

**FOCUS ISSUE: CARDIAC RESYNCHRONIZATION THERAPY****Pacing Schemes and Resynchronization**

# The Incremental Benefit of Rate-Adaptive Pacing on Exercise Performance During Cardiac Resynchronization Therapy

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<b>OBJECTIVES</b>	The purpose of this research was to investigate the effect of using rate-adaptive pacing and atrioventricular interval (AVI) adaptation on exercise performance during cardiac resynchronization therapy (CRT).
<b>BACKGROUND</b>	The potential incremental benefits of using rate-adaptive pacing and AVI adaptation with CRT during exercise have not been studied.
<b>METHODS</b>	We studied 20 patients with heart failure, chronotropic incompetence (<85% age-predicted heart rate [AP-HR] and <80% HR reserve), and implanted with CRT. All patients underwent a cardiopulmonary exercise treadmill test using DDD mode with fixed AVI (DDD-OFF), DDD mode with adaptive AVI on (DDD-ON), and DDDR mode with adaptive AVI on (DDDR-ON) to measure metabolic equivalents (METs) and peak oxygen consumption ( $\text{VO}_{2\text{max}}$ ).
<b>RESULTS</b>	During DDD-OFF mode, not all patients reached 85% AP-HR during exercise, and 55% of patients had <70% AP-HR. Compared to patients with >70% AP-HR, patients with <70% AP-HR had significantly lower baseline HR ( $66 \pm 3$ beats/min vs. $80 \pm 5$ beats/min, $p = 0.015$ ) and percentage HR reserve ( $27 \pm 5\%$ vs. $48 \pm 6\%$ , $p = 0.006$ ). In patients with <70% AP-HR, DDDR-ON mode increased peak exercise HR, exercise time, METs, and $\text{VO}_{2\text{max}}$ compared with DDD-OFF and DDD-ON modes ( $p < 0.05$ ), without a significant difference between DDD-OFF and DDD-ON modes. In contrast, there were no significant differences in peak exercise HR, exercise time, METs, and $\text{VO}_{2\text{max}}$ among the three pacing modes in patients with >70% AP-HR. The percentage HR changes during exercise positively correlated with exercise time ( $r = 0.67$ , $p < 0.001$ ), METs ( $r = 0.56$ , $p < 0.001$ ), and $\text{VO}_{2\text{max}}$ ( $r = 0.55$ , $p < 0.001$ ).
<b>CONCLUSIONS</b>	In heart failure patients with severe chronotropic incompetence as defined by failure to achieve >70% AP-HR, appropriate use of rate-adaptive pacing with CRT provides incremental benefit on exercise capacity during exercise. (J Am Coll Cardiol 2005;46:2292-7) © 2005 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) improves functional class, exercise capacity, and quality of life in patients with systolic heart failure and a wide QRS complex (1-3). No previous studies have addressed the issue of optimal programming of CRT during exercise, and the decision regarding the use of rate-adaptive pacing and adaptive atrioventricular interval (AVI) algorithm during CRT are largely empirical. In patients with heart failure, pharmacologic treatment with beta-blockers (4) and/or co-existing chronotropic incompetence (5-8) frequently limits an increase in heart rate (HR) during exercise, which may have a negative effect on their exercise capacity. Due to the limited ability to increase stroke volume in patients with heart

failure, HR augmentation is a major determinant of cardiac output during exercise. Appropriate rate adaptation with CRT may therefore provide an incremental benefit to patients with heart failure during exercise. Conversely, inappropriate use of rate-adaptive pacing with excessive tachycardia in patients with heart failure may lead to an adverse outcome (9).

Furthermore, changes in atrioventricular nodal conduction of intrinsic rhythm associated with exercise may alter the degree of biventricular capture and affect the efficacy of CRT. The use of an adaptive AVI algorithm to vary the AVI depending on whether atrial activity is paced or sensed and to shorten AVI with increasing rates has been shown to improve exercise capacity during pacing (10). Adaptation of AVI may also maintain biventricular capture for CRT during exercise.

Therefore, the aim of this study was to investigate the effects of rate-adaptive pacing and AVI adaptation algo-

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#### Abbreviations and Acronyms

AP-HR	= age-predicted heart rate
AVI	= atrioventricular interval
CRT	= cardiac resynchronization therapy
HR	= heart rate
METS	= metabolic equivalents
LV	= left ventricle/ventricular
peak $V_{CO_2}$ /peak $V_{O_2}$	= peak respiratory exchange ratio
$V_{CO_2}$	= minute carbon dioxide production
$V_{O_2}$	= minute oxygen consumption
$V_{O_2max}$	= peak oxygen consumption

rhythm on exercise performance in patients who receive CRT and have chronotropic incompetence.

## METHODS

**Study population.** The study population consisted of 20 patients (mean age,  $65 \pm 3$  years; 14 men) with New York Heart Association functional class III ( $n = 11$ ) or IV ( $n = 9$ ) heart failure, left ventricular (LV) dysfunction (mean ejection fraction,  $28 \pm 2\%$ ), prolonged QRS duration (mean QRS duration  $176 \pm 8$  ms), and chronotropic incompetence who received CRT. Patients with a history of chronic atrial fibrillation, inability to exercise on the treadmill, severe obstructive pulmonary disease, recent acute heart failure admission within the last three months, or ongoing symptoms of myocardial ischemia were excluded.

The etiologies of heart failure were idiopathic dilated cardiomyopathy in 13 and ischemic cardiomyopathy in seven patients. All patients received appropriate pharmacological treatments for heart failure that included diuretics in all patients, angiotensin-converting enzyme inhibitors in 12 patients, angiotensin receptor antagonists in 8 patients, beta-blockers in 17 patients, spironolactone in 12 patients, and digoxin in 9 patients. Doses of these background medications were stable for  $\geq 3$  months. The local ethics committee approved the study protocol. All patients provided written informed consent.

**CRT device implantation.** Cardiac resynchronization therapy devices were implanted as previously described (11,12). The atrial lead was positioned at the right atrial appendage and the right ventricular lead at the apex. The LV pacing lead was positioned through a coronary sinus in the posterolateral ( $n = 11$ ) or lateral ( $n = 9$ ) cardiac vein. The pacing leads were connected to a rate-adaptive CRT pacemaker (InSync/InSync III, Medtronic, Minneapolis, Minnesota,  $n = 7$ ; Contak TR/Contak Renewal II, Guidant Inc., St. Paul, Minnesota,  $n = 10$ ) or a CRT defibrillator (InSync III Marquis, Medtronic,  $n = 3$ ).

**Study protocol.** The study protocol was performed at least six months after CRT implantation. For the study protocol, different pacing programmings were assessed using atrioventricular synchronized pacing (DDD mode) ventricular pacing configurations. All patients underwent a cardiopul-

monary exercise treadmill test with their CRT devices programmed to: 1) DDD mode with fixed AVI (DDD-OFF); 2) DDD mode with adaptive AVI algorithm ON (DDD-ON); and 3) DDDR mode with adaptive AVI algorithm ON (DDDR-ON) in a randomized fashion. To verify the changes in ventricular capture during exercise, the QRS morphology and width during exercise were compared with those obtained during baselines electrocardiograms (ECG) at rest.

The device was programmed to a lower rate limit of 50 beats/min and an upper rate limit of 140 beats/min. All the devices had an accelerometer based rate-adaptive sensor, which was programmed to the device nominal setting. The resting AVI during atrial sensed and atrial paced (at 10 beats/min above sinus rhythm) was optimized by echocardiography in order to provide the longest transmitral filling time without truncation of the A wave from pulsed Doppler analysis of the LV filling (13). For the AVI adaptive algorithm, the maximum was programmed equal to the optimal resting AVI during atrial pacing and the minimum AVI to the optimal resting AVI during atrial pacing—50 beats/min in 10-ms decrements.

**Cardiopulmonary exercise testing.** Within four weeks before the study, all patients underwent a trial cardiopulmonary exercise test using DDD-OFF mode to familiarize them with the equipment. All patients then underwent symptom-limited cardiopulmonary exercise test on a treadmill (Q5000, Quinton, Seattle, Washington) using the chronotropic assessment exercise protocol (14). During the test, patients inspired room air through a low-resistance mask, and the expired  $O_2$  and  $CO_2$  partial pressures were measured with a gas analyzer (Cardiopulmonary Exercise Testing System, MedGraphics, St. Paul, Minnesota). The gas analyzer was calibrated with standard gases immediately before the test. Standard 12-lead ECG and non-invasive blood pressures were recorded every 2 min throughout the study. The following variables were determined: exercise workload as measured by metabolic equivalents (METS), peak HR, minute oxygen consumption ( $V_{O_2}$ ), minute carbon dioxide production ( $V_{CO_2}$ ), peak oxygen consumption ( $V_{O_2max}$ ), and peak respiratory exchange ratio (peak  $V_{CO_2}$ /peak  $V_{O_2}$ ), as an index of effort adequacy.

**Chronotropic incompetence.** Chronotropic incompetence was defined by the failure to achieve 85% of the age-predicted HR (AP-HR) and low-percentage HR reserve during the trial cardiopulmonary exercise test. The AP-HR was determined as  $220 - \text{the patient's age}$ . For calculation of percentage HR reserve, the following equation was used:  $[(\text{peak HR} - \text{rest HR}) / (220 - \text{age} - \text{rest HR})] \times 100$  (15). A low-percentage HR reserve was defined as  $< 80\%$  (16).

**Statistical analysis.** Continuous data are presented as mean values  $\pm$  SEM. Comparisons between the two groups were performed by the Mann-Whitney test for continuous variables and by the Fisher exact test for a dichotomous outcome. Linear regression analysis was performed using Pearson correlation coefficients. Multiple comparisons be-

tween the parameters of cardiopulmonary exercise for the three different pacing modes (DDD-OFF, DDD-ON, and DDDR-ON) were performed using two-way repeated measures analysis of variance, followed by Bonferroni *t* tests for individual comparisons. A *p* value <0.05 was considered statistically significant.

## RESULTS

**AVI during CRT.** The mean PR interval during sinus rhythm was 176 ± 10 ms. At rest, the optimal AVI during atrial sensed was 102 ± 5 ms and during atrial paced was 128 ± 5 ms. At peak exercise HR, the minimum AVI was shortened to 76 ± 5 ms using an adaptive AVI algorithm. In 9 of 20 (45%) patients, there was no change in ECGs compared to baseline at peak exercise with (DDD-ON and DDDR-ON modes) or without (DDD-OFF mode) programming the adaptive AVI algorithm on. In 7 of 20 (35%) patients, the ECGs at peak exercise were different from baseline during DDD-OFF mode but not during DDD-ON and DDDR-ON modes. In 4 of 20 (20%) patients, the ECGs at peak exercise were similar to baseline during DDD-OFF mode but were different during DDD-ON and DDDR-ON modes. This was due to an increase in the degree of ventricular capture with shortening of AVI by the adaptive AVI algorithm during exercise.

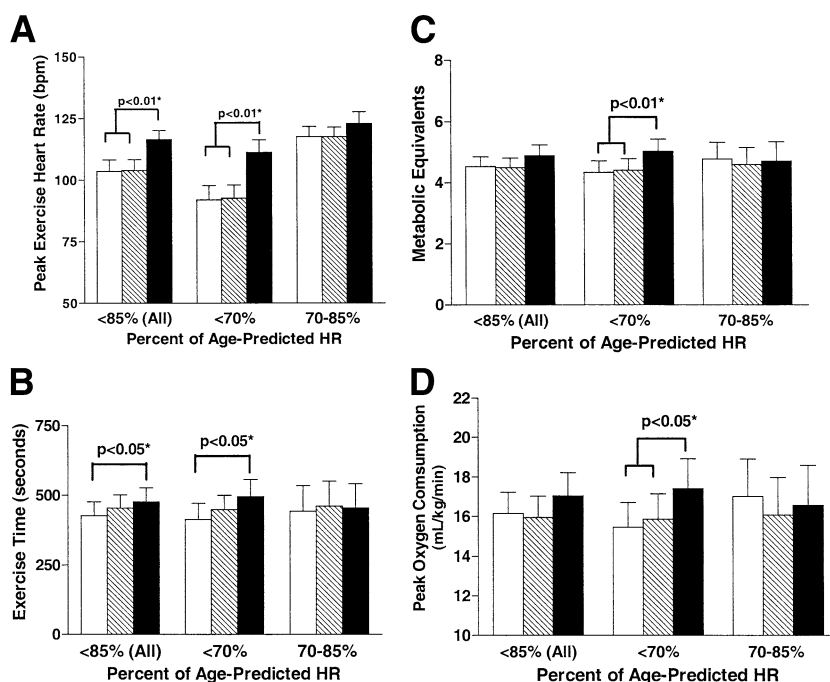
**Cardiopulmonary exercise testing.** In the overall study population, the peak exercise HR achieved during DDDR-ON mode was significantly higher than during DDD-OFF and DDD-ON modes (Fig. 1A) (*p* < 0.05). The exercise time during DDDR-ON mode was significantly longer than during the DDD-OFF mode, but not the DDD-ON mode (Fig. 1B). However, there were no significant differences in METs, VO<sub>2</sub>max and peak VCO<sub>2</sub>/peak VO<sub>2</sub> ratio among the three pacing modes (Figs. 1C and 1D).

As shown in Figure 2, there were significant positive correlations between the percentage changes in HR during exercise with exercise time (*r* = 0.67, *p* < 0.001), METs (*r* = 0.56, *p* < 0.001), and VO<sub>2</sub>max (*r* = 0.55, *p* < 0.001).

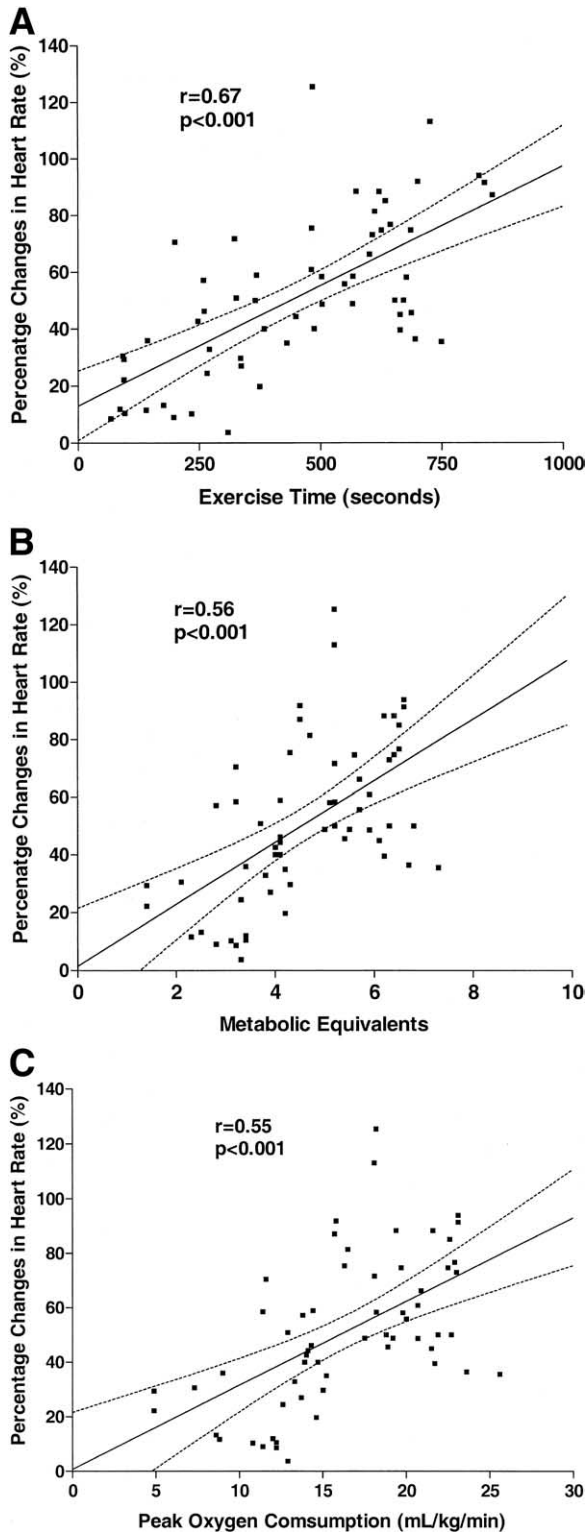
**Relationship between the severity of chronotropic incompetence and response to rate-adaptive pacing.** In DDD-OFF mode, all patients exhibited chronotropic incompetence during cardiopulmonary exercise. The mean percentage of AP-HR achieved was 66 ± 3%, and the mean percent HR reserve was 36 ± 4%. No patient reached 85% of AP-HR during exercise, and 11 patients (55%) failed to achieve 70% of AP-HR. The clinical characteristics of the patients who did or did not reach 70% of AP-HR did not differ significantly. However, patients who failed to reach 70% of AP-HR had significantly lower baseline HR and percent HR reserve (Table 1).

In patients who failed to achieve 70% of AP-HR, DDDR-ON mode significantly increased peak exercise HR, exercise time, METs, and VO<sub>2</sub>max compared with DDD-OFF and DDD-ON modes. However, there were no significant differences in peak exercise HR, exercise time, METs, and VO<sub>2</sub> max between DDD-OFF and DDD-ON modes (Fig. 1).

On the other hand, in patients who achieved >70% of AP-HR, DDDR-ON mode did not significantly increase peak exercise HR, exercise time, METs, and VO<sub>2</sub>max



**Figure 1.** Changes in (A) peak exercise heart rate (HR), (B) exercise time, (C) metabolic equivalents, and (D) peak oxygen consumption during DDD-OFF, DDD-ON, and DDDR-ON modes in patients who achieved <85% (all, n = 20), <70% (n = 11), and 70% to 85% (n = 9) of age-predicted HR during exercise using DDD-OFF mode. Data are expressed as mean values ± SEM. \**p* values determined by analysis of variance with Bonferroni multiple-comparison tests. White bars = DDD-OFF; ruled bars = DDD-ON; black bars = DDDR-ON.



**Figure 2.** Correlation between percentage changes in heart rate during exercise with (A) exercise time, (B) metabolic equivalents, and (C) peak oxygen consumption.

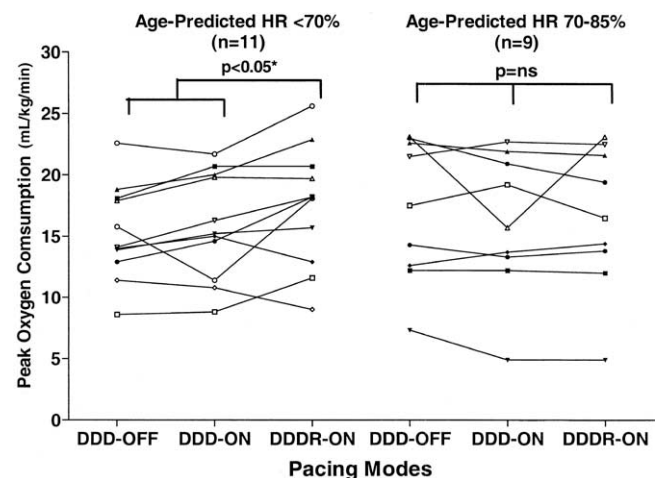
compared with DDD-OFF and DDD-ON modes. There were also no significant differences in peak exercise HR, exercise time, METs, and  $VO_2$ max between DDD-OFF and DDD-ON modes (Fig. 1).

**Table 1.** Baseline Characteristics in Patients Who Did or Did Not Reach >70% AP-HR

	<70% AP-HR (n = 11)	≥70% AP-HR (n = 9)	p Value
Mean age, yrs	65 ± 4	65 ± 4	0.98
Male patients	8 (73%)	6 (67%)	0.77
Resting HR, beats/min	66 ± 3	80 ± 5	0.015
QRS duration, ms	178 ± 7	176 ± 9	0.34
% HR reserve, %	27 ± 5%	48 ± 6%	0.006
LV ejection fraction, %	27 ± 3	28 ± 2	0.93
Ischemic cardiomyopathy	4 (36%)	3 (33.3%)	0.88
Medications			
Beta-blockers	9 (82%)	8 (89%)	0.66
Digoxin	5 (45%)	4 (44%)	0.96

AP-HR = age-predicted heart rate; HR = heart rate; LV = left ventricular.

As shown in Figure 3,  $VO_2$ max improved during DDDR-ON mode pacing in 9 of 11 (82%) patients who failed to achieve 70% of AP-HR compared to only 2 of 9 (22%) patients who reached more than 70% of AP-HR ( $p = 0.022$ ). In the majority of patients who reached >70% of AP-HR,  $VO_2$ max either reduced (3 of 9, 33%) or remained unchanged (4 of 9, 44%) during rate-adaptive pacing. However, there were no significant differences in clinical characteristics between patients with or without improvement in  $VO_2$ max during rate-adaptive pacing (Table 2). Furthermore, there was no difference in the incidence of change in the degree of ventricular capture during DDDR-ON mode between patients with (2 of 11, 18%) or without (2 of 9, 22%) improvement in  $VO_2$ max during rate-adaptive pacing ( $p = 0.99$ ). In patients with improvement in exercise performance during rate-adaptive pacing,  $VO_2$ max during DDDR-ON mode increased by  $2.5 \pm 0.5$  ml/kg/min (range 0.8 to 5.3 ml/kg/min,  $+18 \pm 4\%$ ) compared with DDD-OFF. In contrast, in patients without improvement in exercise performance during rate-adaptive pacing,  $VO_2$ max during DDDR-ON mode decreased by



**Figure 3.** Individual changes in peak oxygen consumption during DDD-OFF, DDD-ON, and DDDR-ON modes in patients who achieved <70% ( $n = 11$ ) and 70% to 85% ( $n = 9$ ) of age-predicted heart rate (HR) during exercise using DDD-OFF mode. \*p values determined by analysis of variance with Bonferroni multiple-comparison tests.

**Table 2.** Clinical Characteristics in Patients With or Without Improvement in VO<sub>2</sub>max During Rate-Adaptive Pacing

	With Improvement (n = 11)	Without Improvement (n = 9)	p Value
Mean age, yrs	64 ± 3	67 ± 4	0.58
Male patients	7 (64%)	7 (78%)	0.64
Resting HR, beats/min	69 ± 4	76 ± 5	0.23
QRS duration, ms	179 ± 6	175 ± 8	0.42
% HR reserve	32 ± 5%	41 ± 7%	0.27
LV ejection fraction, %	26 ± 2	30 ± 2	0.29
Ischemic cardiomyopathy	4 (36%)	3 (33.3%)	0.88
Medications			
Beta-blockers	8 (73%)	9 (100%)	0.22
Digoxin	6 (55%)	3 (33%)	0.41

Abbreviations as in Table 1.

1.4 ± 0.4 ml/kg/min (range -3.6 to 0 ml/kg/min, -9 ± 4%) compared with DDD-OFF.

Furthermore, there were no significant differences in the patient's effort, as measured by peak VCO<sub>2</sub>/peak VO<sub>2</sub> ratio, between patients who did or did not reach 70% of AP-HR and among the three pacing modes (DDD-OFF: 0.89 ± 0.04 vs. 0.91 ± 0.03; DDD-ON: 0.87 ± 0.03 vs. 0.93 ± 0.03; and DDDR-ON: 0.88 ± 0.04 vs. 0.94 ± 0.03, all p > 0.05).

## DISCUSSION

**Main findings.** The present study is the first to examine the impact of optimal programming of CRT devices during exercise in patients with heart failure. In patients with heart failure and severe chronotropic incompetence, HR response to exercise is the major determinant of exercise performance. Exercise time, METs, and VO<sub>2</sub>max are all positively correlated with percentage changes in HR during exercise. Our study further explores the role of AVI adaptation during exercise. In 65% of patients, the degree of biventricular capture using a fixed AVI remained unchanged during exercise, but variable fusion was seen in the remaining patients. In contrast, the use of an adaptive AVI algorithm improved the maintenance of biventricular capture to 80% of patients. However, after optimization of AVI at rest, the use of an adaptive AVI algorithm during CRT did not have any significant effect on exercise capacity, probably reflecting the importance of HR adaptation as the major determinant of cardiac output during exercise in patients with heart failure.

Overall, rate-adaptive pacing during CRT increased peak exercise HR and exercise time in patients with heart failure and chronotropic incompetence, but did not have any incremental benefit on exercise capacity. However, in patients with more severe chronotropic incompetence, who failed to achieve 70% of AP-HR during exercise and had lower baseline HR and percent HR reserve, rate-adaptation during CRT significantly increased peak exercise HR, exercise time, and METs. More importantly, in the majority of these patients (82%), this improvement in HR

response to exercise with rate-adaptive pacing during CRT is associated with ~20% increase in VO<sub>2</sub>max compared to without rate-adaptive pacing. Conversely, in patients who reached >70% of AP-HR, rate adaptation during CRT did not increase peak exercise HR, exercise time, and METs. In the majority of these patients (78%), VO<sub>2</sub>max was either reduced or remained unchanged with rate-adaptive pacing during exercise.

**Determinants of exercise capacity in patients with heart failure.** In normal subjects, the maximal exercise capacity is determined by the LV stroke volume, HR, and the arteriovenous oxygen difference. At a low exercise level, change in LV stroke volume is mainly mediated by an increase in LV filling and end-diastolic volume through the Starling mechanism. At a high exercise level, an increase in HR is associated with a decrease in end-diastolic volume despite a progressive increase in LV filling pressure, so that LV stroke volume must be maintained by increasing myocardial contractility (17). Furthermore, the LV stroke volume during exercise also depended on the ability of the LV to increase filling without an abnormal increase in left atrial pressure (18).

In patients with heart failure, the ability to augment LV stroke volume and LV filling without a concomitant increase in left atrial pressure during exercise was lost (19). This increase in left atrial pressure will limit the atrial contribution to LV stroke volume (20). This may explain the lack of beneficial effect of AVI adaptation on exercise capacity in our patients with heart failure as was observed in the pacemaker population with normal LV function (10). Furthermore, the ability to maintain LV stroke volume during exercise by increasing myocardial contractility is also markedly attenuated in patients with heart failure. As a result, augmentation of HR is a major determinant of cardiac output, and thus exercise capacity during exercise. The results of this study confirm this theory, and demonstrate that changes in HR during exercise in patients with heart failure significantly correlated with exercise capacity as determined by VO<sub>2</sub>max.

**Rate-adaptive pacing for chronotropic incompetence in patients with heart failure.** Chronotropic incompetence (5-8) is common among patients with heart failure, and contributes to the impairment of exercise capacity. Appropriate rate adaptation using a rate-responsive pacemaker may therefore improve exercise capacity in patients with heart failure during exercise. Previous studies have demonstrated that rate-adaptive pacing improved cardiac performance and exercise capacity in patients with impaired LV systolic function (21,22). However, in patients with impaired LV systolic function, increased percentage of right ventricular apical pacing with rate-adaptive pacing might lead to worsening of cardiac function and increase mortality (23,24). Furthermore, in patients with impaired LV function, the optimum upper HR limit during exercise was significantly lower than patients with normal LV function. Patients with heart failure cannot increase LV stroke volume and oxygen uptake despite ongoing exercise with

increasing workloads and increasing pacing rate (25). Therefore, inappropriate increase in HR during exercise with rate-adaptive pacing will not be productive.

In selected patients with advanced heart failure, CRT improves functional and hemodynamic status and reduces heart failure hospitalizations (1-3). Currently, there are no data on the role of rate-adaptive pacing during CRT, and the optimal programming of CRT during exercise remains undefined. The results of this study suggest that appropriate rate adaptation with CRT provides an incremental benefit to patients with heart failure and severe chronotropic incompetence during exercise. However, the use of rate-adaptive pacing with CRT in patients with mild chronotropic incompetence does not improve exercise performance and is potentially harmful.

**Conclusions.** As more patients with advanced heart failure are treated with CRT, the results of this study provide useful information regarding the optimal use of rate-adaptive pacing to improve their exercise capacity. In patients with heart failure implanted with CRT, chronotropic incompetence is one of the potential causes for impaired exercise capacity. Therefore, these patients should undergo exercise testing to assess the HR response during exercise after stabilization of medical therapy. In patients with severe chronotropic incompetence as defined by failure to achieve 70% of AP-HR, appropriate use of rate-adaptive pacing with CRT provides an incremental benefit on exercise capacity during exercise.

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