Intrinsic Heart Rate Response as a Predictor of Rate-Adaptive Pacing Benefit*

Eckhard U. Alt, MD; Michael J. Schlegl; and Markus M. Matula, MD

Objective: More than half of the pacemaker systems now being implanted can be rate adaptively paced. Our objective was to determine which patients benefit from rate-adaptive pacing in terms of improvement in maximum performance and aerobic capacity.

Methods: Thirty patients with implanted accelerometer-driven, rate-adaptive pacemakers underwent a standardized, ergospirometrically and maximally symptoms-limited cardiopulmonary exercise (CPX) stress test with both rate-adaptive and fixed-rate stimulation in a randomized order. The patients were divided into three groups depending on the intrinsic heart rate achieved during maximum workload: group 1 achieved ≤90 beats per minute (bpm), group 2 achieved 90 to ≤110 bpm, and group 3 achieved >110 bpm.

Results: Group 1 demonstrated a significant increase (p≤0.01) in maximum oxygen uptake from 16.4±5.6 mL/kg/min with fixed-rate pacing to 23.2±11.1 mL/kg/min (+41.5%) with rate-adaptive pacing. At the anaerobic threshold, oxygen uptake significantly increased (p≤0.01) from 11.8±2.7 mL/kg/min to 15.7±5 mL/kg/min (+31.1%). Group 2 patients showed an increase in maximum oxygen uptake from 23.3±5.4 mL/kg/min to 25.3±4.9 mL/kg/min (+8.5%, p≤0.05) as well as an increase in oxygen uptake at the anaerobic threshold from 15.9±2.6 mL/kg/min to 18.1±2.9 mL/kg/min (+13.8%, p≤0.05) with rate-adaptive pacing. Group 3 demonstrated no significant difference between the two pacing methods (from 25.6±9.4 mL/kg/min to 25.9±9.3 mL/kg/min and from 15.8±5.5 mL/kg/min to 16.3±6.2 mL/kg/min). No difference in maximum oxygen uptake and in oxygen uptake at the anaerobic threshold was evident among the three groups when paced rate adaptively (not significant).

Conclusion: The second-generation, accelerometer controlled rate-adaptive pacemakers used in testing enabled a stress-oriented heart rate increase and an age- and gender-dependent adequate matching of maximum performance. The benefit from a rate-adaptive system to the patient increases as his or her chronotropic reserve limitation became more pronounced.

(Chest 1995; 107:925-30)

Key words: accelerometer; aerobic capacity; intrinsic heart rate; rate-adaptive cardiac pacing

A human's maximum performance and aerobic capacity are strongly dependent on the cardiovascular system, respiration, and muscular fitness. With physical exercise, an increase in the individual's oxygen uptake effects an increase in stroke volume and heart rate (HR) and thus an increase in cardiac output. Analysis of respiratory gas exchange facilitates determination of maximum performance and aerobic capacity in both healthy patients and in those with cardiac disease.1 Oxygen uptake (VO2) demonstrates a mostly linear relationship to performance and heart rate.2,3 The individual correlation is influenced by the patient's physical fitness; the relationship between HR and VO2 varies from 2 to 6 beats per minute (bpm) per milliliter per kilogram per minute.3

This correlation is vital in pacemaker therapy, since chronotropic incompetence is common to many patients with pacemakers and limits their physical performance and aerobic capacity.4 Rate-adaptive pacing stimulation attempts to normalize HR relative to VO2.

An objective of our study was to determine the relationship of stimulation rate in a new generation of activity-controlled pacemakers (accelerometer-driven systems: Relay/Dash, Intermedics, Angleton, Tex) to performance and oxygen uptake. A further objective was to determine if and when chronotropic incompetent patients benefit from rate-adaptive stimulation relative to their maximum exercise capacity and their aerobic capacity.

Methods and Materials

Patients and Study Groups

The study comprised a total of 30 patients (17 women, 13 men) with a mean age of 63.7 years. Mean weight was 71.9 kg; mean height was 169.2 cm. Indications for pacing were third-degree atrioventricular (AV) block in 7 patients, sinus node dysfunction in 11 patients, bionodal disease in 9 patients, and bradycardia/tachycardia syndrome with atrial fibrillation in 3 patients.

Patients were divided into three chronotropic groups according to the maximum intrinsic heart rate achieved during tream-

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mill testing with fixed rate stimulation: group 1, patients with a maximum intrinsic HR of \(\leq 90\) bpm; group 2, patients with a maximum intrinsic HR of \(90\) to \(\leq 110\) bpm; and group 3, patients with a maximum intrinsic HR of \(>110\) bpm. No significant differences in age, height, weight, and pacemaker-programmed setting were evident in the three groups (Tables 1 through 3).

The heart rate and pacemaker rates were continuously monitored during patient trials and recorded (ECG Sircreust BS 1, Siemens, Erlangen, Germany, and model MT 9500 stripchart recorder, Astro Med, West Warwick, RI). The rate profile of the pacemaker was recorded internally and interrogated poststudy. Monitoring by the three different means enabled a continuous registration of pacemaker and intrinsic HR during treadmill exercise. Cardiopulmonary parameters were recorded on a beat-to-beat basis utilizing a zirconia to measure \(\text{VO}_2\) and an infrared sensor to measure carbon dioxide production (CFX Medical Graphics, St. Paul, Minn). Patients were exercised using a standard protocol on a treadmill ergometer (Ergotest Junior, Jäger, Höchberg/Germany) that allows for independent adjustment of speed and slope.

### Experimental Protocol

The patients underwent a standardized, maximally symptom-limited treadmill stress test with both rate-adaptive and fixed-rate stimulation in a randomized order. Both trials were separated by a rest period of at least 30 min or until pulse rate, oxygen uptake, and respiratory quotient returned to baseline level.

A 5-min accommodation period preceded each treadmill test, giving the patient adequate time to adjust to the experimental instrumentation. Thereafter the stress test followed our treadmill protocol designed for pacemaker patient assessment.\(^5\) Treadmill speed and slope were alternatingly increased, beginning at 3.2 km/h and 0% and increasing to 5.6 km/h and 16%. For a body weight of 72 kg, each 2-min treadmill stage corresponded to a 25-W increase.

The stress test end point was defined as limited symptoms with maximal exertion, ie, angina pectoris complaints, ECG abnormalities, claudication, or new rhythm disorders.

### Pacemaker Description

The second-generation, activity-controlled pacemakers used in the study were multiprogrammable, rate-adaptive devices that sensed body activity in an anterior-posterior plane via an accelerometer attached to the pacemaker hybrid.\(^6\) In contrast to earlier activity-controlled pacemakers utilizing a piezosensor attached to the titanium pacemaker can and measuring direct pressure at the pacemaker can, accelerometer-driven systems are not affected by disruptive external stimuli.\(^6,10\) Accelerometer-driven pacing systems react to low-frequency acceleration signals (\(\leq5\) Hz); unphysiologically high noise signals are filtered out by an inbuilt band pass filter (0.1 to 4.0 Hz).\(^9\) Activity-controlled systems do not require lead-based sensors or additional electrodes, making implantation less restrictive and simplifying pacemaker replacement.

### Pacemaker Programming

The objective of pacemaker programming was to match the pacing profile of the rate-adaptive pacemaker to age-matched normals during maximal and submaximal exercise. Submaximal pacing rate was optimized using criteria previously described by Wilkoff et al.\(^11\)

Pacemakers were individually tailored to each patient. Each patient was asked to walk normally on a treadmill for 5 min at the slow pace of 2.5 km/h with a target rate of 90 bpm.

The programmer-recommended rate response slope values varied between three and eight. Recommended values were programmed and retained for the duration of the treadmill trials. Lower rates were programmed to 60 bpm and upper rate to 160 bpm for both trials.

### Data Analysis and Statistics

The ventilatory parameters were measured, saved, and averaged over a 10-s duration. Cardiopulmonary data were converted posttrial from the initial DOS to a different format (Macintosh). The last three values of cardiopulmonary data for workload level (data from the last 30 s) were averaged and implemented in further analysis. Determination of patient anaerobic threshold was via both the V-slope method according to Beaver et al.\(^7\) and visual criteria. The analysis for each method was performed by two independent examiners. A third examiner was called when thresholds differing by more than 10% were determined. The described method enabled determination of the anaerobic threshold in 98% of the patients. The determination of the anaerobic threshold by measurement of respiratory gas kinetics has been shown to be a safe, appropriate, and objective method of measuring anaerobic capacity.\(^12\)

Further data processing was completed using a computer (Macintosh II, Apple, Cupertino, Calif). Statistical analysis was performed with a program (StatView) in conjunction with the Mann-Witney \(U\) and the Wilcoxon tests. A \(p\) value of \(\lesssim0.05\) was determined to be statistically significant.

When interpreting the median values, it must be taken into account that maximal treadmill exercise levels were patient symptom limited. Processing and analysis of rates achieved were performed only to the workload levels at which a statistically significant \((n=7)\) conclusion could be made, minimizing interpretation errors.

### Results

#### Heart Rate

For all three chronotropic groups, the maximum rates achieved during treadmill testing were higher for rate-adaptive mode than intrinsic sinus rate (Fig 1). The largest difference in rates achieved was recorded in patient group 1 with a highly significant increase \((p\lesssim0.01)\) from 72±13 per minute to

![Figure 1: Maximum pacemaker stimulation rate in the rate-adaptive (RR) and maximum intrinsic heart rate (IR) of the patients with pacemakers (n=30) under maximum exertion according to their chronotropic incompetence. Group 1=maximum intrinsic heart rate \(\leq90\) bpm; group 2=maximum intrinsic heart rate 90 to \(\leq110\) bpm; group 3=maximum intrinsic heart rate >110 bpm. The mean values and SDs are shown.](http://journal.publications.chestnet.org/pdaccess.asashx?url=/data/journals/chest/21712/ on 04/02/2017)
Performance two pacing demonstrated no significant difference (p<0.01) in maximum oxygen uptake during treadmill ergometry. The increase in VO\(_2\) was 33.1%. At the anaerobic threshold, group 2 patients also showed a significant increase (13.8%) in VO\(_2\) compared to 15.9±2.6 mL/kg/min with fixed-rate pacing to 18.1±2.9 mL/kg/min (p≤0.05) with rate-adaptive pacing. No significant difference regarding VO\(_2\) at the anaerobic threshold with rate-adaptive pacing was evident in group 3 patients (15.8±5.5 mL/kg/min to 16.3±6 mL/kg/min). There was also no significant difference (NS) among the three groups regarding VO\(_2\) at the anaerobic threshold.

**Oxygen Uptake vs Heart Rate**

Figure 3 depicts the relationship between HR and VO\(_2\) with rate-adaptive pacing (15.7±5 mL/kg/min) compared with fixed-rate pacing (11.8±2.7 mL/kg/min) (Fig 2, bottom). The increase in VO\(_2\) was 33.1%. At the anaerobic threshold, group 2 patients also showed a significant increase (13.8%) in VO\(_2\) from 15.9±2.6 mL/kg/min with fixed-rate pacing to 18.1±2.9 mL/kg/min (p≤0.05) with rate-adaptive pacing. No significant difference regarding VO\(_2\) at the anaerobic threshold with rate-adaptive pacing was evident in group 3 patients (15.8±5.5 mL/kg/min to 16.3±6 mL/kg/min). There was also no significant difference (NS) among the three groups regarding VO\(_2\) at the anaerobic threshold.

**Maximum Performance and Aerobic Capacity**

Figure 2 (top) illustrates group 1’s significant increase (p≤0.01) in maximum oxygen uptake from 16.4±5.6 mL/kg/min with fixed-rate pacing to 23.2±11.1 mL/kg/min (+41.5%) with rate-adaptive pacing. Group 2 resulted in an increase of maximum oxygen uptake from 23.3±5.4 mL/kg/min to 25.3±4.9 mL/kg/min (+8.5%, p≤0.05). Group 3 demonstrated no significant difference between the two pacing methods (from 25.6±9.4 mL/kg/min to 25.9±9.3 mL/kg/min). For rate-adaptive pacing, no difference in maximum VO\(_2\) (not significant [NS]) could be seen among the three groups.

Oxygen uptake also significantly increased (p≤0.01) at the anaerobic threshold in group 1 under rate-adaptive pacing (15.7±5 mL/kg/min) compared with fixed-rate pacing (11.8±2.7 mL/kg/min) (Fig 2, bottom). The increase in VO\(_2\) was 33.1%. At the anaerobic threshold, group 2 patients also showed a significant increase (13.8%) in VO\(_2\) from 15.9±2.6 mL/kg/min with fixed-rate pacing to 18.1±2.9 mL/kg/min (p≤0.05) with rate-adaptive pacing. No significant difference regarding VO\(_2\) at the anaerobic threshold with rate-adaptive pacing was evident in group 3 patients (15.8±5.5 mL/kg/min to 16.3±6 mL/kg/min). There was also no significant difference (NS) among the three groups regarding VO\(_2\) at the anaerobic threshold.

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Table 1—Group 1 (Maximal Intrinsic Heart Rate ≤90 bpm)*

<table>
<thead>
<tr>
<th>Patient/Sex/Age, yr</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>Indication</th>
<th>Mode</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/18</td>
<td>52</td>
<td>167</td>
<td>Brady/tachy</td>
<td>AAI-R</td>
<td>5</td>
</tr>
<tr>
<td>2/F/70</td>
<td>75</td>
<td>160</td>
<td>Binodal</td>
<td>DDD-R</td>
<td>6</td>
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<tr>
<td>3/M/60</td>
<td>88</td>
<td>185</td>
<td>AV-block 3</td>
<td>VVI-R</td>
<td>5</td>
</tr>
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<td>4/M/59</td>
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<td>AV-block 3</td>
<td>VVI-R</td>
<td>7</td>
</tr>
<tr>
<td>5/M/70</td>
<td>88</td>
<td>176</td>
<td>AV-block 3</td>
<td>VVI-R</td>
<td>5</td>
</tr>
<tr>
<td>6/M/79</td>
<td>69</td>
<td>172</td>
<td>AV-block 3</td>
<td>VVI-R</td>
<td>4</td>
</tr>
<tr>
<td>7/F/44</td>
<td>70</td>
<td>180</td>
<td>Brady/tachy</td>
<td>VVI-R</td>
<td>7</td>
</tr>
<tr>
<td>8/M/85</td>
<td>80</td>
<td>172</td>
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<td>VVI-R</td>
<td>7</td>
</tr>
<tr>
<td>9/F/54</td>
<td>64</td>
<td>163</td>
<td>AV-block 3</td>
<td>VVI-R</td>
<td>7</td>
</tr>
</tbody>
</table>

*n=9 4F/5M 59.9±20.1

*Brady/tachy=bradycardia/tachycardia; AAI-R=atrial stimulating, atrial-inhibited, rate-adaptive pacing mode; DDD-R=dual-chamber stimulating, dual-chamber inhibited and triggered rate-adaptive pacing mode; VVI=ventricular-inhibited pacing mode.

Table 2—Group 2 (Maximal Intrinsic Heart Rate 90 to ≤110 bpm)*

<table>
<thead>
<tr>
<th>Patient/Sex/Age, yr</th>
<th>Weight, kg</th>
<th>Height, cm</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>168</td>
<td>SSS</td>
<td>AAI-R</td>
<td>4</td>
</tr>
<tr>
<td>11/M/72</td>
<td>58</td>
<td>172</td>
<td>SSS</td>
<td>AAI-R</td>
<td>7</td>
</tr>
<tr>
<td>12/M/82</td>
<td>61</td>
<td>158</td>
<td>SSS</td>
<td>AAI-R</td>
<td>3</td>
</tr>
<tr>
<td>13/F/65</td>
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<td>168</td>
<td>Binodal</td>
<td>DDD-R</td>
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</tr>
<tr>
<td>14/F/65</td>
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<td>Binodal</td>
<td>DDD-R</td>
<td>6</td>
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<tr>
<td>15/M/71</td>
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<td>Binodal</td>
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<td>8</td>
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<tr>
<td>16/F/44</td>
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<td>179</td>
<td>Brady/tachy</td>
<td>VVI-R</td>
<td>6</td>
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<tr>
<td>17/F/71</td>
<td>73</td>
<td>163</td>
<td>AV-block 3</td>
<td>VVI-R</td>
<td>3</td>
</tr>
</tbody>
</table>

*n=8 5 F/3 M 66.6±10.9

*See Table 1 for explanation of abbreviations. SSS=sick sinus syndrome.

VO₂. Rate-adaptive pacing effected a pronouncedly more steep slope (3.7 bpm/[mL VO₂/kg/min]) compared with fixed-rate pacing (0.4 bpm/[mL VO₂/kg/min]). The slopes of the increase in HR with rate-adaptive and fixed-rate pacing differed significantly (p≤0.05) for group 1 patients. A significant difference was also found between fixed-rate (1.7 bpm/[mL VO₂/kg/min]) and rate-adaptive (3.1 bpm/[mL VO₂/kg/min]) pacing in group 2. Group 3 showed no significant difference (3.1 bpm–VO₂/kg with rate-

Table 3—Group 3 (Maximal Intrinsic Heart Rate >110 bpm)*

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<tr>
<th>Patient/Sex/Age, yr</th>
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<th>Indication</th>
<th>Mode</th>
<th>Slope</th>
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</thead>
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<td>6</td>
</tr>
<tr>
<td>19/F/58</td>
<td>65</td>
<td>157</td>
<td>SSS</td>
<td>AAI-R</td>
<td>7</td>
</tr>
<tr>
<td>20/M/65</td>
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<td>174</td>
<td>SSS</td>
<td>AAI-R</td>
<td>4</td>
</tr>
<tr>
<td>21/M/57</td>
<td>80</td>
<td>180</td>
<td>SSS</td>
<td>AAI-R</td>
<td>7</td>
</tr>
<tr>
<td>22/M/67</td>
<td>70</td>
<td>169</td>
<td>SSS</td>
<td>AAI-R</td>
<td>6</td>
</tr>
<tr>
<td>23/F/59</td>
<td>64</td>
<td>159</td>
<td>SSS</td>
<td>AAI-R</td>
<td>7</td>
</tr>
<tr>
<td>24/F/55</td>
<td>84</td>
<td>166</td>
<td>SSS</td>
<td>AAI-R</td>
<td>6</td>
</tr>
<tr>
<td>25/F/54</td>
<td>74</td>
<td>174</td>
<td>SSS</td>
<td>AAI-R</td>
<td>4</td>
</tr>
<tr>
<td>26/F/78</td>
<td>57</td>
<td>163</td>
<td>Binodal</td>
<td>DDD-R</td>
<td>5</td>
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<tr>
<td>27/F/75</td>
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<td>159</td>
<td>Binodal</td>
<td>DDD-R</td>
<td>3</td>
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<td>28/M/70</td>
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<td>DDD-R</td>
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<tr>
<td>29/M/72</td>
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<td>DDD-R</td>
<td>7</td>
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<tr>
<td>30/F/67</td>
<td>62</td>
<td>164</td>
<td>Binodal</td>
<td>DDD-R</td>
<td>7</td>
</tr>
</tbody>
</table>

*n=13 8 F/5 M 64.5±7.8

*See Tables 1 and 2 for explanation of abbreviations.
adaptive and 2.5 with fixed-rate pacing). The rate increase for rate-adaptive pacing showed no significant difference among the three groups. Patients in all groups showed significantly higher rates at all levels for rate-adaptive pacing than for fixed-rate pacing (p ≤ 0.05).

**DISCUSSION**

The maximum exercise capacity of healthy humans and even more so of patients with cardiac disease is dependent on the heart’s ability to increase its intrinsic rate under stress. A limited rate increase during stress therefore usually effects decreased maximum performance capacity and a limited aerobic capacity. Dual-chamber pacemaker therapy attempts to reestablish atrioventricular synchronization and restore chronotropic response to exercise for chronotropically incompetent patients.

Due to the close relationship between VO$_2$ and cardiac output, the rate behavior and the effect of pacemaker programming can be evaluated by analyzing the respiratory gas exchange. According to Treese et al., a pacemaker is set optimally relative to metabolic requirements when a rate increase of 2 to 5 bpm effects an increase in oxygen uptake of 1 mL/kg/min. The results of this study show that for all patients with pacemakers as well as for chronotropic subgroups, a tailoring of the rate increase behavior to metabolic requirements was possible with rate-adaptive pacing. The patients with pacemakers demonstrated an average rate increase with rate-adaptive pacing of 3.2 bpm/mL VO$_2$/kg increase (Fig 4) corresponding to the rate/VO$_2$ correlation of an age- and sex-matched normal population. The profile of rate increase to VO$_2$ showed no significant difference from the rate profile described by Wilkoff et al. and Astrand and Ryhming in comparable patient groups.

The analysis of respiratory gas exchange reveals information regarding the maximum anaerobic performance capability and aerobic capacity of the patient. Many studies reported improvement in maximum performance and anaerobic capacity for rate-adaptive pacing compared with non-rate-adaptive single chamber pacing.

Aerobic capacity and maximum performance were also ergospirometrically examined in first-generation activity-controlled pacemakers. For example, Benditt et al. reported in their study that a rate-adaptive VVIR-setting resulted in a 22% increase in maximum VO$_2$ compared with fixed-rate settings. Also, Humen et al. reported a significant increase in oxygen uptake at the anaerobic threshold with rate-adaptive pacing (13.0 ± 2.2 mL/kg/min to 10.8 ± 2.3 mL/kg/min).

Previous studies have not differentiated between patients who benefitted from rate-adaptive pacing. Our study aimed to determine both the influence of accelerometer-driven pacing on all patients as well as which patients benefitted from rate-adaptive pacing relative to their individual chronotropic reserves.

Rate-adaptive pacing proved to most beneficial for the strongly chronotropically incompetent group 1 patients with an intrinsic HR of 90 bpm maximum: aerobic capacity increased 33.1%, maximum VO$_2$ increased 41.5%. Patients with a maximum intrinsic HR between 90 and 110 bpm (group 2) benefitted less from rate-adaptive pacing, but showed an absolute increase in maximum VO$_2$ (8.5%) as well as higher VO$_2$ at the anaerobic threshold (13.8%) compared with fixed-rate settings. Group 3, with an intrinsic HR above 110 bpm, showed no improvement in performance ability and aerobic capacity with rate-adaptive pacing.

The rate-adaptive pacemakers demonstrated a total increase of 10.8% in aerobic capacity and 11.2% in maximum VO$_2$. It should be noted herein that 13 of the 30 patients were in group 3.

In prior studies comparing the rate profile according to physiologic needs, accelerometer-driven pacemakers fared better than activity-controlled pacemakers. Lau et al. and Bacharach et al. for example, reported that acceleration signals produced by an accelerometer-driven pacemaker during treadmill exercise correlated more closely to the heart rate than those from an activity-controlled pacemaker (r = 0.8 vs r = 0.27) and could thereby more closely correlate to sinus rhythm behavior. Alt et al. also reported a close correlation of accelerometer-driven stimulation to sinus rhythm during changes in pace and changes in treadmill slope. In former treadmill studies, a rate increase with activity-controlled pacemakers was
possible only by an increase in speed. When using a treadmill ergometry protocol in which VO2 increases in almost linear fashion relative to physical exercise (r = 0.98), our study showed an almost linear rate increase (r = 0.99) for accelerometer-driven pacemakers with increasing workload.

The new accelerometer-driven pacemakers offer advantages over the first-generation activity-controlled pacemakers described in past studies. The benefit can be seen particularly in the linear increase of heart rate to increase in VO2. Activity sensors allow for an age-dependent linear correlation of rate profile respective of submaximal heart rate according to Wilkoff et al.11 to exertion and VO2.

Our results furthermore show that chronotropically incompetent patients with a maximum intrinsic heart rate during physical exercise of no more than 110 bpm benefit from rate-adaptive pacing. And, of importance, this benefit is evident not only during maximum workload, but also within the aerobic range corresponding to most activities of everyday routine.

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