Influence of Permanent Right Ventricular Pacing on Cardiorespiratory Exercise Parameters in Chronic Heart Failure Patients With Implanted Cardioverter Defibrillators*

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Study objectives: Patients with chronic heart failure and implanted cardioverter-defibrillators (ICDs) may have a higher incidence of new-onset or worsening heart failure requiring hospitalization with dual-chamber ICDs compared with single-chamber ICDs.

Design and setting: The purpose of this study was to show the impact of permanent right ventricular (RV) pacing on exercise capacity and related cardiorespiratory parameters in patients with chronic heart failure and ICDs.

Patients and interventions: Seventeen patients with chronic heart failure and a dual-chamber ICD performed cardiopulmonary exercise testing (CPX) on 3 different days. After CPX 1, patients were randomized either to back-up pacing or permanent RV pacing. After 3 months, CPX 2 was performed and patients changed groups (crossover design); CPX 3 was performed after 3 additional months.

Measurements and results: Maximal values for workload (108 ± 46 W vs 117 ± 48 W, p < 0.01), oxygen uptake (V̇O₂) (21.0 ± 5.3 mL/min/kg vs 22.5 ± 6.4 mL/min/kg, p < 0.05), oxygen pulse (13 ± 3.7 mL vs 14 ± 4.0 mL, p < 0.05), and metabolic equivalent (6.0 ± 1.5 vs 6.4 ± 1.8, p < 0.05) were significantly lower with permanent RV pacing compared to back-up pacing. Workload, V̇O₂, and oxygen pulse were significantly reduced at the ventilatory anaerobic threshold, while workload and V̇O₂ were significantly lower at the respiratory compensation point. No differences were found for maximal heart rate, minute ventilation V̇E, and respiratory exchange ratio. The V̇E/carbon dioxide production slope was significantly steeper with permanent RV pacing compared to back-up pacing.

Conclusions: Permanent RV pacing significantly reduced maximal and submaximal measures of exercise. For patients with chronic heart failure and sufficient atrioventricular conduction, every effort should be made to minimize permanent right ventricular pacing.

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Key words: cardiopulmonary exercise testing; dual-chamber implantable cardioverter defibrillator; maximal oxygen consumption; minute ventilation/carbon dioxide production slope; respiratory compensation point; ventilatory anaerobic threshold; ventilatory efficiency

Abbreviations: CPX = cardiopulmonary exercise testing; DDD = dual-chamber pacemaker; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; RV = right ventricular; V̇CO₂ = carbon dioxide production; V̇E = minute ventilation; V̇O₂ = oxygen uptake; V̇O₂max = maximal oxygen uptake

The implantable cardioverter-defibrillator (ICD) improves survival in patients with life-threatening ventricular arrhythmias. Recently, prophylactic implantation of a defibrillator in patients with prior myocardial infarction and advanced left ventricular dysfunction has been shown to be superior to standard medical therapy. However, a higher incidence of new-onset or worsening heart failure requiring hospitalization was found with dual-chamber ICDs.

The Dual Chamber and VVI Implantable Defibrillator trial confirmed these findings in chronic heart failure patients without an indication for antiarrhythmia pacemaker therapy. Direct comparison of back-up pacing using right ventricular (RV) back-up pacing programming to permanent atrioventricular-sequential RV pacing showed a significantly lower number of deaths or first hospitalizations for congestive heart failure in ICD patients with back-up
The different components of the composite end point, mortality, and hospitalization for congestive heart failure also trended in favor of RV back-up pacing.

Information from the atrial chamber allows better device programming and individualization of drug therapy for ventricular arrhythmias. Therefore, most currently implanted ICDs are dual-chamber devices. Moreover, positive short-term and long-term effects of dual-chamber RV pacing in the treatment of end-stage idiopathic dilated cardiomyopathy have been shown. However, 4 to 18% of ICD patients were found to need antibradycardia pacing. At the moment, however, it is unclear whether dual-chamber pacemakers (DDDs) should be implanted, or whether permanent DDD pacing should be activated in modern ICDs in every patient with chronic heart failure regardless of the intrinsic atrioventricular conduction delay.

The maximal oxygen uptake (VO2max) is used for risk stratification in chronic heart failure patients. In some cases, VO2max might be underestimated because of reduced patient motivation or premature termination of exercise on the examiner's decision. Furthermore, patients with severe heart failure tend to perform activities of daily life that involve submaximal measures of exercise. Submaximal exercise parameters such as the ventilatory anaerobic threshold, the respiratory compensation point, and ventilatory efficiency (minute ventilation [VE]/carbon dioxide production [VCO2] slope) are less subject to these influences. The VE/VCO2 slope in particular was found to be a reliable predictor of prognosis in patients with chronic heart failure.

The purpose of this study was to show the impact of permanent RV pacing on exercise capacity and submaximal cardiorespiratory parameters in patients with chronic heart failure and dual-chamber ICDs.

**Inclusion Criteria**

Inclusion criteria included the following: chronic atrial fibrillation, history of paroxysmal atrial fibrillation, sick sinus syndrome, need for permanent atrioventricular-synchronous RV pacing, an atrioventricular delay < 150 ms, female patients with child-bearing potential, age > 80 years, and hypertrophic obstructive cardiomyopathy.

**Exclusion Criteria**

Exclusion criteria included the following: chronic atrial fibrillation, history of ventricular tachycardia or survivor of sudden cardiac death, age > 18 years, left ventricular ejection fraction (LVEF) < 40%, permanent sinus rhythm, and medication not changed during the investigation period.

**Programming of the ICD**

*Antitachycardia Parameters:* The device was programmed individually according to the underlying ventricular arrhythmia. This programming was maintained during the 6-month follow-up period unless ventricular tachyarrhythmias developed for which the antitachycardia stimulation therapy was inappropriate or ineffective.

*Antibradycardia Parameters:* The lower rate was programmed to 40 to 50 beats/min for all patients. The upper rate of the pacemaker was programmed according to the age-predicted maximal heart rate, 130 to 160 beats/min.

Patients were randomized in a crossover design to either of the following: (1) intrinsic atrioventricular-segmental conduction without ventricular stimulation (DDD with a long atrioventricular delay or DDD [back-up pacing group]; or (2) fixed atrioventricular delay of 100 to 120 ms ensuring permanent RV stimulation. At the 3-month follow-up, programming was switched to correspond to the other group so that the study patients served as their own control group.

**CPX**

Subjects completed CPX on an electronically braked cycle ergometer (ER 900; Jaeger; Wuerzburg, Germany) to volitional exhaustion on 3 different days: The first test (CPX 1) was intended to familiarize patients with the testing procedure and to determine their maximal workloads. To obtain baseline values, patients were asked to sit quietly on the cycle ergometer for 10 min. Resting values were collected in the last minute before the onset of the workload. Exercise was started with a workload of 10 W followed by an increase of 10 W for men and 7 W for women every minute thereafter. A 12-lead ECG (Jaeger) was used to monitor and record ECG tracings. A physician supervised each test. During CPX, subjects wore an airtight mask over their nose and mouth. Oxygen uptake (VO2) and VCO2 were analyzed continuously during the tests using a breath-by-breath system.
(Oxycon-Pro; Jaeger). Averaged values of these parameters were recorded every 20 s. To obtain an optimal exercise time of approximately 10 min, an individual approach for workload increments was chosen for the following two tests. The workload achieved from CPX 1 was divided by 10 to determine the incremental workload step for further testing.

In this randomized crossover study, CPX 2 and CPX 3 were done after 3 months and 6 months with either permanent atrioventricular synchronous ventricular pacing (permanent RV pacing) or permanent intrinsic atrioventricular conduction (back-up pacing) [Fig 1]. To keep the observer blinded, ECG tracings at CPX 2 and CPX 3 were stored but not shown on-line during the testing procedure.

Subjects were encouraged to continue until exhaustion. The highest level of VO₂ achieved during the test was defined as VO₂max regardless of the establishment of a VO₂ plateau. The respiratory equivalents for oxygen (Ve/VO₂) and carbon dioxide (Ve/VO₂) were calculated off-line.

The Ve/VO₂ slope was calculated off-line as an index of the ventilatory response to exercise. This slope represents the regression line relating Ve to VO₂ using all unaveraged (ie, breath-by-breath) data points from rest to peak exercise. The slope computed from all data points for the entire range of an exercise test has been shown to have the highest prognostic value compared to submaximal measurements.

The oxygen pulse, as the quotient of VO₂ (in milliliters) divided by the heart rate, is determined by stroke volume and the arteriovenous oxygen difference.

Submaximal Values: Two submaximal values based on a three-phase model were analyzed with a computer-aided linear regression breakpoint analysis. The ventilatory anaerobic threshold was defined as the point that corresponded to the initial deviation from linearity in Ve and the onset of a systematic rise in the respiratory equivalent for VO₂ without a simultaneous increase in the respiratory equivalent for VCO₂. The respiratory compensation point was defined between the ventilatory anaerobic threshold and maximal workload as follows: the secondary rise in Ve that corresponded to the secondary rise in the respiratory equivalent for VO₂. This point is compatible to the nadir of the respiratory equivalent for VCO₂ and is followed by a marked rise in respiratory equivalent for VCO₂.

Statistics: Continuous data were tested for normality using the Kolmogorov-Smirnov test. Data are reported as mean ± SD values. The paired Student t test was used to determine significant differences between permanent RV pacing and back-up pacing for all measured and calculated variables. The level of significance was set at p < 0.05.

Results

A total of 198 patients were screened for eligibility. After application of inclusion and exclusion criteria, 28 patients were eligible for the study. Five patients refused to participate; furthermore, two
patients were not able to perform exercise testing due to osteoarthritis. One patient had to be excluded after CPX 1 due to exercise-induced ventricular tachycardia. After CPX 1, 20 patients could be randomized (Fig 1). During the investigation period, one patient died of cardiac decompensation. One patient had to be excluded due to ventricular tachycardia with successful shock administration by the ICDs during CPX 3, which was caused by a lead defect. One patient refused to continue in the study during follow-up. Thus, a total of 17 patients (14 male and 3 female; age, 59 ± 8 years; weight, 80 ± 15 kg) were available for final analysis. The baseline characteristics of these patients were as follows: mean LVEF was 28 ± 7%, heart failure was of ischemic origin in 12 patients, and 5 patients suffered from idiopathic dilated cardiomyopathy. Thirteen patients were in New York Heart Association functional class III, and 4 patients were in New York Heart Association functional class II, and 4 patients were in New York Heart Association with successful shock administration by the ICDs during CPX 3, which was caused by a lead defect. One patient refused to continue in the study during follow-up. Thus, a total of 17 patients (14 male and 3 female; age, 59 ± 8 years; weight, 80 ± 15 kg) were available for final analysis. The baseline characteristics of these patients were as follows: mean LVEF was 28 ± 7%, heart failure was of ischemic origin in 12 patients, and 5 patients suffered from idiopathic dilated cardiomyopathy. Thirteen patients were in New York Heart Association functional class III, and 4 patients were in New York Heart Association functional class II, and 4 patients were in New York Heart Association class II. During the investigation period, medications were not changed (65% were receiving angiotensin-converting enzyme inhibitors, 82% were receiving β-blockers, 30% were receiving angiotensin type 2 blockers, 70% were receiving diuretics, and 41% were receiving digoxin); weight was unchanged during follow-up.

Mean intrinsic atrioventricular delay for all patients at baseline was 191 ± 23 ms. Intrinsic left bundle-branch block was found in 7 patients, and normal QRS complex was found in the remaining 10 patients. A significant difference (p < 0.001) was found for mean QRS width during back-up pacing (125 ± 32 ms) and permanent RV pacing (176 ± 31 ms). During the back-up pacing period, 3.6 ± 5% of RV beats were paced. During the permanent RV pacing period, RV pacing was found in 99 ± 2% of beats.

**CPX**

**Resting Values:** Resting values for heart rate, VO2, VE, and oxygen pulse (measured at CPX 2 and CPX 3) did not differ between back-up pacing and permanent RV pacing (Table 1).

**Maximal Values:** Maximal values during the first exercise test (CPX 1) were as follows: VO2max, 21.5 ± 5.5 mL/kg/min; metabolic equivalent, 6.1 ± 1.6; maximum testing time; 708 ± 220 s; maximum heart rate, 135 ± 23 beats/min; maximum VE, 62 ± 14 L/min; maximal oxygen pulse, 12.8 ± 4.0 mL; and maximal respiratory exchange ratio, 1.03 ± 0.1. Permanent RV DDD pacing significantly reduced maximal workload by −8%, maximal VO2 by −7%, metabolic equivalent by −6%, and exercise time by −8% compared to back-up pacing (Table 1). Maximal oxygen pulse as surrogate parameter of stroke volume was also significantly reduced by −7% with permanent RV pacing. No differences were found for maximal heart rate, maximal VE, and maximal respiratory exchange ratio at peak exercise (Table 1).

**Submaximal Parameters:** The ventilatory anaerobic threshold could be determined for every patient in all tests. Permanent RV pacing significantly reduced workload by −23%. VO2 by −10%, and oxygen pulse by −9% at the ventilatory anaerobic threshold compared to back-up pacing. No significant difference was found for heart rate at the ventilatory anaerobic threshold (Table 2). The respiratory compensation point could be determined in 14 patients in the permanent RV pacing group and 15 patients in the back-up pacing group. Means ± SD were only calculated with the complete data set for every patient (n = 14). Permanent RV pacing significantly reduced workload by −18% and VO2 by −8% at the respiratory compensation point compared with back-up pacing. Heart rate at the respiratory compensation point also tended to be lower with permanent RV pacing. Although the oxygen pulse at the respiratory compensation point was found to be higher for back-up pacing, this

Table 1—Cardiorespiratory Parameters at Rest and at Maximal Effort

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Maximal Values</th>
<th>Maximal Values</th>
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<tbody>
<tr>
<td></td>
<td>Back-up Pacing</td>
<td>Permanent RV Pacing</td>
</tr>
<tr>
<td>VO2, mL/kg·min</td>
<td>4.8 ± 0.8</td>
<td>4.8 ± 0.8</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>71 ± 15</td>
<td>72 ± 18</td>
</tr>
<tr>
<td>VE, L/min</td>
<td>12 ± 3</td>
<td>12 ± 3</td>
</tr>
<tr>
<td>Oxygen pulse, mL</td>
<td>5.5 ± 1.4</td>
<td>5.5 ± 1.3</td>
</tr>
<tr>
<td>Maximal respiratory exchange ratio</td>
<td>1.02 ± 0.1</td>
<td>1.04 ± 0.1</td>
</tr>
<tr>
<td>Maximal workload, W</td>
<td>6.4 ± 1.8</td>
<td>6.0 ± 1.5</td>
</tr>
<tr>
<td>Metabolic equivalent</td>
<td>34 ± 6</td>
<td>37 ± 7</td>
</tr>
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</table>

*Significantly different (p < 0.05).
†Significantly different (p < 0.01).
The difference did not reach statistical significance (Table 2). The VE/VCO₂ slope was significantly steeper with permanent RV pacing than with back-up pacing (Table 1).

### Discussion

In patients with chronic heart failure and sufficient intrinsic atrioventricular conduction, we found no benefit of permanent RV pacing using DDD mode with short atrioventricular delay compared with back-up pacing. Actually, in our study the opposite was found to be the case. Permanent RV pacing significantly reduced exercise capacity and submaximal cardiorespiratory parameters.

Permanent RV pacing is uncommon in patients with pacemakers having adequate atrioventricular conduction. Cardiac stimulation in the apex of the right ventricle has unfavorable effects with induction of a left bundle-branch block and consequent disturbances in the contractility and hemodynamic parameters. However, RV apical pacing has been used as an adjunctive treatment for heart failure regardless of intrinsic atrioventricular conduction. Improvement of hemodynamics was demonstrated using a short atrioventricular delay, but results were not consistent. All the above-mentioned studies used an atrioventricular delay between 90 ms and 130 ms. In our study, the atrioventricular delay for permanent pacing was programmed at 100 to 120 ms according to the studies that showed the greatest benefit. Although an additional negative influence of a too-short atrioventricular interval cannot fully be excluded, an atrioventricular delay of at least 100 ms was found to be the shortest possible delay that does not significantly impair cardiac function in patients with DDD pacemaker therapy. Furthermore, in patients with the need for permanent RV pacing, it has been shown that small differences in atrioventricular delay have far less influence on left ventricular systolic function than pacing site.

### Maximal Measures of Exercise

VO₂max measured during CPX has been considered as a reference measurement in patients with heart failure. Patients with left bundle-branch block show lower exercise capacity and higher mortality. Biventricular pacing resulted in higher exercise capacity due to a normalization of the QRS width and normalization of contraction abnormalities. Moreover, in patients with preexisting left bundle-branch block, a close relation has been found between the degree of QRS narrowing with biventricular pacing and clinical improvement.

The oxygen pulse was significantly reduced at maximal workload (Table 1). The VO₂ per heart beat represents a substitute for the stroke volume, as the arteriovenous oxygen difference is constant. The decrease in VO₂max was independent of heart rate response, as shown by the significantly higher oxygen pulse with back-up pacing. This would be consistent with the increase in stroke volume observed with biventricular pacing compared with an uncorrected left bundle-branch block.

A possible explanation could be impaired coronary blood flow due to RV pacing. Alterations in regional myocardial blood flow associated with permanent RV pacing were found in experimental animal and human studies. An impairment of microvascular flow was found to be the underlying mechanism. Reduced regional myocardial work, VO₂, and free fatty acid metabolism have been observed in the early activated region during ventricular pacing.

### Submaximal Measures of Exercise

An important aim of treatment for severe heart failure is to increase the patient’s ability to perform activities of daily life. Parameters that reflect submaximal activities may be more useful than maximal exercise parameters for the assessment of the efficacy of treatment. A significant improvement of workload and VO₂ at the ventilatory anaerobic threshold did not reach statistical significance (Table 2). The VE/VCO₂ slope was significantly steeper with permanent RV pacing than with back-up pacing.

### Table 2—Submaximal Cardiorespiratory Parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ventilatory Anaerobic Threshold</th>
<th>Respiratory Compensation Point</th>
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<tbody>
<tr>
<td></td>
<td>Back-up Pacing</td>
<td>Permanent RV Pacing</td>
</tr>
<tr>
<td></td>
<td>44 ± 21</td>
<td>34 ± 14†</td>
</tr>
<tr>
<td>Workload, W</td>
<td>12.7 ± 2.4</td>
<td>11.4 ± 2.1†</td>
</tr>
<tr>
<td>VO₂, mL/kg/min</td>
<td>89 ± 16</td>
<td>89 ± 16</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>11.5 ± 3.2</td>
<td>10.4 ± 2.6*</td>
</tr>
<tr>
<td>Oxygen pulse, mL</td>
<td>44 ± 21</td>
<td>34 ± 14†</td>
</tr>
<tr>
<td></td>
<td>44 ± 21</td>
<td>34 ± 14†</td>
</tr>
<tr>
<td></td>
<td>12.7 ± 2.4</td>
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<tr>
<td></td>
<td>89 ± 16</td>
<td>89 ± 16</td>
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<tr>
<td></td>
<td>111 ± 21</td>
<td>105 ± 19§</td>
</tr>
<tr>
<td></td>
<td>12.5 ± 2.8</td>
<td>12.1 ± 2.9</td>
</tr>
</tbody>
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*Significantly different (p < 0.05).
†Significantly different (p < 0.01).
‡Significantly different (p < 0.001).
threshold and the respiratory compensation point was seen with back-up pacing compared to permanent RV pacing.

The VE/VCO₂ slope provides a noninvasive assessment of the appropriateness or efficiency of ventilation during exercise and has been shown to be useful for risk stratification in chronic heart failure patients with intermediate exercise capacity. 11,16 We found a small but significantly steeper slope with permanent RV stimulation. In chronic heart failure, this slope is generally increased, implying increased ventilatory drive. Normalization of left bundle-branch block with biventricular pacing has been shown to increase cardiac output 28 and to reduce left atrial pressure, 34 leading to less pulmonary congestion, which in turn may improve ventilatory efficiency. Such changes might be expected to reduce ventilation-perfusion mismatch and to account for the dramatic improvement in ventilatory drive observed with biventricular pacing.

Methodologic Considerations and Limitations

This was a single-center study. Although a total of 198 ICD patients were available, only 17 could be analyzed. Differences were small but reached statistical significance.

The study duration was fairly short, with each intervention performed for 3 months. Further changes would have been seen between the two different pacing interventions over a longer period resulting in more pronounced differences in measured parameters.

A change in training status could influence maximal and submaximal parameters of exercise. Although we did not control for physical activity or exercise during the 3 months of back-up pacing and permanent RV pacing, due to the crossover design of the study an influence seems very unlikely.

Exercise parameters may be of importance for the explanation of previous results found by the Second Multicenter Automated Defibrillator Implantation Trial 2 and the Dual Chamber and VVI Implantable Defibrillator trial. 3 Parameters such as humoral factors or quality of life might be of interest in future studies.

CONCLUSION

Large, randomized, multicenter trials 2,3 have shown a higher rate of hospitalization in heart failure patients with dual-chamber ICDs. As a possible explanation, this study has shown that permanent RV pacing significantly reduces exercise capacity and submaximal measures of exercise performance. In patients with normal atrioventricular conduction, even “optimized” atrioventricular-sequential permanent RV pacing is unphysiological. In view of these observations, every effort should be made to minimize ventricular pacing in chronic heart failure patients with dual-chamber pacing systems and intrinsic atrioventricular conduction.

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