Proarrhythmic Effect of Pacemaker Stimulation in Patients With Implanted Cardioverter-Defibrillators

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Background—We sought to determine the potential of right ventricular VVI backup pacing to induce ventricular tachyarrhythmias in patients with implanted cardioverter-defibrillators.

Methods and Results—All consecutive patients presenting exclusively with pacemaker-induced tachycardias (PITs) were included in a prospective study using a crossover protocol. Patients were randomized to either group 1 (augmentation of the baseline frequency of the pacemaker to 60 bpm) or group 2 (pacemaker turned off) and were followed up for 1 year and then crossed over to the other programming, looking for reoccurrence of PIT. Of 150 consecutive patients, 39 (26%) had PIT, 13 of them exclusively (8.6%). Forty of 1063 analyzed tachyarrhythmias of all the patients were PIT (3%). Before inclusion in the study, the patients had 2.7±0.9 PITs in 11±6.5 months with their pacemakers programmed empirically at 42.3 bpm. During the study phase, no PIT occurred while the pacemaker was turned off, whereas programming to 60 bpm led to the recurrence of PIT in 5 of 6 patients (1.4±0.6 per patient). At the end of the study, 9 patients underwent a prolonged follow-up with their pacemakers turned off, resulting in spontaneous episodes of ventricular tachycardia/fibrillation in 5 patients, but PITs were no longer observed.

Conclusions—This crossover protocol proves the potential proarrhythmic effect of pacemaker stimulation in implantable cardioverter-defibrillator patients. Resulting PITs led to clinical symptoms and antitachycardia therapy by the implantable cardioverter-defibrillator. Thus, in patients presenting with PIT but without a pacemaker indication, the pacemaker feature should be turned off, or, alternatively, the longest possible escape interval should be programmed. (Circulation. 2003;108:192-197.)

Key Words: electrical stimulation ■ tachyarrhythmias ■ pacing ■ cardioverter-defibrillator

Third-generation implantable cardioverter-defibrillators (ICDs) from all manufacturers incorporate a pacemaker feature for bradycardia therapy. The necessity of such a feature is derived from the occurrence of postdefibrillation bradycardia.1–3 In patients without a recognized indication for a pacemaker, the benefit of this feature remains unclear. Conversely, there have been reports on the occurrence of so-called pacemaker-induced ventricular tachycardia/fibrillation (PIT) in ICD patients with an otherwise faultless bradycardia pacing feature.4,5 Similar cases have been reported in patients provided with regular pacemakers.6–8 We are unaware of a study that addresses the question of whether these are actually cases of ventricular tachycardia/fibrillation (VT/VF) induced by a single pacemaker impulse or whether this is a casual coincidence of pacemaker stimulation and arrhythmia and, hence, the arrhythmia would have occurred even without ventricular stimulation.4,6–9

Using a crossover procedure, we identified the first case of a PIT at our hospital in February 1993 and subsequently developed the defining criteria for pacemaker-induced VT/VF as well as the following study design.

The aim of this randomized, crossover study, therefore, was to prove a proarrhythmic effect of right ventricular VVI-backup pacing in patients with an ICD.

Methods

Patients

Between February 1993 and December 1997, all patients showing exclusively the phenomenon of a PIT caused by right ventricular backup pacing were enrolled in the study. Patients showing PIT and spontaneous VT/VF in the course of the study were excluded from the evaluation. This strict selection process largely excluded the possibility that the documented episodes of VT/VF were a mere coincidence of ventricular stimulation and spontaneous arrhythmia.

Other criteria for enrollment were as follows: (1) documentation of VT/VF in stored electrograms showing the start of the tachycardia, (2) faultless functioning of pacemaker feature and ICD (especially no sensing problems at follow-up), and (3) written informed consent. Exclusion criteria were age <18 years, a recognized pacemaker indication according to American Heart Associa-
tion/American College of Cardiology guidelines, a myocardial infarction or coronary revascularization (bypass surgery or angioplasty) in the course of the study, or progression to NYHA stage IV heart failure. For the analysis, nonsustained VT/VF episodes and inappropriate shock discharges were not taken into consideration.

Pacemaker and ICD Programming
The pulse amplitude for pacemaker stimulation was set at double the pacing threshold with a pulse width of 0.4 ms. The sensitivity was usually programmed at nominal values (0.28 mV, Guidant and 0.3 mV, Medtronic). The tachycardia detection rate was programmed depending on the patients’ needs (mean, 156–190 bpm). Duration of detection was set at 1 second for the VF zone and 5 seconds for the VT zone. In the VT zone, burst, scan, and ramp therapy were all admissible.

Study Protocol
The baseline frequency of the pacemaker was initially set at an empirical value of 40 to 50 bpm. After a reproducible PIT phenomenon had been documented (≥2 episodes per patient), patients were randomly assigned to 1 of 2 study groups: in group 1, the baseline frequency of the pacemaker was elevated to 60 bpm; in group 2, the pacemakers were switched off. After 12 months, the baseline frequency was reprogrammed in a crossover procedure (Figure 1), and the patients were followed for another 12 months. The end point was defined as the occurrence of a PIT.

During the follow-up, all patients were seen in our outpatient clinic every 3 to 4 months for physical check-ups, ICD interrogation, and a function test of the device. The latter evaluated battery status, pacing threshold, pacing and defibrillation lead impedance, and if applicable, frequency of ventricular pacing since the last visit. Intracardial and body surface ECGs were recorded simultaneously to document the morphology of spontaneous and effectively paced ventricular rhythms. Episode data, including event counters and stored electrograms, were interrogated, documented on printout and a patient’s disk, and subsequently deleted. Each patient underwent annual echocardiography. At the end of the study, patients were followed up for another period of 24 months looking for episodes of spontaneous VT/VF.

Randomized reprogramming of the pacemaker baseline frequency for PIT prevention was approved by the Ethics Commission of Medical Council in Rheinland-Pfalz, Germany.

Implanted Electrodes and ICDs
Patients enrolled in the study received transvenously implanted electrodes from Medtronic or Endotak electrodes from Guidant allowing either unipolar or integrated bipolar pacing. Single-chamber ICDs from Guidant and Medtronic were implanted.

Definition of PIT
An episode of VT was considered to be pacemaker induced if the onset was after a single visible and effective pacemaker stimulus. The stimulus was considered effective if the morphology of the intracardial QRS complex was identical to the morphology of QRS complexes proven to be of effective ventricular stimulation through cross-checking with the surface ECG during previous follow-up visits. In addition, the stimulated ventricular complex was required to show a change of morphology on the intracardial ECG compared with the morphology of the tachycardia and of normal rhythm (sinus rhythm or atrial fibrillation) (Figures 2 and 3).

If the pacemaker impulse was not visible (Figure 3), the pause before the onset of tachycardia was required to correspond with the programmed escape interval. Furthermore, the QRS complex after the pause had to show a morphology identical to that of QRS complexes of proven effective ventricular stimulation.

Episodes were not defined as PIT if ≥1 consecutive effective ventricular pacemaker stimulus preceded the onset of the tachycardia.

Statistical Analysis
The statistical analysis was performed using McNemar’s test and Student’s t test.

Results
Regarding cardiac and noncardiac diseases and indications for device implantation, patients enrolled in this study represent a typical cross section of ICD patients (Table 1). The ejection fractions before randomization and at conclusion of the study were similar in our patients (36.5±7.6% versus 35.4±5.2%).

Incidence of Ventricular Stimulation
Before randomization, ventricular stimulation was ≥1% (maximum, 5%) in 7 of 9 patients and <1% in 2 patients with ICDs from Guidant. The average number of ventricular
stimuli in patients with devices from Medtronic was 36,117 ± 38,277 per month. Hence, (sporadic) ventricular stimulation in ICD patients without an indication for a pacemaker occurs frequently.

Incidence of PIT Episodes
Using the criteria outlined above, we identified a total of 39 patients (26%) of 150 of our overall patient cohort with appropriate therapy delivery showing a PIT phenomenon. In 26 of these patients, PIT (n = 67) occurred in addition to spontaneous episodes of VT/VF (n = 158). The 13 patients enrolled in this study (8.6% of 150) showed only PIT; episodes of spontaneous VT/VF were not observed. Of the 1063 analyzed episodes of sustained VT/VF, 40 episodes (3%) were pacemaker-induced.

During the screening period of 11 ± 6.5 months before randomization, 40 episodes of VT/VF occurred in our study group (mean, 2.7 ± 0.92 PITs per patient; minimum 2, maximum 5 episodes) with the baseline frequency of the pacemaker set empirically at 40 bpm in 10 patients and at 50 bpm in 3.

Incidence of PIT After Pacemaker Reprogramming
According to randomization (Figure 1), the baseline frequency of the pacemaker of the 6 patients in group 1 was increased from 42.3 ± 4.4 to 60 bpm. During the following 12 months, 5 of 6 patients continued to experience appropriate therapy delivery. Without exception, all treated tachyarrhythmias were PIT episodes resulting in an average of 1.4 ± 0.6 PITs per patient (minimum 1, maximum 3). In 1 patient, no episodes of VT/VF were seen. This patient never exhibited a ventricular arrhythmia in the total period of observation spanning 36 months after conclusion of the crossover phase. Thus, in this case, it cannot be proved whether the absence of VT/VF was caused solely by increasing the baseline frequency.

No episodes of VT/VF were recorded in group 2 patients, ie, with the bradycardia therapy deactivated.

Five patients in group 1 and 3 patients in group 2 underwent the crossover procedure. One patient in group 1 died of progressive heart failure before crossover. Two patients in group 2 withdrew their consent because of concern about the possibility of shock delivery (hence, pacemakers

Figure 2. Initiation of spontaneous and pacemaker-induced polymorphic VT. After pause 1 (1470 ms), sinus rhythm returns. Pause 2 with consecutive ventricular stimulation leads to a ventricular run. Pause 3 (1290 ms) is followed by 1 sinus beat and thereafter a nonsustained VT. After pause 5 and consecutive pacemaker stimulation, a sustained polymorphic VT is initiated. QRS morphologies of spontaneous tachycardia and PIT are similar; thus, it remains unclear whether sustained VT is a result of ventricular stimulation or would have occurred even without. PVCs, couplets, or runs occur after every paced beat.

Figure 3. Six and 8 months after ICD implantation, 2 PITs occurred (study enrollment), of which 1 is displayed in A. At 39 (B) and 40 (C) months after implantation (prolonged follow-up, pacemaker off), spontaneous monomorphic VTs are documented. Decrease of PQ interval at onset of VT proved atrioventricular dissociation and hence a ventricular arrhythmia. N indicates normal sinus rhythm; S, short interval; L, long interval; arrow, p wave.
In all 40 PIT episodes, a pause of exclusively PIT. During this period, an average of 1.3 patients in group 2 showed tachyarrhythmias that were frequency reprogrammed at 60 bpm), each of the 3 remaining patients in group 2 showed tachyarrhythmias that were exclusively PIT. During this period, an average of 1.3±0.4 (minimum 1, maximum 2) episodes per patient was observed. In these cases, the pacemaker was turned off for the additional observation period after crossover.

In summary, the incidence of PIT at a pacemaker baseline frequency of 42.3 bpm was 100% (enrollment criterion); at a baseline frequency of 60 bpm, it was reduced to 89% (P>0.05), and the incidence went down to 0% when the pacemaker was switched off (P<0.001 compared with initial pacemaker programming as well as baseline frequency of 60 bpm).

During follow-up, none of the patients with their pacemakers deactivated suffered a syncope that was not a result of a tachyarrhythmia.

**Characteristics of PIT Episodes**

In all 40 PIT episodes, a pause of ≥1200 ms was observed at the onset of tachycardia; in 26 cases (65%) after ≥1 PVC, in 8 cases during bradycardia in atrial fibrillation, and in 6 cases during sinus bradycardia. Of the PIT episodes, 80% (32 episodes) were polymorphic VT or VF, and 20% displayed a monomorphic VT.

**Characteristics of Spontaneous Episodes After Conclusion of the Study**

After conclusion of the crossover phase, the pacemakers of 8 of the remaining 9 patients were deactivated, and the patients were followed up for another 24 months to identify cases of spontaneous ventricular arrhythmia. In 5 of the patients (55.6%), a total of 26 spontaneous VT/VF episodes were seen by the end of the prolonged follow-up. Of the 26 episodes, 19 (73%) were monomorphic VT; the other tachyarrhythmias were episodes of polymorphic VT or VF. Only 2 of these cases (7.7%;) had a pause of ≥1000 ms at the onset of the tachycardia: 1 case of bradycardia in atrial fibrillation and 1 case of sinus bradycardia. In 14 episodes (53.8%), the tachycardia began suddenly, ie, without a preceding pause (Figure 3C), and in the other 10 cases (38.5%), either a short-long-short or a short-short-(short)-long-short sequence was seen at onset. The average “long interval” in these episodes was 833±131 ms (minimum 520, maximum 961 ms). In 4 patients, no spontaneous VT/VF episodes were seen.

**Comparison of Spontaneous Tachycardia and PIT**

The intraindividual analysis of spontaneous tachycardia and PIT in 5 patients (Table 2) showed a more frequent occurrence of polymorphic VT or VF in PIT (84%) compared with spontaneous VT/VF (27%; P<0.05). A significantly higher frequency was also shown for the occurrence of a pause after an ectopic ventricular beat, couplets and triplets in cases of PIT.

**Discussion**

So far, the phenomenon of pacemaker-induced tachyarrhythmias has been described only in case reports, in which it was seen by chance on the surface ECG in pacemaker patients or on stored ECGs in ICD patients. However, previous publications have not yet defined criteria for PIT. VTs were assumed to be pacemaker induced if they occurred immediately after a pacemaker stimulus. The analysis of the corresponding published ECGs reveals that in most cases, the morphology of the QRS complex after ventricular stimulation and that of the induced tachycardia are identical or highly similar, suggesting a fusion beat or ineffective ventricular pacing (Figure 2 of Lefroy et al,10 Figure 3 of Roelke et al,4 Figures 1 to 4 of Karbenn et al.7 Figure 4 of Zehender et al9).

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=6)</th>
<th>Group 2 (n=7)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.5±16.2</td>
<td>56.0±9.1</td>
<td>NS</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>4/6 (67)</td>
<td>3/7 (43)</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2/6 (33)</td>
<td>3/7 (43)</td>
<td>NS</td>
</tr>
<tr>
<td>Long-QT syndrome</td>
<td>0</td>
<td>1/7 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction (echocardiography), %</td>
<td>36.5±7.6</td>
<td>35.4±5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Resuscitated</td>
<td>4/6 (67)</td>
<td>5/7 (71)</td>
<td>NS</td>
</tr>
<tr>
<td>Documented VT</td>
<td>2/6 (33)</td>
<td>2/7 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial pacemaker baseline frequency</td>
<td>42.3±5.2</td>
<td>41.6±4.9</td>
<td>NS</td>
</tr>
<tr>
<td>No. of PITs per patient</td>
<td>3.0±1.1</td>
<td>2.4±0.84</td>
<td>NS</td>
</tr>
<tr>
<td>ICD implantation: study enrollment, mo</td>
<td>10.2±5.3</td>
<td>11.7±7.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are n (%) or mean±SD.

remained off), another patient was lost to follow-up 11 months after randomization because of a change of address, and 1 patient died after valve surgery 13 months after study enrollment.

None of the 5 patients in group 1 had episodes of sustained ventricular arrhythmia after crossover (pacemaker turned off). In contrast, after crossover (pacemaker baseline frequency reprogrammed at 60 bpm), each of the 3 remaining patients in group 2 showed tachyarrhythmias that were exclusively PIT. During this period, an average of 1.3±0.4 (minimum 1, maximum 2) episodes per patient was observed. In these cases, the pacemaker was turned off for the additional observation period after crossover.

In summary, the incidence of PIT at a pacemaker baseline frequency of 42.3 bpm was 100% (enrollment criterion); at a baseline frequency of 60 bpm, it was reduced to 89% (P>0.05), and the incidence went down to 0% when the pacemaker was switched off (P<0.001 compared with initial pacemaker programming as well as baseline frequency of 60 bpm).

During follow-up, none of the patients with their pacemakers deactivated suffered a syncope that was not a result of a tachyarrhythmia.

### Table 2. Intraindividual Comparison of Pacemaker-Induced and Spontaneous VTs

<table>
<thead>
<tr>
<th></th>
<th>Pacemaker-Induced VT/VF (n=20)</th>
<th>Spontaneous VT/VF (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden onset without pause</td>
<td>0/20</td>
<td>14/26 (54)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Onset with pause after PVC, couplet or triplet</td>
<td>13/20 (65)</td>
<td>10/26 (38)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pause ≥1000 ms in sinus rhythm or atrial fibrillation</td>
<td>7/20 (35)</td>
<td>2/26 (7.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of pause after PVC, couplet, or triplet, ms</td>
<td>1418±175</td>
<td>833±131 (n=12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Polymorphic VT or VF</td>
<td>16/20 (80)</td>
<td>7/26 (27)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Monomorphic VT</td>
<td>4/20 (20)</td>
<td>19/26 (73)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Therefore, the occurrence of a spontaneous tachycardia in these cases is a possibility that cannot be excluded with certainty. Because of the similarity of QRS morphologies, it would otherwise have to be assumed that the VTs originated exclusively from the localization of the electrode tip. Other published ECGs, including our own example, however, cannot prove without a doubt that the tachycardia was mediated by the stimulated impulse, because VTs with the same morphology had also occurred in the absence of a preceding pacemaker stimulation (Figure 1 of Callans et al,6 Figures 1 and 2 of Goldman et al,8 Figures 5 and 6 of Zehender et al).

For the first time, our randomized crossover study with highly selected patients exhibiting only PIT could show that sustained ventricular arrhythmias no longer occurred after the pacemaker feature was deactivated. Reactivating the feature led to a resurgence of exclusively pacemaker-induced tachyarrhythmias. Therefore, it can be asserted that the stimulated impulse was actually responsible for the induction of the VT/VF in these cases and that the arrhythmia did not occur coincidentally with the ventricular stimulation. In our view, this clearly proves a proarhythmic effect of antibradycardia backup pacing.

The pathophysiology of PIT is still unclear, and it will not be clarified through this study. However, it appears obvious that a pause followed by a ventricular stimulus is to be held responsible. Earlier studies have shown that a sudden pause and a short-long-short sequence cause dispersion of the ventricular refractory period, which is regarded as a prerequisite for ventricular arrhythmia.11–15 If the pacemaker feature was deactivated. Reactivating the feature led to a resurgence of exclusively pacemaker-induced tachyarrhythmias. Therefore, it can be asserted that the stimulated impulse was actually responsible for the induction of the VT/VF in these cases and that the arrhythmia did not occur coincidentally with the ventricular stimulation. In our view, this clearly proves a proarhythmic effect of antibradycardia backup pacing.

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Nevertheless, it must be assumed that a pause with a consecutive ventricular stimulation is not the sole cause of PIT. The large number of ventricular stimuli per year, as high as 350,000, is several times higher than the PIT incidence of 2 to 5 episodes per year as documented in our study. Therefore, it seems that PIT, like spontaneous VT/VF, can occur only in a setting of additional factors promoting electrical instability (eg, ischemia, electrolyte imbalance, influence of the autonomic nervous system). A pause occurring at this very moment with a consecutive ventricular stimulus could destabilize the ventricle to such an extent that a VT results that would not have occurred spontaneously. The more often a ventricle is paced, the higher is the chance of accidental coincidence of electrical instability and proarhythmic ventricular stimulation.

Our investigation shows that the incidence of PIT was similar at escape intervals of 1000 and 1500 ms. Thus, the duration of the pause seems to be of minor relevance for the occurrence of PIT (Figures 1 and 2).

On the basis of our results and the following reasoning, one may presume that it is not the pause but rather the ventricular stimulation that is the responsible proarhythmic factor. First, a pause >1000 ms at the start of tachycardia was rarely documented during spontaneous VT/VF episodes (7.7%; Table 2). Second, it is very likely that pauses >1000 ms also occurred after the pacemaker feature was switched off. This, however, did not lead to VT/VF during crossover. It is therefore doubtful that a long pause plays a crucial role in the origin of the PIT phenomenon. In an attempt to answer that question, a prospective randomized study (Prevent Study) is currently under way testing special algorithms such as frequency smoothing, which shortens the pause after an ectopic beat or after a sudden drop in frequency.

Practical Suggestions

Recipients of ICDs with documented PIT should have the pacemaker feature switched off when possible (not postshock stimulation). As an alternative, the baseline frequency could be programmed as low as possible or the hysteresis may be programmed at 30 bpm where applicable. Frequency-smoothing algorithms should be programmed only in patients with syncope and a documented sudden drop in frequency.

In patients with implantable pacemakers, the rate of sudden cardiac death is 23% of all deaths, which is much higher than that in comparable cohorts without pacemakers.8 Several pacemaker recipients have structural heart disease, and PITs may occur that lead to lethal tachyarrhythmias in these patients. Therefore, with the results of the MADIT II study in mind, we recommend that for patients with paroxysmal bradycardia and structural heart disease with depressed left ventricular function, the indication for the implantation of an ICD instead of a pacemaker should be discussed.16

Limitations

The study described was performed as a prospective and randomized crossover study but was not designed as a multicenter investigation. Primarily endocardial electrodes that allow for integrated bipolar stimulation were used in this study. Exclusive bipolar stimulation could have altered the incidence of PIT. Pauses not associated with the start of an episode of tachycardia did not appear on stored ICD electrograms. Therefore, the assumption that pauses of duration >1000 to 1500 ms continued to occur after the pacemaker was switched off is speculation. Future investigations may avoid this disadvantage by using subthreshold ventricular stimulation (pseudopacing) and hence prove the existence of pauses.

In our investigation, statistical significance was not achieved for the reduction of the PIT incidence by increment of the pacemaker baseline frequency. The number of patients in the group may not be sufficient to allow for a clear statistical analysis.

This study could not analyze the relationship between the incidence of ventricular stimulation and the incidence of PIT on the basis of characteristics of counteralgorithms (Guidant, Medtronic).

Why PITs occur only in some patients and what the risk factors might be for pacemaker-induced arrhythmias remains unclear.
References

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