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Effects of atrioventricular and interventricular delays on gas exchange during exercise in patients with heart failure

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BACKGROUND: Cardiac resynchronization therapy (CRT) has been an important treatment for heart failure. However, it is controversial as to whether an individualized approach to altering AV and VV timing intervals would improve outcomes. 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, in this study we investigated changes in non-invasive gas exchange by altering AV and VV timing intervals during light exercise.

METHODS: Patients ($n = 20$, age 66 ± 9 years) performed two walking tests post-implantation. The protocol evaluated AV delays (100, 120, 140, 160 and 180 milliseconds), followed by VV delays (0, −20 and −40 milliseconds) 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 VE/VCO_2 averaging 10%; O_2 pulse 11% and $PETCO_2$ 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 of 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.
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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% to 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] showed that no echo-based technique led to improved outcomes with CRT. Hence, there is a need for new approaches for CRT optimization and individualization.

CRT 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, such as end-tidal CO_2 ($PETCO_2$), ventilatory efficiency (VE/VCO_2) and oxygen

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pulse (O_2 pulse), 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 heart and lungs,[5] and exercise testing is used clinically to determine disease severity and prognosis in HF.[6–8] In addition, in HF sub-maximal 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 $PETCO_2$, VE/VCO_2 and O_2 pulse via AV and VV interval modifications during sub-maximal exercise may reflect dynamic changes in cardiac function. The purpose of the present study was to determine whether changes in AV and VV timing intervals during low-intensity exercise influence non-invasive gas exchange measures and whether 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 of age, with New York Heart Association (NYHA) Class II to IV status, QRS duration >120 ms and left ventricular ejection fraction (LVEF) $<35\%$. For our study, 20 HF patients (17 men and 3 women, 66 ± 9 years of age) 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 80% power and alpha = 0.05 ($n = 20$). 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 sub-maximal exercise without significant orthopedic limitations. The study was approved by the institutional review board of the Mayo Clinic, and informed consent 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 status and quality of life, according to the Minnesota Quality of Life Questionnaire). Patients revisited the clinic within 1 to 4 weeks post-implantation for assessment of classical outcome measures and sub-maximal walking tests. At that time, all patients underwent two separate low-intensity walking tests (sub-maximal 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 mass spectrometer (MGA-1100; Perkin Elmer, Pomona, 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-minute time window, we chose a very low level of exercise for 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 1.5 mph/1.0% grade during the trials. The timing delays were evaluated after 2 minutes of rest and 3 minutes of steady-state walking (warm-up). For AV delay modification, there were 5 discrete settings 20 milliseconds apart using AV interval sequences of 100, 120, 140, 160 and 180 milliseconds, whereas there were 3 settings, 0, −20 and −40 milliseconds, for VV intervals. Each setting was 2 minutes in duration and data obtained during the second minute were averaged for the analysis. Optimum intervals were determined based on a simple gas exchange scoring system. To provide a quantitative assessment of the optimal choice of AV and VV delays and to 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 [VE/VCO_2], end-tidal CO_2 [$PETCO_2$] and oxygen uptake per heart beat [O_2 pulse]) were applied, primarily because they have previously been most closely associated with HF disease severity, prognosis and cardiac function.[7,11–13]

In the literature, VE/VCO_2 and $PETCO_2$ are the most recognized parameters that closely track with disease severity in HF. An elevated VE/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] $PETCO_2$ 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 $PETCO_2$ is typically inversely related to VE/VCO_2 and it is therefore expected that $PETCO_2$ and VE/VCO_2 would show similar patterns in which $PETCO_2$ decreases when VE/VCO_2 increases. Therefore, we primarily applied these two parameters with 90% of total available score (45% for $PETCO_2$ and 45% for VE/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 $PETCO_2$ was received 45 points and then 36, 27, 18 and 9 points, respectively. The lowest averaged value of VE/VCO_2 received 45 points and then 36, 27, 18 and 9 points, respectively. The highest averaged value of O_2 pulse received 10 points and then 8, 6, 4 and 2 points, respectively. The points from each variable were added, and the timing interval, which gained the highest point total, was selected as the optimal choice for AV and VV delays. Total points ranged from 20 to 100. As the optimal choice for AV delay was obtained from the first 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 before the second exercise assessment for VV delay, which influences forward flow.

Results

Before implantation, mean NYHA score was 2.7 ± 0.5, LVEF was 28 ± 7 and quality of life (QOL) was 45 ± 26.