Incidence of ventricular tachyarrhythmias during permanent pacemaker therapy in low-risk patients results from the German multicentre EVENTS study

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Received 23 October 2006; revised 6 May 2007; accepted 18 May 2007; online publish-ahead-of-print 18 July 2007

Aims Current studies found an incidence of 12–31% ventricular tachyarrhythmias and sudden cardiac death during cardiac pacing months or even years after pacemaker insertion. MADIT2 and MUSTT13 demonstrated that patients with poor LV function after myocardial infarction (MI) showing non-sustained ventricular tachycardia (nsVT) and inducibility during electrophysiologic testing benefit from an ICD. The present study was dedicated to assess the global incidence of non-sustained ventricular arrhythmias in a general population of pacemaker patients. Special regard was on patients with a potential ICD indication, e.g. those matching the MADIT/MUSTT criteria.

Methods and results Two hundred and thirty-one patients (72 ± 11 years; 134 men) with an indication for dual chamber pacing entered the study. In all patients pacemaker systems capable of automatic storing of intracardiac electrocardiograms were implanted (Pulsar®, Discovery®, Guidant). Follow-up time was 15 months after inclusion. In 54 (25.7%) of 210 patients with at least one follow-up, episodes of nsVT were documented by stored electrocardiograms (up to 30 beats, >200 b.p.m.). Multiple—up to nine—episodes of ventricular tachycardia were retrieved in 31 of these patients. Three out of 14 patients with an LVEF <40% after MI presented nsVT during the follow-up. One of these patients received an ICD.

Conclusion A significant number of pacemaker patients present with ventricular tachycardia. Intracardiac electrocardiograms and alert functions from pacemakers may enhance physicians’ awareness of the patient’s intrinsic arrhythmic profile and help uncover underlying mechanisms of arrhythmias by storing the initiation of the arrhythmia.

KEYWORDS
Ventricular arrhythmia; Pacemaker; Sudden death

Introduction
The cause of death in patients with an implanted pacemaker continues to be of considerable clinical importance since it is generally accepted that cardiac pacing markedly improves prognosis and quality of life in patients with severe disorders of impulse formation and conduction independent of the underlying heart disease.1–4 Studies reported an incidence of malignant ventricular tachyarrhythmias and sudden cardiac death during cardiac pacing of 12–31% of patients months or even years after pacemaker insertion.5–8 Since in patients with coronary artery disease or congestive heart failure, death often results from ventricular arrhythmias (25–40% of cases), death of patients with pacemakers is frequently considered to be the result of the progression of the underlying heart disease.

On the other hand, it has also been well recognized that pacing impulse formation may deleteriously interact with spontaneous cardiac depolarization due to sense, pace, or accidental inhibition defects of the pacemaker and consequently may generate malignant arrhythmias.9–11

The EVENTS study was dedicated to assess the global incidence of ventricular arrhythmias in paced patients with special regard to those patients matching the MADIT/MUSTT criteria [e.g. non-sustained ventricular tachycardia (nsVT)] and the potential need for ICD implantation.

Methods
Patient population
A total population of 231 consecutive patients (mean age 72 ± 11 years; 134 men) admitted to 20 German study centres with the approved indication for a dual-chamber pacemaker implantation entered the study between 1998 and 2000. The study protocol was approved by the Ethical Board of the Freiburger Ethikkommission International and all patients had given written consent before entering the prospective study. Patient characteristics at the time of implant are shown in Table 1.

In each patient, standardized assessment of medical history and clinical data were performed at admission. During the first 24 h
after admission, a standard investigational protocol was performed including 12-lead surface electrocardiogram (EGM), a 24 h Holter recording when appropriate, and a two-dimensional echocardiography or cardiac catheterization at the beginning and at the end of the study (Table 2).

Measurements and definitions

In all patients, a dual-chamber pacemaker system was implanted and programmed to store a maximum of 40 s (up to eight episodes of 5 s) of intracardiac atrial and ventricular EGMs simultaneously initiated by triggering on fast ventricular depolarizations. An arrhythmic event was classified and stored as VT when the programmed rate (>120 b.p.m.) and duration (four ventricular cycles) as well as the atrial/ventricular rate ratio criterion (ventricular rate > atrial rate) was met. If more than eight episodes were stored, previous episodes were replaced by the latest rhythm event (‘first in-first out’).

Pacemaker function, content of pacemaker storage (intracardiac EGMs, arrhythmia log book, histograms, counters), and clinical history (syncope, myocardial infarction (MI), heart failure, angina pectoris, medication) were regularly assessed at 3, 9, and 15 months. Every patient ≥18 years with a dual-chamber pacemaker capable of automatic storing of intracardiac EGMs (Pulsar®, Discovery®; Guidant Corp., St Paul, MN, USA) with written informed consent could be enrolled. Patients were not eligible when either persistent or present atrial fibrillation was present or an indication for ICD implantation according to the AHA/ACC guidelines was given.

Electrocardiogram analysis

Taking into consideration that the trigger event (the so-called ‘onset’) was not stored by the pacemaker system, the EGMs were analysed as follows.

1. nsVT was diagnosed if a minimum of three visible fast ventricular cycles and atrioventricular dissociation (ventricular rate > atrial rate) were stored after the programmed trigger (four cycles of >120 b.p.m.).
2. nsVT was defined as unproven if just one or two fast ventricular cycles were stored after the trigger of four fast cycles had been met (‘nsVT only with onset’).
3. EGMs were classified as atrial fibrillation or atrial flutter if fast atrial activity in the atrial channel of the system transmitted fast irregular ventricular response (all AF episodes were longer than the programmed storage capacity of 5 s per episode).

4. EGMs were classified as supraventricular tachycardia (sinus tachycardia or atrial focus) if atrial activity of more than 100 b.p.m. transmitted ventricular 1:1 conduction.
5. EGMs were classified as sinus rhythm if atrial activity transmitted ventricular 1:1 conduction of less than 100 b.p.m.

Statistical methodology/sample size

Up to now, there are no reliable data on the incidence of VT in pacemaker patients. Thus, the sample size for the EVENTS study was set ad hoc to 200 patients. Expecting a 10–25% incidence of patients with EGM-proven nsVT, this sample size corresponds with a two-sided confidence interval in the range of ±5%. (Pearson–Clopper method for a sample size of 200 patients: incidence 10%; CI 6.2–15.0/15%: 10.4–20.7/20%: 14.7–26.2/25%: 19.2–31.6.) This range was considered to be relevant and acceptable.

Event free survival rates were analysed according to the Kaplan–Meier method.

Results

A total number of 231 patients were enrolled into the study. Twenty-one patients withdrew their consent, died, or were lost of follow-up before the first follow-up. Thus, 210 patients with at least one follow-up could be analysed. Out of these, 151 patients (72%) completed the follow-up of 15 months, 31 patients (15%) could be followed for 9 months and 28 patients (13%) for 3 months. The median follow-up was 451 days (inter-quartile range: 304–476 days).

A total number of 3263 intracardiac EGMs were stored in these patients by the pacemaker, triggered by the preset definition and subsequently retrieved from the arrhythmia logbook. 2520 EGMs underwent systematic analysis, 743 EGMs were not further processed because of missing print-outs (e.g. only one representative EGM was sent in for analysis), low quality, or artefacts.

Electrocardiogram analysis

The pacemaker storage capacity was completely used in 69% (storage of eight EGMs) of cases. Ventricular arrhythmias were documented in 348 (14%) of all analysed EGMs (proven nsVT: 135, unproven nsVT: 67, couplets/VPB: 146; definitions see Methods); proven nsVT were diagnosed in 54 patients.

Four hundred and thirty-seven recordings (17%) displayed atrial flutter or other supraventricular arrhythmias after the trigger had been met. Atrial fibrillation in each case exceeding the programmed EGM duration of 5 s was found in 617 of the documented EGMs (24%). In 20 EGMs (1%), ventricular
oversensing was seen and in 1.098 EGMs (44%), no arrhythmia could be verified (EGM showing normal sinus rhythm), either due to arrhythmias not exceeding the onset portion or due to unspecific storage.

Ventricular tachycardia

With respect to the defined classification criteria, 202 EGM recordings were revealed during the follow-up of 13 ± 5 months showing ventricular tachycardia with different levels of complexity. Because of the study design, no differentiation could be made between sustained or nsVT if the stored episode was longer than 5 s. As a major result of the present study, in a subset of 54 patients (25.7% of all patients, 95% CI 19.95–32.18) with a mean age of 74 years (65% men), a total number of 135 episodes of nsVT, or 5 s (Figure 1) or > 5 s (Figure 2) occurred. In one patient, an episode of > 30 beats was documented (EGM length 10 s). In 54 non-sustained episodes (26%), the duration of ventricular tachycardia was more than eight cycles and in 43 episodes (21%) > 10 cycles. A subset of EGMs revealed ventricular tachycardia lasting at least 5 s (programmed storage capacity in this study for a single event). Owing to storage limitation, further differentiation between sustained (> 30 s) and non-sustained (< 30 s) VT could not be made. Rate evaluation revealed in 13% of patients nsVT exceeding 175 b.p.m. and in 4% nsVT exceeding 200 b.p.m. Descriptive classification of ventricular tachycardia is given in Figure 3. The overall incidence of EGM documented ventricular tachycardia (non-sustained or > 5 s duration) during the observation period of 450 days was 25.7% and is shown in the Kaplan–Meier-curve (Figure 4). The increased number of nsVT documentation close before each follow-up may be due to the pacemaker storage algorithm (new episodes overwrite older ones).

In 31 patients, recurrent episodes of ventricular tachycardia were retrieved with up to nine episodes in the same individual. Forty patients (74%) suffered from a maximum of three episodes and 14 patients (26%) from more than four episodes of ventricular tachycardia during follow-up.

Clinical risk factors for ventricular arrhythmias

Coronary artery disease

In the group of patients suffering ventricular tachycardia, 17 patients (32%) had a clinically relevant coronary artery disease with a history of MI in six patients (11%). Conversely, in the group of patients with no documented ventricular tachycardia (156 patients), coronary artery disease occurred in 61 patients (39%) of whom 26 patients had a history of MI.

Left ventricular ejection fraction

The left ventricular ejection fraction (LVEF) was estimated by means of echocardiography or left ventriculography in 195/210 patients at the beginning and in 134/151 patients at the end of the study. The mean ejection fraction in the...
Discussion

The present study followed the concept of systematic evaluation of a consecutive pacemaker population for spontaneous ventricular arrhythmias. Dual chamber sensing and diagnostic algorithms in modern pacemaker devices provide a valuable tool for systematic arrhythmia evaluation.

On the basis of stored intracardiac EGMs supported by data from the arrhythmia log book, histograms, and counters, the implanted pacemakers were able to identify a subset of patients suffering from ventricular tachycardias with an incidence of 26% compared with 5% in a normal population. Furthermore, the study was able not only to quantify the episodes but also to qualify the arrhythmia by means of the stored intracardiac EGMs.

Most electrograms showed slow nsVT (<200 b.p.m.), an observation that could be explained by either the preserved LVEF in most patients or the high sensitivity of the pacemaker programming (setup trigger 120 b.p.m.).

Interestingly, only in a few number of the individuals with ventricular arrhythmias, known cardiac risk factors (e.g. LV dysfunction, MI) were present. Thus, the majority of patients in the arrhythmia group did not match the MADIT/MUSTT criteria and consequently would have not been considered as a high-risk group. The population equals a common pacemaker population in which 26% of patients would have required further cardiac evaluation, e.g. coronary angiography, EP study, and possibly ICD implantation. Thus, the data strongly indicate that patients eligible for pacemaker implantation due to electrical disorders of the heart need to be stratified for underlying heart disease as a potential cause of future ventricular arrhythmias and subsequent sudden cardiac death prior to insertion of the device. In particular, as modern concepts of combined pacing modalities are available (ICD, cardiac resynchronization), sufficient information of the patients’ cardiac status is mandatory for most benefit and safety.

Although it is known from studies and case reports that up to 20% of deaths during permanent pacemaker therapy are related to fatal interaction of spontaneous rhythm and arrhythmias with pacemaker activity, the present study was not designed to verify the concept of pacemaker induced ventricular arrhythmias: due to the storage mode of the pacemaker, the initiation of the arrhythmic event was not documented. Consequently, possible interaction between the device and the spontaneous cardiac rhythm in the studied patient group can only be speculative. Meanwhile, this lack of diagnostic capacity has been overcome in new-generation pacemakers that also provide information on the onset portion of the stored arrhythmia.

Matching to MADIT/MUSTT criteria

None of the patients completely matched the MADIT criteria (post-MI, reduced LVEF, nsVT, inducibility in EP study) when entering the EVENTS study.

In 14/32 post-MI patients, the LVEF was ≤40%. During the follow-up period in three of these patients (21%), nsVT were uncovered by pacemaker-stored EGM, recommending further evaluation for ICD indication. One of these patients fulfilling the main MADIT criteria additionally presented with symptomatic arrhythmias and was subsequently implanted with an ICD, the second one was not inducible in the EP study, and the third patient underwent heart transplant only a few months after enrolment, both getting no ICD.

Conclusion and clinical implications

In summary, a significant number of pacemaker patients present with non-fatal ventricular arrhythmias. Particularly, patients with poor LV function after MI often show nsVT, thus potentially being candidates for an ICD.

Intracardiac EGMs and alert functions from pacemakers may enhance physicians’ awareness of the patient’s intrinsic arrhythmic profile (ventricular and atrial) and may help uncover underlying mechanisms of arrhythmias.

Existing heart disease did not seem to predict arrhythmia in the general pacemaker population. However, it may be advisable to complete pre-implantation risk assessment and continuous arrhythmic risk evaluation in routine pacemaker patients and even more in patients receiving multifunctional therapeutic platforms which increasingly are available (e.g. cardiac resynchronization by LV pacing). Extended and reliable EGM storage and capacity will be a powerful tool in this assessment.
Limitations of the study

High-quality EGMs could be captured in the present study, anyhow concessions had to be made to the extension of the stored EGMs in which the onset of the arrhythmia generally was not documented. Thus, the initiating mechanisms like short–long–short phenomena, spontaneously arising VT, or fatal interactions of the pacemaker stimulus with spontaneous electrical activity of the myocardium could not be differentiated. The influence of the pacing frequency on the LVEF was not evaluated in this study.

The EVENTS study was primarily designed to screen a general unselected pacemaker population for ventricular tachyarrhythmias. Thus, the incidence of nsVT in high-risk patients (low LVEF ≤ 40% after MI) could only be evaluated in a subgroup of the total study population.

Conflict of interest: The EVENTS Study was sponsored by Guidant GmbH, Germany. T.S.F., R.G., C.B., M.Z., and J.B. do not have any potential conflict of interest and did not receive any grant or honoraria. S.T. and C.M. are employees (Clinical research scientists) of Guidant GmbH.

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