Therefore we added this parameter contributing 10% to the total score. In our pilot testing, the algorithm based on these parameters appeared to reduce noise and yet allow large enough differences in score to detect the optimal intervals. Table 1 demonstrates the variable set and the point distribution based on rank according to gas exchange variable. The highest averaged value of $P_{ET}CO_2$ received 45 points and then 36, 27, 18 and 9 respectively. The lowest averaged value of V_E/VCO_2 received 45 points and then 36, 27, 18 and 9 respectively. The highest averaged value of O_2 pulse received 10 points and then 8, 6, 4 and 2 respectively. The points from each variable were added, and the timing interval, which gained the highest total point, was selected as the optimal choice for AV and VV delays. The range of total point is from 20 to 100. As the optimal choice for AV delay was obtained from the 1st exercise assessment, AV delay was programmed first before testing VV delay. The rationale behind this procedure is that AV delay influences diastolic filling, and this should be optimized prior to 2nd exercise assessment for VV delay which influences forward flow.

RESULTS

Prior to implantation mean NYHA was 2.7 ± 0.5 , LVEF was 28 ± 7 and QOL was 45 ± 26 . Though not an aim of this study, these outcomes were improved almost immediately after implantation (1–4 weeks); NYHA was 2.5 ± 0.7 , LVEF was 32 ± 10 and QOL was 22.4 ± 24 ($p < 0.05$). All 20 HF patients successfully completed 2 submaximal walking tests. Modest changes in breathing pattern and gas exchange variables across the AV and VV timing intervals selected were observed (table 2). However, as a group, there were no consistent patterns of change (increase or decrease) in the gas exchange score as timing increased or decreased. The average changes in V_E/V_{CO_2} , $P_{ET}CO_2$ and O_2 pulse were 10.0%, 5.2% and 10.6% respectively for AV timing intervals. For VV timing intervals, variations in V_E/V_{CO_2} , O_2 pulse and $P_{ET}CO_2$ were smaller and averaged 4.2%, 7.9% and 2.3%, respectively.

Figure 1 shows an individual example of the breath-by-breath changes in V_E/V_{CO_2} following modification of AV timing intervals, and the solid lines represent a smoothing algorithm (moving 5 of 7 average). Figure 2-A to D shows individual examples of 1 min averaged $P_{ET}CO_2$, V_E/V_{CO_2} and O_2 pulse following AV modification (*upper portion of each panel*) and the combined score distribution across AV and VV delays (*lower portion of each panel*). These demonstrate representative cases showing different patterns of change in the gas exchange variables. Figure 2-A yields a subject with the highest combined scores at 100ms for AV delay and 0ms for VV delay. Figure 2-B (*upper portion of each panel*) shows a case where the highest $P_{ET}CO_2$ and the lowest V_E/V_{CO_2} occurred at a similar AV delay, and yields an optimal score at 120ms for AV delay and –40m for VV delay. Figure 2-C and D (*upper portion of each panel*) show cases where the highest $P_{ET}CO_2$ and the lowest V_E/V_{CO_2} occurred simultaneously with the highest O_2 pulse with optimal settings at 140, –20 and 160, 0 for AV and VV delays, respectively. For the most part, V_E/V_{CO_2} and $P_{ET}CO_2$ were mirror images of each other, although in Figure 2-C $P_{ET}CO_2$ demonstrates a more marked change than V_E/V_{CO_2} . In the 2-A example the trend in gas exchange was to deteriorate as AV timing intervals lengthen while this trend was generally opposite for 2-D as this interval lengthens. Figures 2-B and C tend to showed more variability and despite an initial optimization of the AV interval, gas exchange with VV timing changes were also variable and not consistent across subjects.

Table 3 illustrates individual nominal settings (the settings made initially) and proposed settings (proposed settings based on gas exchange scoring). Each Individual showed different optimal combinations for AV and VV delays, and 17 out of 20 individuals had different proposed AV and VV delay settings from nominal.

DISCUSSION

Summary of findings

The goal of the present study was to determine the effect of changing AV and VV timing intervals on non-invasive respiratory gas exchange during very light steady state exercise. In this experiment, gas exchange variables were altered as AV and VV timing intervals were adjusted. However, as a group no consistent pattern of change in these variables was observed. Individuals demonstrated different gas exchange responses across AV and VV timing intervals, and thus this type of approach may allow a more individualized method for setting timing intervals that take into account the unique inter-relationships of variables that determine integrated cardiac and lung functions.

Gas exchange reflects cardiac function – selecting key variables

The lungs and heart are closely linked and thus changes in breathing pattern and gas exchanges are dynamic as they reflect changes in cardiac function.^{13, 14, 19, 20} Alterations in cardiopulmonary gas exchange via light or submaximal exercise are clinically used to determine the prognosis or severity of HF and $P_{ET}CO_2$, V_E/VCO_2 and O_2 pulse have been suggested as specific gas exchange measures to track HF.^{6, 7, 11, 21} A lower $P_{ET}CO_2$ and a higher V_E/VCO_2 indicate high dead space ventilation, altered breathing pattern and an increase in V/Q mismatch which is associated with impaired cardiac output.^{6, 7, 21–23} O_2 pulse is also used as an indicator of stroke volume and arteriovenous O_2 difference¹⁷ and appears to be reduced as heart failure severity increases.⁷ In HF, cardiac dyssynchrony induces a reduced cardiac output and increased mitral regurgitation, and in turn results in increased left wall thickness and delayed relaxation.¹ It may also increase ventricular interdependence. The end result may be a rise in pulmonary vascular pressures and/or altered perfusion to the lungs which in turn leads to secondary pulmonary hypertension and ventilation-perfusion (V/Q) mismatching, thus resulting in inefficient gas exchange.^{24, 25} Unlike healthy adults where $P_{ET}CO_2$ and partial pressure of arterial CO_2 ($PaCO_2$) values are similar, HF patients show greater difference between these two variables with a lower $P_{ET}CO_2$.^{24, 26} The decrease in $P_{ET}CO_2$ is derived from decreased perfusion and cardiac output, causing V/Q mismatching.^{8, 15} In addition, $P_{ET}CO_2$ is correlated with cardiac index.¹² Consequently, both increased V_E/VCO_2 and decreased $P_{ET}CO_2$ seems to be closely associated with poor perfusion and cardiac output in HF. By re-synchronizing the two ventricles with CRT implantation, it is expected that pacing both ventricles will improve cardiac function so that blood flows through the heart and lungs more efficiently. This ultimately improves forward flow, reduces pressure and work in the heart and lungs and in turn improves gas exchange.

The scoring system that integrates multi gas exchange variables

Since HF patients tend to have more variability in their breathing pattern and thus their breath by breath gas exchange, we took several steps to reduce this variability and improve the resolution – sensitivity of assessing differences across timing intervals. This not only included taking a moving 5 of 7 breath averaging approach – common to many of the commercially available breath by breath systems, but also took the average of the last minute of data of each 2 min testing interval. In addition, to further enhance the “signal” to noise ratio, we performed an averaging method emphasizing V_E/VCO_2 and $P_{ET}CO_2$ as well as a contribution from O_2 pulse. In our preliminary work this method accentuated the best combination of gas exchange variables to isolate the optimal interval for each subject. This also helped alleviate noise or artifact that could exist in any single measure and combines measures that dynamically integrate breathing pattern, non-invasive measures of stroke volume and that have been shown to correlate with pulmonary vascular pressures and neural control of ventilation. There are a number of other gas exchange metrics or combinations that could be trailed and thus these data represent one approach for using gas exchange during a light exercise load to optimize CRT timing intervals.

Gas Exchange and Individualized approach for CRT optimization

In some respects it is not surprising that there was marked variation across subjects in how timing intervals influenced gas exchange. Patients with HF have different intrinsic and extrinsic physiological characteristics that could differentially be altered by changing AV and VV delays.²⁷ This includes variables that alter venous return and pre load, general volume load and afterload, pulmonary vascular resistance, the interaction between the heart and lungs, including cardiac size, intrathoracic pressure fluctuations during breathing, lung mechanics, as well as variable changes in interventricular dependence. In addition, slight variations in lead placement across subjects and conduction patterns may also influence the

measures. Therefore, different responses in these variables to AV and VV delays may be reflected through gas exchange parameters, and it allows individualizing CRT optimization with gas exchanges. As remodeling of the heart occurs post CRT, such optimization may even be beneficial over time

For CRT optimization, Doppler echocardiography has been widely used.^{1, 2, 28} However, a recent study by Chung et al.³ reported that echo-based Doppler does not appear to improve the response rate to CRT. Although there are alternative clinical techniques, including electrocardiography, there is no gold standard for CRT optimization.

In the present experiment, we confirmed that 1) there was no consistent pattern of change in gas exchange measures across subjects (e.g., tendency for a rise or fall with lengthening delays), 2) on an individual subject basis, gas exchange measures can be improved by optimization of AV and VV timing delay, and 3) the combination of three gas exchange measures allowed a more sensitive tool than single variables. This suggests that an individualized approach with gas exchange measures could be a novel technique for CRT optimization. We presented 3 representative examples (figure 2A-D) from our cohort on how gas exchange was altered while walking through the various AV and VV delays. While many of the gas exchange variables demonstrated only small changes, even small variations in measures such as $P_{ET}CO_2$ can be physiologically important and the scoring system helps highlight these differences in gas exchanges between timing delays.

Limitations

This is a preliminary study examining the potential use of gas exchange to optimize CRT timing intervals. There are a number of limitations. First the numbers are relatively small, however, the data do demonstrate that altering timing intervals within a general physiological range alters respiratory gas exchange and that this is variable across subjects suggesting it may be a good way to individualize the optimization. Second, we relied on step changes over a short window of time (2min) at extremely low work intensity. One might argue that this is a short window of time and that the adjustment period may be too quick for the slowed gas exchange kinetics associated with HF, however, the patients were at an extremely low work load, within a steady state and only the last minute of each interval were assessed. Longer intervals would have been difficult for some patients. Perhaps using a recumbent cycle ergometer with minimal (or no) resistance may provide just enough cardiac load for testing with less fatigue. Third, we did not directly measure cardiac function, but presume that gas exchange from the lungs, due to the intimate association with the heart, reflect integrated cardiac function (balancing issues regulating pre and afterload) under mild stress. Finally, although we observed the variation in gas exchanges via VV delay was smaller than those via AV delay, there was no evidence that AV delay influenced VV delay because we did not randomized the order of AV and VV delay settings. Moreover, we are not sure which timing interval needs to be set first to elicit the best outcomes including improved hemodynamics. The present study applied AV delay setting first followed by VV delay due to the theoretical aspect that AV delay is related to the duration of diastolic filling while VV delay is related to cardiac output via synchrony of contraction between two ventricles.

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Figure 1.
An individual subject's changes in breath by breath V_E/V_{CO_2} across AV delay modifications. Black boxes depict the 2 minute-time in duration for each delay setting.

A. A sample of 100ms (upper) and score distribution (lower)

B. A sample of 120ms (upper) and score distribution (lower)

C. A sample of 140ms (upper) and score distribution (lower)

D. A sample of 160ms (upper) and score distribution (lower)

Figure 2.

A, B, C and D. Representative individual subject measures of key pulmonary gas exchange variables during AV delay modification (upper portion of figures) and score distributions (table and lower portion of figures) in four subjects. One subject had optimal pulmonary gas exchange (i.e. highest V_E/V_{CO_2} , lowest P_{ETCO_2} , highest O_2 pulse) at 100 ms (Fig. A), one at 120 ms (Fig. B), one at 140 ms (Fig. C) and one at 160 ms (Fig. D).

Table 1

The scoring system and point distribution according to the values of gas exchange (5 discrete setting for AV delay and 3 settings for VV delay).

AV Delay							
P _{ET} CO ₂		V _E /VCO ₂		O ₂ pulse			
Rank	Point	Rank	Point	Rank	Point	Sum	
highest	45	lowest	45	highest	10	100	
2nd	36	4th	36	2nd	8	80	
3rd	27	3rd	27	3rd	6	60	
4th	18	2nd	18	4th	4	40	
lowest	9	highest	9	lowest	2	20	
VV Delay							
P _{ET} CO ₂		V _E /VCO ₂		O ₂ pulse			
Rank	Point	Rank	Point	Rank	Point	Sum	
highest	45	lowest	45	highest	10	100	
2nd	36	2nd	36	2nd	8	80	
lowest	27	highest	27	lowest	6	60	

Table 2

Group Changes in gas exchange parameters during submaximal exercise following AV and VV delay modification (Mean±SD).

	AV Delay					VV Delay		
	100 ms	120 ms	140 ms	160 ms	180 ms	0 ms	-20 ms	-40 ms
$P_{ET}CO_2$ (mmHg)	36.5±4	37.7±7	36.6±4	36.3±4	36.5±4	36.8±4	36.7±4	36.7±4
V_E/VCO_2	36.8±6	36.4±6	38.1±10	37.9±9	37.3±9	36.6±7	36.9±7	37.0±7
O_2 Pulse	10.5±2	10.6±2	10.6±2	10.6±3	10.3±3	10.5±2	10.7±3	10.7±3
V_E (l/min)	25.3±8	25.9±7	26.4±8	27.0±7	26.2±8	24.7±8	25.6±7	25.6±7
VO_2 (l/min)	0.84±0.15	0.84±0.15	0.84±0.15	0.85±0.18	0.84±0.16	0.83±0.17	0.84±0.18	0.84±0.17
VCO_2 (l/min)	0.70±0.16	0.71±0.16	0.72±0.18	0.74±0.18	0.73±0.17	0.68±0.17	0.71±0.19	0.71±0.17
V_T/T_I	1200±441	1245±477	1238±414	1281±407	1267±426	1159±425	1220±410	1219±396
RR	24.7±5	25.5±6	25.3±6	26.2±8	25.3±7	24.9±6	25.1±7	26.3±7
HR (bpm)	81±12	80±12	81±12	81±13	82±13	79.7±123	80.2±12	80.2±12
SpO_2 (%)	97.6±2	97.7±2	97.8±2	97.5±2	97.5±2	97.7±2	97.4±2	97.5±2
RER	0.83±0.1	0.84±0.1	0.85±0.1	0.86±0.1	0.86±0.1	0.82±0.1	0.84±0.12	0.83±0.1
RPE	9.0±1.7	10.0±2.6	10.4±2.2	10.8±2.5	10.7±2.3	9.6±1.9	10.0±2.0	10.4±2.5
Dyspnea	1.8±1.1	1.9±1.1	2.2±1.4	2.5±1.7	2.4±1.4	1.7±1.0	2.1±1.2	2.2±1.3

Table 3

Score distributions obtained from the scoring system and proposed individual optimum settings.

	Score										Nominal Setting (AV/VV)	Proposed Setting (AV/VV)
	AV Delay					VV Delay						
Subjects	100ms	120ms	140ms	160ms	180ms	0ms	-20ms	-40ms				
S1	22	46	80	83	69	89	78	91		120/0	160/-40	
S2	94	82	51	53	-	89	87	64		100/0	100/0	
S3	87	67	82	35	29	98	78	64		100/0	100/0	
S4	29	40	53	78	100	60	91	89		100/0	180/-20	
S5	22	71	42	100	65	98	73	69		140/0	160/0	
S6	31	73	51	92	71	96	62	82		100/0	160/0	
S7	38	40	42	82	98	80	64	96		150/0	180/-40	
S8	82	96	26	58	38	91	78	71		100/0	120/0	
S9	60	29	76	100	44	60	82	98		100/0	160/-40	
S10	42	49	100	53	56	73	98	71		100/0	140/-20	
S11	28	76	51	98	47	96	82	62		100/30	160/0	
S12	33	94	71	73	29	69	100	71		100/0	120/-20	
S13	98	82	40	38	42	100	60	80		100/0	100/0	
S14	98	55	76	29	60	80	73	96		110/30	100/-40	
S15	67	69	100	35	29	98	69	73		100/0	140/0	
S16	29	73	98	49	51	87	64	89		100/0	140/-40	
S17	24	55	76	80	65	78	82	89		100/0	160/-40	
S18	76	46	87	71	-	96	73	71		100/0	140/0	
S19	44	37	96	47	76	71	100	69		100/0	140/-20	
S20	38	94	26	64	78	64	78	98		100/0	120/-40	

Bold numbers in AV and VV delays are the highest scores which represent the optimum choices of delay

Bold numbers in Proposed Settings are AV and VV delay settings which is different from Nominal Settings.