Long-Term Reduction of Ventricular Tachycardia Using Right Ventricular Pacing in Patients with Chronic Atrial Fibrillation

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Summary
Continuous ventricular overdrive pacing in patients with chronic atrial fibrillation (AF) has a stabilizing effect on the typically irregular ventricular rhythm characteristic of AF, which may cause dizziness, discomfort, and palpitations in many patients. This effect has been evidenced in previous studies; however, these studies did not investigate the efficacy during daily activity and over long-term follow-up. In this study, data taken from the pacemaker diagnostic memory were used to assess the reduction of fast ventricular rates over 88 beats/min (bpm), defined as tachy-AF, in patients with VVI pacing at 80 bpm over a period of 3 months. In 46 patients with chronic AF and permanent VVI pacing, the pacemaker memory data from the 3-month follow-up (basic rate 80 bpm) were compared with data from two consecutive 1-day follow-up controls (basic rate 40 bpm and 80 bpm, respectively) performed approximately 1 month after implantation (results: mean ± standard deviation; statistics: Wilcoxon matched pairs test). We found a significantly lower percentage of tachy-AF episodes with VVI pacing at 80 bpm at the 3-month follow-up as compared with VVI pacing at 40 bpm at the one-day follow-up (9% ± 9% versus 24% ± 16%, p-value < 0.05), though only the ventricular rates in the ranges between 88 and 120 bpm were significant. Conversely, the mean ventricular rate as well as the percentage of ventricular pacing was significantly higher at VVI pacing at 80 bpm at the 3-month follow-up as compared with VVI pacing at 40 bpm at the 1-day follow-up: 81 ± 3 bpm versus 68 ± 10 bpm (p-value < 0.01) and 7% ± 13% versus 86% ± 12% (p-value < 0.01). No significant differences were found between VVI pacing at 80 bpm at the 3-month follow-up and at the 2-day follow-up in all analyzed parameters (values of VVI pacing at 80 bpm at the 2-day follow-up: ventricular rates over 88 bpm = 13% ± 15%, mean ventricular rate = 81 ± 3 bpm, ventricular pacing = 86% ± 16%). We conclude that the reduction of tachy-AF by VVI overdrive pacing at 80 bpm is stable over a long-term period of 3 months, and that this effect is predictable immediately after implantation in a short-term, one-day follow-up which enables the identification of the responders to continuous ventricular overdrive pacing.

Key Words
Chronic atrial fibrillation, ventricular pacing, heart rate stabilization, pacemaker diagnostic memory

Introduction
The most frequent sustained arrhythmia, occurring in up to 1% of the general population [1,2], is atrial fibrillation (AF), which results in increased morbidity and mortality [3-7]. The ventricular rhythm in AF is usually irregular and may cause discomfort, dizziness, and palpitations in many patients [7-9]. It is also well known that AF produces significant hemodynamic changes, and diminishes contractile function [10].
Longstanding AF with its fast rate and/or irregularity negatively influences the heart's hemodynamic parameters and may cause tachycardiomopathy [10-13]. It is important to treat patients with chronic AF with therapies that control the ventricular rate. Pharmacological therapy aimed at ventricular rate control during AF is often associated with proarrhythmic side effects [14-16], and with a reduction of exercise capacity. For years, atrioventricular (AV) junction ablation followed by pacemaker implantation has been the only non-pharmacological treatment available for patients with chronic AF. This method is very aggressive and causes complete AV block.

Studying the electrocardiograms in AF patients with implanted ventricular pacemakers, Wittkampf observed in 1985 that right ventricular pacing stabilized irregular ventricular rhythm [17]. Subsequent studies have shown that continuous ventricular pacing in patients with AF has a stabilizing effect on the irregular ventricular rate during AF [18-21]. These studies suggested that right ventricular pacing, by inducing retrograde concealed atrioventricular nodal conduction, could eliminate short RR cycles during AF and may be used as a non-pharmacological means to control ventricular responses during AF [22]. The pacing rate had to be set above the mean ventricular rate to maximally suppress spontaneous ventricular activity. Previous studies have investigated the effect of ventricular overdrive pacing on rate control in patients with AF during the resting state [23,24], and during exercise with the aid of a computer with special heart rate stabilization algorithms [25]. However, these studies did not investigate the efficacy of rate stabilization during daily activity and over long-term follow-up. It is also generally accepted that control of the heart rate during AF requires values between 60 and 90 beats/min (bpm) [26].

The purpose of this study was to assess the efficacy of VVI pacing at 80 bpm for the reduction of tachy-AF episodes in the ventricle during a 3-month follow-up period, and to determine the value of the Actros S (Biotronik, Germany) heart rate histogram in controlling the ventricular rate in patients with AF.

Materials and Methods:

Fifty-five patients (27 male, 28 female; mean age 71 ± 8 years) with chronic AF (AF from 6 months to 5 years, mean 1.8 years) and intact AV node conduction were enrolled in the study. Because 9 patients were excluded from the study (the reasons are explained in the results), only data from 46 patients (20 male, 26 female; mean age 70 ± 8 years) were ultimately analyzed. The detailed patient demographics were described in an earlier publication [27]. Ejection fraction ranged from 22% to 80% with a mean of 62% ± 17%. Table 1 shows the clinical characteristics of the patients. The patients' antiarrhythmic medication remained unchanged during the entire course of this study.

All patients received Actros S pacemakers and either an SX 60-BP, TIR 60-BP, or PX 60-BP passive fixation, endocardial ventricular lead (Biotronik, Germany). Between 2 and 84 days (mean 26 ± 16 days) after pacemaker implantation, the mode was set to VVI with a basic rate of 40 bpm for one day. After the 1-day follow-up, the basic rate was switched to 80 bpm until 2-day follow-up. For the following 3 weeks the pacemaker programming was changed as described earlier in another publication [27]; the procedure was identical for each patient and the data served to support another aspect of the study. Then every pacemaker was reprogrammed to a basic rate of 80 bpm until the 3-month follow-up.

Data from the 1-day, 2-day, and 3-month follow-ups stored in the pacemaker memory were printed out. The following data from the various Actros S diagnostic memory functions were analyzed:

- Event counter data: percentage of ventricular paced events.

**Table 1. Clinical characteristics and drug therapy history of the 55 patients enrolled in the study. NYHA = New York Heart Association; CCS = Canadian Cardiac Society.**

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction past history</td>
<td>5</td>
</tr>
<tr>
<td>Stenocardia CCS-class I/II</td>
<td>10</td>
</tr>
<tr>
<td>Stenocardia CCS-class III/IV</td>
<td>0</td>
</tr>
<tr>
<td>Valvular heart disease with heart failure NYHA-class III/IV</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug therapy</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>25</td>
</tr>
<tr>
<td>β-blocker</td>
<td>37</td>
</tr>
<tr>
<td>Calcium&lt;sup&gt;2+&lt;/sup&gt; channel blocker</td>
<td>12</td>
</tr>
</tbody>
</table>
• Activity report data: mean of the ventricular rate
• Heart rate histogram data: percentages of ventricular rates over 88 bpm within certain heart rate ranges. The ventricular rhythm over 88 bpm was considered as tachy-AF.

The Wilcoxon matched pairs test was used to compare data from the 3-month follow-up with those from the 1-day and 2-day follow-up, respectively. The p-value < 0.05 was considered significant.

Results
From the original 55 patients, nine were subsequently excluded from the study due to night-time heart palpitations, resulting in pacemaker reprogramming to VVI mode with a basic rate of 80 bpm during the day and 70 bpm at night. Therefore, all results were calculated from data obtained from a total of 46 patients. The mean ventricular rate was significantly higher during VVI pacing at 80 bpm at the 3-month follow-up than during VVI pacing at 40 bpm at the 1-day follow-up (p-value < 0.01): the increase was between 13 bpm and 81 ± 3 bpm at both the 2-day follow-up and at the 3-month follow-up. The statistical testing of the mean ventricular rates from the 2-day follow-up versus the 3-month follow-up in VVI pacing at 80 bpm, respectively, resulted in a p-value of 0.73. Additionally, the mean percentage of ventricular pacing was the same for VVI pacing at 80 bpm at the 2-day follow-up as at the 3-month follow-up: 86% ± 16% and 86% ± 12% respectively (p-value = 0.93). For VVI pacing at 40 bpm at the 1-day follow-up the Vp was 7% ± 13%, which was significantly lower than VVI pacing at 80 bpm at the 3-month follow-up (p < 0.01). The means and standard deviation as well as the statistical results for both parameters are shown in Table 2.

The mean percentages of ventricular rates above 88 bpm in certain ranges during VVI pacing at 40 bpm and VVI pacing at 80 bpm are shown in Table 3. A significant reduction of ventricular rates in the three heart rate ranges between 88 – 120 bpm (88 – 96 bpm, 97 – 107 bpm, 108 – 120 bpm; p-value < 0.001, respectively) was found at the 3-month follow-up (VVI pacing at 80 bpm) compared to the 1-day follow-up (VVI pacing at 40 bpm). The p-value for the heart rate range between 121 and 137 bpm was < 0.06. The differences at higher heart rate ranges were not statistically significant, but there were only a few such rhythms at all pacing modes. There were no statistical differences in the percentages of ventricular rates in all heart rate ranges during VVI pacing at 80 bpm at the 2-day and 3-month follow-ups (p-values ranged between 0.11 and 0.81). A reduction of ventricular rates above 88 bpm, which were defined as tachy-AF episodes, was achieved for every patient during VVI pacing at 80 bpm at the 3-month follow-up as compared with VVI pacing at 40 bpm at the 1-day follow-up: 9% ± 9% versus 24% ± 16%, p-value < 0.05. The mean percentage of tachy-AF episodes during VVI pacing at 80 bpm during the 2-day follow-up was 13% ± 15%, but the difference was not significant compared to the 3-month follow-up (p-value = 0.59).

### Table 2. Comparison of VVI 80 (basic rate = 80 bpm) at 3-month follow-up with VVI 40 (basic rate = 40 bpm) at 1-day follow-up and VVI 80 at 2-day follow-up. Mean values and standard deviations are shown. Data are collected from the Actros S (Biotronik) pacemaker memory in 46 patients. Statistics: Wilcoxon matched pairs test; ** = p-value < 0.01.

<table>
<thead>
<tr>
<th>Mean ventricular rate (bpm)</th>
<th>VVI 40 1-day FU</th>
<th>VVI 80 2-day FU</th>
<th>VVI 80 3-month FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>88 – 96</td>
<td>9 ± 5 ***</td>
<td>4 ± 4</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>97 – 107</td>
<td>7 ± 5 ***</td>
<td>3 ± 4</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>108 – 120</td>
<td>5 ± 4 ***</td>
<td>2 ± 3</td>
<td>1 ± 2</td>
</tr>
<tr>
<td>121 – 137</td>
<td>3 ± 3 **</td>
<td>2 ± 2</td>
<td>1 ± 2</td>
</tr>
<tr>
<td>138 – 160</td>
<td>1 ± 2</td>
<td>1 ± 4</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>161 – 192</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>&gt; 192</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

### Table 3. Comparison of VVI 80 (basic rate = 80 bpm) at 3-month follow-up with VVI 40 (basic rate = 40 bpm) at 1-day follow-up and VVI 80 at 2-day follow-up. Mean values and standard deviations for different heart rate (HR) ranges over 88 bpm (tachy-AF) are shown. Data are collected from the Actros S (Biotronik) pacemaker memory in 46 patients. Statistics: Wilcoxon matched pairs test; *** = p-value < 0.001, ** = p < 0.06, * = p < 0.05.

<table>
<thead>
<tr>
<th>HR-Range (bpm)</th>
<th>VVI 40 1-day FU</th>
<th>VVI 80 2-day FU</th>
<th>VVI 80 3-month FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>88 – 96</td>
<td>24 ± 16 *</td>
<td>13 ± 15</td>
<td>9 ± 9</td>
</tr>
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</table>

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Discussion

According to prior studies which described ventricular overdrive pacing or special algorithms for heart rate stabilization in patients with chronic AF and intact AV nodal conduction, the percentage of ventricular pacing should be over 75% [17,23,25]. Algorithms with a low ventricular pacing rate did not result in a decrease of tachy-AF episodes in long-term follow-ups [26]. In this study, a high mean ventricular pacing rate of 86% was achieved in VVI pacing with a basic rate of 80 bpm at the 3-month follow-up as well as at the 1-day follow-up at approximately 1 month after implantation. Our previous published study results confirmed that rate regularization can be achieved using a pacing rate between the mean and maximum heart rate in patients with chronic AF [27]. Wittkampf noted a high correlation between pacing percentage, mean heart rate, and heart rate stability in AF [17]. Therefore, ventricular pacing rate retrieval from the Actros S memory function may be an indicator of rate stabilization in AF in long-term follow-up. The mechanism of rate control by ventricular pacing is believed to be caused by an induction of concealed VA conduction that reduces the frequency of antegrade conducted impulses [20,28].

Due to the high right ventricular pacing rate, we found a mean ventricular rate of 81 ± 3 bpm during VVI pacing at 80 bpm at the 3-month follow-up and at the 2-day follow-up, which was slightly higher than the basic rate. In contrast, the mean ventricular rate during VVI pacing at 40 bpm was significantly lower, but the mean value of 68 ± 10 bpm was only 13 bpm below the mean value during VVI pacing at 80 bpm. This difference should be tolerable in most patients, especially if the number of tachy-AF episodes can be reduced as discussed below.

In this study, right ventricular pacing at a basic rate of 80 bpm reduced tachy-AF episodes by half, by eliminating ventricular rates above 88 bpm, though only the ventricular rates in the ranges between 88 and 120 bpm were significant. In another, recently published part of this study, ventricular pacing was found to reduce the incidence of tachy-AF episodes in patients with chronic AF over the course of 7 days [27]. This study is one of the first to attempt to assess the influence of pacing for heart rate stabilization during normal daily activity over a long-term follow-up period of 3 months. Additionally, there were no statistical differences in the mean ventricular rate, percentage of ventricular pacing, and ventricular rates over all heart rate ranges during VVI pacing at 80 bpm between the 2-day and 3-month follow-up results. It seems that a short follow-up period of one day immediately after pacemaker implantation will be a good predictor for estimating the reduction of tachy-AF episodes for long-term follow-up. There does remain an unsolved question: What is the optimal pacing rate for patients with chronic AF? Maybe one-day results will be able to find "good responders" for rate stabilization during various pacing rates. This will allow physicians to set an individualized basic rate for each patient with chronic AF.

The effects of decreased tachy-AF episodes on symptoms such as palpitations and shortness of breath are unknown. Recent studies examined the effect of ventricular rate stabilization on hemodynamic parameters, demonstrating a trend towards improvement in cardiac output [29-33]. Very little is available in the literature regarding improvement in cardiac performance and/or survival as the result of heart rate control [34]. Some reports show a reversible effect of successful control of rapid heart rate on tachycardia-induced cardiomyopathy [35,36]. It is also well known that rhythm irregularity and tachy-AF rate effect cardiac contractility and cause decreased cardiac output [31]. Future studies should address the potential long-term quality of life and the effect on hemodynamic parameters. Ventricular pacing will never replace another non-pharmacological method of treating patients with chronic AF, AV junction ablation. Its efficacy has been proven by several randomized, controlled follow-up studies [37,38]. Although ablation has a very high success rate of more than 95%, it is not a risk-free method because it results in permanent tissue damage, has potential side effects, and can cause complications [34]. According to our study, perhaps 1-day results will enable a better selection of patients for "Ablate and Pace" therapy. We have to remember that right ventricular pacing at a basic rate of 80 bpm did not significantly reduce ventricular rates over 120 bpm as compared to VVI pacing at 40 bpm. Therefore, one-day results will help select candidates for long-term ventricular pacing at a basic rate of 80 bpm or for "Ablate and Pace" therapy.

Continuous pacing with a high percentage of ventricular pacing is necessary for ventricular rate stabilization. Right ventricular pacing from the apex results in asynchronous ventricular contraction and interventricular motion abnormalities with negative inotropic

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effects [39]. The influence of right ventricular pacing on left ventricle function and other stimulation sites, such as the right ventricular outflow tract, should be studied. An alternative pacing location is the left ventricle. It was also surmised that biventricular pacing improves the contraction synchrony of the left ventricle in cases of severe contractile dysfunction [40-43]. A fixed basic rate of 80 bpm might not provide the most appropriate pacing rate for all patients. An estimation of the most appropriate pacing rate for each patient needs further investigation in order to find the best pacing rate during AF. Perhaps one-day results (or even shorter periods) at various pacing rates will be a good predictor for finding the best pacing rate for each patient.

**Conclusion**

- Right ventricular pacing at 80 bpm significantly reduces tachy-AF episodes (> 88 bpm) in patients with chronic AF, during daily activity in the long-term period of 3 months.
- One-day results of the reduction of tachy-AF episodes in all heart rate ranges predict long-term 3-month results.
- Memory diagnostic functions (event counter and heart rate histogram) may be useful in estimating heart rate stability (percentage of ventricular pacing) and reduction of tachy-AF episodes during follow-up.

**References**


