Rate responsive pacing using cardiac resynchronization therapy in patients with chronotropic incompetence and chronic heart failure

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Aims
Chronotropic incompetence (CI) is a common finding in patients with advanced chronic heart failure (CHF) and is associated with a worse functional capacity. Whether rate responsive pacing with cardiac resynchronization therapy (CRT) would acutely improve exercise performance in patients with advanced CHF and severe CI (<70% age-predicted maximum heart rate) is unknown.

Methods and results
Patients (n = 13) with CHF, a CRT device, and severe CI were randomized in a double-blind crossover pilot study to either DDD (control) or DDDR (rate responsive) pacing. Six minutes walk test (6MWT) distance, oxygen consumption at anaerobic threshold (VO₂ @ AT), and maximal oxygen consumption (VO₂ max) were measured. One week later, testing was repeated in the alternate pacing mode.

Rate responsive pacing commenced with standard settings in only 9 of 13 (69%) patients. In these 9 subjects, 6MWT distance improved acutely from 358.5 ± 40.7 to 376.8 ± 24.5 m with DDDR pacing (P = 0.05). VO₂ max did not improve with DDDR pacing (14.0 ± 3.2 mL/kg/min) compared with DDD pacing (13.9 ± 3.0 mL/kg/min; P = 0.69). VO₂ @ AT tended towards improvement with DDDR pacing (10.8 ± 2.9 mL/kg/min) compared with DDD pacing (9.6 ± 1.8 mL/kg/min; P = 0.29). There was a linear relationship between the increase in heart rate at minute 3 during rate responsive pacing and improvement in VO₂ @ AT (r = 0.83, P < 0.05).

Conclusion
When rate responsive pacing using a CRT device is achieved in patients with advanced CHF and severe CI, parameters of aerobic exercise performance improve acutely. Routine exercise testing to ensure successful restoration of heart rate response may be beneficial to optimize CRT settings in this patient population.

Keywords
Chronotropic incompetence • Cardiac resynchronization therapy • Chronic heart failure • Rate responsive pacing

Chronotropic incompetence (CI), defined as an inability to reach 80% of age-predicted maximum heart rate (APMHR), is a common finding in patients with advanced chronic heart failure (CHF). Approximately 43–46% of patients with CHF manifest CI.¹,² The prevalence of CI is highest in patients with the most advanced CHF and the worst exercise capacity, occurring in 72% of patients with a peak oxygen consumption (pVO₂) <14 mL/kg/min.¹ In addition to being a marker of diminished exercise capacity, severe CI may be an independent predictor of mortality or the need for cardiac transplantation or ventricular assist device placement.³

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In the last decade, electrical therapy has revolutionized the care of CHF patients. Implantable cardioverter-defibrillators (ICDs) have shown impressive reduction in mortality in patients with CHF.15 However, when dual-chamber ICDs were used to provide antibradycardia pacing in the DAVID (Dual Chamber and VVI Implantable Defibrillator) trial,6 the study was stopped prematurely owing to an increased rate of death or first hospitalization due to CHF. It is now recognized that the induction of dysynchrony from continuous right ventricular pacing resulted in the adverse outcomes.7,8 Since the DAVID trial was organized, cardiac resynchronization therapy (CRT) with a biventricular pacemaker has been shown to improve morbidity and mortality in patients with CHF.9 In a small study, Tse et al.10 examined patients with CHF, CI, and a CRT device and found that using rate responsive pacing as a pacemaker-based therapy to modulate severe CI acutely improved maximal exercise capacity. However, Van Thienen et al.11 were unable to replicate this important finding. We sought to examine the acute effects of rate responsive pacing with CRT on patients with advanced CHF and severe CI on maximal as well as submaximal exercise performance.

Methods

Patients

Patients referred to the cardiopulmonary exercise laboratory with systolic CHF were invited to participate if they were in sinus rhythm, had evidence of severe CI (defined as an inability to achieve 70% APMHR on a maximal effort cardiopulmonary exercise test (CPET)), and had a CRT device implanted. Cardiac resynchronization therapy device was placed in all patients due to New York Heart Association (NYHA) class III or ambulatory class IV symptoms despite optimal medical therapy in the presence of an ejection fraction <35% and a QRS complex >120 ms. Patients were excluded if they had atrial fibrillation or atrial flutter, were unable to perform a treadmill exercise test (e.g. severe arthritis, chronic obstructive pulmonary disease requiring bronchodilators), had an admission for pulmonary disease requiring bronchodilators, or had ongoing symptoms of myocardial ischaemia. This study complied with the Declaration of Helsinki. The study protocol was approved by the Colombia University Medical Center institutional review board and each patient provided informed written consent.

Study protocol

This was a double-blind crossover pilot study testing two pacing modes: DDD (control) and DDDR (rate responsive pacing). At the initial study visit, all subjects underwent a history and physical examination. All CRT devices were interrogated to ensure appropriate sensing and pacing functions of the atrial, right ventricular, and left ventricular leads. The CRT device was randomly programmed to DDD or DDDR mode by an individual not involved with the clinical testing. A 6 min walk test (6MWT) with a holter monitor worn by the subject to record rhythm and heart rate was performed. After a 30 min rest period, the patient underwent a CPET. At the conclusion of the CPET, the subject’s CRT device was reprogrammed back to its pre-study settings. At a second study visit 1 week later, testing was repeated in the alternate pacing mode.

Pacemaker programming

For the DDD mode, no changes were made to any of the CRT device’s current settings. The device programmer was manipulated (sham reprogramming) before and after testing so that both the patient and the person conducting the test were unaware of the subject’s pacing mode. For the DDDR mode, the CRT device was reprogrammed from DDD to DDDR and the standard manufacturer settings for rate responsive pacing that pre-populated the device programmer’s fields were used. The maximum tracking rate was programmed to 75% the APMHR.12 Lower pacing rate, atioventricular (AV) interval, and V–V interval were not changed.

Exercise testing

Cardiopulmonary exercise tests were performed using a standard treadmill according to the Naughton protocol. Exercise was symptom limited. Heart rate and electrocardiogram were recorded continuously. Blood pressure was recorded every 2 min. Patients inspired room air through a low-resistance mouthpiece. Oxygen and carbon dioxide partial pressures were measured using a gas analyser (MedGraphics, St Paul, MN, USA) that was calibrated using standard gases immediately prior to the test according to the manufacturer’s specifications. Oxygen consumption at the anaerobic threshold (VO2 @ AT), maximal oxygen consumption (VO2 max), and respiratory exchange ratio (RER) were measured. VO2 max was defined as the highest value of oxygen uptake in the final 20 sec of exercise when the RER was >1.0.

Statistics

Continuous variables are presented as mean ± standard deviation. Categorical variables are listed as frequencies or percent. The Mann–Whitney U test was used to compare parameters of CPET for the different pacing modes. A correlation analysis was performed between the change in heart rate at minute 3 of exercise between DDDR and DDD pacing and the change in VO2 @ AT between DDDR and DDD pacing using Pearson correlation coefficients. SPSS version 16 statistical software (Chicago, IL, USA) was used to analyse the data. A P value <0.05 was considered significant.

Results

Baseline characteristics for the patients are shown in Table 1. The study population consisted of 13 subjects with an average age of 59 ± 16 years. Eleven subjects were male and 12 patients had NYHA class III symptoms. Sixty-nine percent of patients had non-ischaemic cardiomyopathy as the aetiology of their CHF. Ejection fraction was 17 ± 7%. Hundred percent of patients were receiving a beta-blocker and either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Ten CRT devices were manufactured by Medtronic (Minneapolis, MN, USA), two were from St Jude Medical (St Paul, MN, USA), and one was from Boston Scientific (Natick, MA, USA). All patients had severe CI with an average percent of APMHR achieved of 60 ± 6%.

When rate responsive pacing was turned on (DDDR mode), rate responsive pacing commenced with exercise using standard rate responsive settings in 9 of 13 subjects (69%) (Figure 1). For the four subjects where rate responsive pacing failed to activate, there was no rate responsive increase in heart rate on Holter monitoring during the 6MWT or on the treadmill during CPET (Figure 2).
In the nine subjects where rate responsive pacing did activate, 6MWT distance improved from 358.5 ± 40.7 m for DDD pacing to 376.8 ± 24.5 m with DDDR pacing (P = 0.05). Seven subjects had their 6MWT distance improve and two subjects had their 6MWT distance worsen (Figure 3). VO2 max did not improve with DDDR pacing (14.0 ± 3.2 mL/kg/min) compared with DDD pacing (13.9 ± 3.0 mL/kg/min) (P = 0.69). VO2 @ AT tended towards improvement from 9.6 ± 1.8 mL/kg/min for DDD pacing compared with 10.8 ± 2.9 mL/kg/min with DDDR pacing (P = 0.29). There was a linear relationship between the increase in heart rate at minute 3 during rate responsive pacing and improvement in VO2 @ AT (r = 0.83, P < 0.05) (Figure 4). There was no difference in patient effort between DDD testing (RER 0.99 ± 0.06) and DDDR testing (RER 0.99 ± 0.05).

Discussion

In a pilot study, we examined the acute effects of rate responsive pacing with a CRT device on exercise performance in patients with CHF and CI. Our principal findings are as follows: first, the use of standard manufacturer settings for rate responsive pacing does not reliably cause rate responsive pacing to activate with exercise. Secondly, when rate responsive pacing does activate, there is a small increase in 6MWT distance with DDDR pacing. Thirdly, submaximal exercise performance, as measured by VO2 @ AT, improves linearly in relation to the increase in heart rate at minute 3 of exercise with rate responsive pacing. Finally, VO2 max does not improve acutely with rate responsive pacing.

The role of CI in patients with advanced CHF is gaining increased recognition. In patients with CHF, CI is a common finding, with 43–46% of patients exhibiting an inability to reach 80% of APMHR.1,2 The prevalence of CI is highest among patients with the most limited exercise capacity (72% for pVO2 ≤ 14.0 mL/kg/min, 48% for pVO2 14.0–20.0 mL/kg/min, and 24% for pVO2 > 20.0 mL/kg/min).1 Chronotropic incompetence has been thought to be a manifestation of beta-blocker or antiarrhythmic drug (AAD) therapy and therefore a protective mechanism afforded by medical therapy.2 However, more recent work has shown no association between the use of beta-blockers and AADs and the presence of CI.1,13 Chronotropic incompetence has also recently shown to be harmful. In an analysis of 170 patients with systolic CHF and a pVO2 < 14.0 mL/kg/min, the presence of severe CI (< 70% APMHR) conferred a 2.5 times increased proportional hazard ratio for death, cardiac transplantation, or ventricular assist device placement.3

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<th>Table 1 Baseline characteristics</th>
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<td>Patients, n</td>
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<td>Age, years</td>
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<td>Male/female</td>
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<td>Aetiology of CHF (%)</td>
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<td>Ischaemic</td>
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<td>NYHA functional class (%)</td>
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<td>Medical therapy (%)</td>
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<td>ACEi or ARB</td>
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<td>Aldosterone antagonist</td>
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<td>Percent of APMHR</td>
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CHF, chronic heart failure; NYHA, New York Heart Association; ACEi, angiotension-converting enzyme inhibitor; ARB, angiotensin receptor blocker; APMHR, age-predicted maximum heart rate.
Pacing therapies to provide rate support in patients with CHF have had mixed success. In the DAVID trial, a dual-chamber ICD programmed to DDDR with a lower rate limit of 70 beats per minute (bpm) was compared with VVI backup pacing with a heart rate of 40 bpm. The trial was stopped prematurely as per minute (bpm) was compared with VVI backup pacing with a ICD programmed to DDDR with a lower rate limit of 70 beats per minute (bpm). The development of biventricular pacemakers has made it possible to provide rate support for patients with CHF and CI without introducing ventricular dysynchrony with RV apical pacing. The PEGASUS CRT (Pacing Evaluation—Atrial Support Study in Cardiac Resynchronization Therapy) study was a multicentre study randomizing 1433 patients with CRT devices to DDD with a ventricular rate of 40 bpm (control), DDD with a ventricular rate of 70 bpm, or DDDR with a ventricular rate of 40 bpm. The primary outcome in the study was a clinical composite endpoint including mortality, CHF events, NYHA class, and patient global self-assessment. No differences were found in the two atrial rate support groups compared with the control group. Unfortunately in this study, CI was not specifically examined. A substudy of PEGASUS CRT enrolled 375 patients and conducted CPETs to assess exercise capacity at baseline and after treatment. While this substudy did not specifically enroll patients with CI, based on the high prevalence of CI in patients with CHF, there may be enough patients with CI to determine the chronic effect of rate responsive pacing on exercise performance. The results of this substudy are yet to be reported.

Two small studies examined rate responsive pacing with CRT devices in CHF patients who specifically manifest CI. Tse et al. studied 20 patients with advanced CHF and CI (<85% APMHR) who had a CRT device. Three pacing modes were tested in succession: DDD with a fixed AV interval, DDD with an adaptive AV interval, and DDDR with an adaptive AV interval. In 11 patients with severe CI (<70% APMHR), DDDR pacing produced an acute improvement in pVO2 of 2.5 mL/kg/min compared with DDD pacing. In contrast, in our study, we observed no acute improvement in VO2 max between DDD and DDDR pacing. This difference in findings may be explained by the fact in our study, subjects were randomly assigned to DDD or DDDR pacing for the first CPET with the subsequent CPET performed in the alternate pacing mode. In Tse et al.’s study, all patients underwent two DDD CPETs prior to the DDDR CPET that may have introduced a training effect, allowing for the highly significant increase in pVO2. Van Thiel et al. studied 14 patients with CHF and severe CI (<70% APMHR) with a CRT device using CPET and echocardiography. No change in pVO2 was found for rate responsive pacing (DDD mode pVO2 17.8 mL/kg/min compared with DDDR mode pVO2 17.4 mL/kg/min (P = not significant). Non-invasive cardiac index did increase significantly however from 3.0 to 3.5 L/min/m2 (P < 0.001) for DDD pacing compared with DDDR pacing. An increase in cardiac index index without an improvement in pVO2 suggests that peripheral factors (skeletal muscle and vasculature) play a role in the lack of an increase in pVO2. In our study, we observed a linear relationship between improvement in heart rate at 3 min and improvement in VO2 @AT (Figure 4). VO2 @AT is a useful measurement and endpoint as most activities of daily living occur below this stratum. Formal exercise training programmes for patients with CHF have shown an increase in pVO2. By improving VO2 @AT with rate responsive pacing, de facto exercise training may occur that may allow for an improvement in peripheral factors and pVO2 with chronic rate responsive pacing.

Cardiac resynchronization therapy has shown impressive improvements in morbidity and mortality in patients with CHF and evidence of dysynchrony. However, ~30% of patients eligible for CRT do not respond to this therapy. To date, efforts to identify responders pre-CRT implantation have been unsuccessful. Maass et al. found that in patients with CRT devices in sinus rhythm, CI was found more frequently in non-responders compared with responders (36 vs. 10%). As evidenced by our study, correcting CI by turning on rate responsive pacing using standard manufacturer settings does not routinely work. Potentially, the number of non-responders to CRT could be decreased by...
optimizing the CRT device rate responsive settings and ensuring that rate responsive pacing activates with exercise.

Our study has several limitations, the most important of which are the small sample size and low statistical power. Only two of the subjects in this study were women. Routine echocardiographic optimization of device settings, which could have influenced the haemodynamic response to an increased heart rate, was not performed in this study. A fixed AV interval was not tested although a fixed AV interval previously was not found to be beneficial in rate responsive pacing with CRT.10

Conclusion

In patients with CHF and severe CI who have a CRT device, rate responsive pacing does not routinely activate during exercise using standard manufacturer settings. When rate responsive pacing does activate, 6MWT distance improves acutely and VO2 @AT improves acutely in a linear relationship to the improvement of heart rate. Exercise testing to optimize settings and ensure rate responsive pacing activation in patients with CI should be considered and may improve response to CRT.

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References