Temporal variability of atrial tachyarrhythmia burden in bradycardia–tachycardia syndrome patients

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Received 26 July 2004; revised 25 August 2004; accepted 16 September 2004; online publish-ahead-of-print 6 December 2004

See page 110 for the editorial comment on this article (doi:10.1093/eurheartj/ehi056)

Aims Several studies have tested non-pharmacological therapies for atrial tachyarrhythmias (ATs) by measuring the cumulative time (burden) the patient spends in arrhythmia. Contradictory results questioned either therapy efficacy or statistical power of the trials. We studied AT burden variability in patients paced for sinus node disease (SND) in order to interpret currently published data appropriately and to evaluate reliable sample sizes.

Methods and results One hundred and five patients with AT and SND received a dual chamber pacemaker with antitachyarrhythmia-pacing capability, and were followed for 13 months. Seventy-eight patients (74%) suffered AT recurrences. Device-gathered diagnostic measures were used to simulate results of randomized studies both with crossover and parallel design. The sample size required for statistically significant results was calculated as a function of the expected therapy-induced burden reduction. AT burden intra-patient variability was high: 43% of patients showed intrinsic fluctuations hiding any therapy-induced burden reduction lower than 30%. Demonstrating therapeutic breakthrough through a 6 month study would require 290 patients with crossover design and 5800 patients with parallel design. Doubling the study period requires 400 and 3000 patients, respectively.
Conclusion Patients with AT and paced for SND showed high intra-patient burden variability, which could possibly hide an AT burden reduction induced by a therapy. Previous studies involving non-pharmacological therapies utilizing AT burden endpoints could lack the power to reach statistical significance.

Methods

Eligibility

Patients that were included in this analysis met the following criteria: they had SND and at least two symptomatic AT episodes in 3 months prior to implant or at least three episodes in the prior year. At least one of these episodes was documented with an electrocardiogram. Patients were in sinus rhythm at the time of implant. All patients were followed for 13 months post-device implantation.

Device characteristics and protocol programming

Patients were implanted with a dual chamber pacemaker with antitachyarrhythmia-pacing capability (AT500™, Medtronic Inc., Minneapolis, MN, USA), a device that has been previously described.20,21 Briefly, this pacemaker includes two programmable, automatic, rate-adaptive atrial anti-tachycardia pacing (ATP) therapies and three programmable pacing prevention algorithms. The device detects and discriminates atrial and ventricular tachyarrhythmias using rate and pattern information derived from dual chamber bipolar electrograms.20,22 In all enrolled patients the device was programmed such that an AT episode was defined by median atrial cycle length less than 360 ms and A/V conduction consistently greater than 1:1 for at least 24 ventricular cycles. With these settings, AT episodes of about 15 s or longer are detected by the device and are used towards the burden measurement. Prior studies showed that the AT detection algorithm is characterized by a specificity of 100% and a sensitivity of 97%26 and that the accuracy of the burden measurement is 92%.23 The number and total duration of AT episodes is stored daily by the device for up to 14 months. There are no separate counters for different types of AT. The device also stores electrogram and marker channel prior to episode onset and detection for 35 episodes.

AT500 pacemakers are characterized by a fixed and short post-ventricular blanking period to fulfill the need of high detection sensitivity in the atrium. At implantation, a specific care for P-wave amplitude and far-field R-wave over-sensing measurements was recommended in order to avoid atrial under-sensing, inappropriate arrhythmia detection, and consequently, pacemaker malfunction. Atrial sensitivity was programmed at 0.15, 0.3, 0.45, 0.6, and 0.9 ms in 9, 66, 8, 18, and 4 patients respectively.

Pacing mode was programmed to DDD or DDDR in patients with chronotropic incompetence. The lower and upper rates were programmed according to physician discretion: in 90% of patients the lower rate was set at 60 or 70 beats per minute, while upper rate was programmed at 120 beats per minute. Following device implantation and a 1 month stabilization period, prevention

Introduction

There has been a significant increase in awareness of the morbidity and mortality associated with atrial tachyarrhythmias (AT) in recent years. Atrial fibrillation is an independent predictor of mortality1 and it is estimated that 15% of strokes occur in the context of tachyarrhythmia.2 Its impact on healthcare costs is indicated by its high prevalence at hospital discharge, which has doubled in patients older than 65 years from 1982 to 1993.3

Patients with sinus node disease (SND) receiving an implanted cardiac pacemaker also exhibit a high AT prevalence. About 31% of these patients have AT at implant and, within 6 years, the prevalence increases to 52%.4 A significant number of these patients remain asymptomatic.5 The incidence of anticoagulation in such patients with clinical risk factors is significantly low and varies between 15 and 28%.6–7 The clinical significance of pacemaker-detected AT frequency has also been recently reported in patients with SND,8 showing that atrial high rate episodes, lasting at least 5 min, identify patients that are more than twice as likely to die or have a stroke.

Although death, stroke, and quality of life are the preferred endpoints for the evaluation of treatment strategies, in order to reduce the size and duration of clinical trials, other surrogate endpoints have been proposed such as time to first recurrence9–10 or percentage of time a patient is in AT, i.e., burden.11–17

Rhythm control is a frequently utilized strategy for management of AT patients and burden is a cumulative measure of rhythm control over the follow-up period. Inverse correlation between AT burden and quality of life has been observed.18 The choice of AT burden as an endpoint in clinical trials has also been supported by the observation that asymptomatic atrial arrhythmias are associated with an increased risk of stroke.19 Furthermore, it has been hypothesized that the use of burden as a surrogate endpoint may make it possible to screen new therapies with smaller studies before committing to a large clinical trial. In reality, prospective, randomized studies performed so far to test non-pharmacological atrial therapies failed to show strong evidence of a therapeutic break-through measured as AT burden reduction. Contradictory results have been reported in trials testing pacing algorithms,11–16 pacing site,13–14,17 or right atrial radiofrequency ablation.17 This may either be due to limited therapy efficacy or to unexpectedly high burden variability causing the study to be underpowered.

The goals of the present analysis were to evaluate inter-patient and intra-patient variability of AT burden in order to estimate reliable sample sizes of parallel and crossover study designs that utilize burden as an endpoint, and to allow interpretation of currently published trials results.
eating features were enabled according to default settings. At the same time, ATP therapies were programmed in order to treat AT episodes with cycle length longer than 220 ms lasting more than 1 min.

Data analysis

AT episodes collected by device diagnostics were manually reviewed, studying device-stored atrial electrograms (EGMs) and marker channels, to evaluate detection appropriateness. All episodes were true atrial arrhythmias; no over-sensing phenomena were observed.

Data from the first month after implant were collected but not used in AT burden analyses and sample size evaluation since the first month was considered a stabilization period. AT burden was measured as the total duration of AT episodes over a certain follow-up period divided by this follow-up period, therefore it represents the average time the patient is in AT during the follow-up period and is expressed in min per day.

Statistical methods and sample size estimations

Categorical variables were expressed in terms of percentages and continuous variables were expressed in terms of means and standard deviation. Median values and interquartile ranges were computed for skewed distributions.

Sample size calculations were performed using Monte Carlo simulations. Briefly, the patient population for a particular study design was constructed by randomly selecting patients, with replacements, from our 105 sample patients. For a parallel design, this simulated patient population was randomly divided into two halves that were then assigned to therapy ON and therapy OFF arms. For the crossover design, this simulated patient population was divided into two halves; one half was assigned to therapy ON and therapy OFF arms. For the crossover design, this simulated patient population was randomly divided into two halves; one half was assigned to therapy ON followed by OFF and the other half to therapy OFF followed by ON. In the therapy ON arm, the AT burden for each patient was reduced by a fixed percentage. For example, assume that a patient in our original data had 10 min/day of AT burden between the 1st and the 7th month and 3 min/day of AT burden between the 7th and 13th month. If this patient was assigned to the ON arm and then to the OFF arm of a simulated 6 month crossover design study with a desired 30% reduction in burden with therapies, the observed AT burden would have been 7 min/day in the ON and 3 min/day in the OFF periods. The comparison of burden between therapy ON and OFF periods was evaluated by non-parametric tests: Wilcoxon Sum Rank and Mann Whitney U tests for crossover and parallel design studies, respectively. These tests were chosen because our data were not normally distributed and there was no period effect (see Results). Simulated studies were repeated 5000 times. The study power was calculated as the percentage of times (out of 5000) the result of the statistical test reached significance, i.e. $P < 0.05$. The 5000 repeated simulations had a 0.5% error on the power estimate. For each study design tested, the number of patients that gave an 80% power for therapy effects ranging from 40 to 20% AT burden reduction was reported.

For all the statistical analysis, the SPSS (SPSS Inc., Chicago, USA) software, version 11.5, was used.

Results

Patient population

Table 1 shows the demographic characteristics of the 105 patients in this analysis. Before implantation, 87 (83%) patients had paroxysmal AT, while 18 (17%) patients had persistent AT.

In the 12 month study period (1st to 13th month post-implant), anti-arrhythmic medications were either changed or added in 14 patients (13%). Electrical cardioversion was performed in five patients.

Seventy-eight patients (74%) experienced AT recurrences during the follow-up period. Kaplan–Meier cumulative survival from detected AT episodes is shown in Figure 1.

AT burden inter-patient variability

The inter-patient AT burden variability at the 1, 3, 6, and 12 month follow-up periods is shown in Figure 2. The percentage of patients without any AT episode during the 1, 3, 6, and 12 month follow-up was 55, 44, 33, and 26%, respectively. The distribution of AT burden across patients was highly skewed regardless of the follow-up period.

<table>
<thead>
<tr>
<th>AT history (non-exclusive), %</th>
</tr>
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<tbody>
<tr>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>Congenital cardiopathy</td>
</tr>
<tr>
<td>Coronary artery disease</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Cardiomyopathy</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Valvular disease</td>
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<tr>
<td>Hypertension</td>
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<table>
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<tr>
<th>Left atrium dimensions, mm³</th>
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<td>42.3 ± 6.9</td>
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<table>
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<tr>
<th>New York Heart Classification, n (%)</th>
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<tbody>
<tr>
<td>Class I</td>
</tr>
<tr>
<td>Class II</td>
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<tr>
<td>Class III</td>
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<td>Class IV</td>
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<table>
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<tr>
<th>Anti-arrhythmic drug treatment, n (%)</th>
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<tbody>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Sotalol</td>
</tr>
<tr>
<td>Flecaainide</td>
</tr>
<tr>
<td>Propafenone</td>
</tr>
<tr>
<td>Anti-arrhythmic drug association</td>
</tr>
<tr>
<td>Anti-arrhythmic drug association +2 of previous drugs</td>
</tr>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

Mean ± SD
The percentage of patients with a burden greater than the mean burden at the 1, 3, 6, and 12 month follow-up periods was 17, 17, 20, and 20%, respectively. The inter-patient variability, i.e. the interquartile difference of the AT burden among patients increased from 52 min/day for the 6 month to 92 min/day for the 12 month follow-up period.

**AT burden intra-patient variability**

Intra-patient variability was evaluated by calculating the difference in AT burden between two consecutive periods. We found no AT burden change or period effect between the first and second 3 month observation periods (6 month study duration, \( P = 0.34 \)) or the first and second 6 month observation periods (12 month study duration, \( P = 0.53 \)). However, a change in the variability of the AT burden differences between two consecutive periods was found. The distribution of AT burden differences between two consecutive periods became wider (interquartile range) as the duration of the periods increased (height of solid bars in Figure 3). This unexpected observation suggests that temporal fluctuations of the AT burden increase the randomness of the burden measurement as the observation periods increase from 3–3 to 6–6 months.

**Sample size evaluations**

The sample size needed to demonstrate, with 80% power and 95% confidence level, that a therapy will reduce the AT burden was calculated for several fixed-percentile reductions of burden in each patient. Figure 4 shows sample size as a function of the expected AT burden reduction for crossover study designs of 6 months (3 months in each arm) and 12 months (6 months in each arm). Sample size as a function of the expected AT burden reduction for parallel study designs of 3 months, 6 months, and 12 months total duration is shown in Figure 5. For a 30% burden reduction, the 3–3 months crossover study design required 290 patients while the parallel 3 month study design required 6000 patients. Therefore, for a 3 month AT burden endpoint, the crossover design required only 5% of the total number of patients needed for a parallel design. Increasing the duration of parallel study designs decreased the required sample size (Figure 5). In contrast, increasing the duration of crossover study designs from 3–3 to 6–6 months increased the required sample size (Figure 4).

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**Figure 1** Kaplan–Meier cumulative atrial fibrillation (AF) recurrence survival in the study population.

**Figure 2** AF burden distribution for four different observation windows, respectively 1 month (A), 3 months (B), 6 months (C), and 12 months (D) follow-up (FU) duration periods. The white column represents the percentage of patients with no AT recurrences, while black columns represent the percentage of patients with atrial fibrillation (AF) burden higher than zero. AF burden median and 25th and 75th quartile are reported in each panel.
Additional sample size estimations were performed to simulate studies that randomized only the patients who had at least one AT episode in the first month observation period. There were 51 patients who met this criterion. The percentage of patients without episodes in the subsequent study period, using this selection, decreased from 33 to 8% for the 6 month study duration and from 26 to 2% for the 12 month study duration. Inclusion of these 51 patients only resulted in further sample size reduction to 100 and 160 patients for the 3–3a and 6–6 months cross-over designs, requiring a 30% burden reduction respectively (Figure 4). For the 6 and 12 month parallel designs requiring a 30% burden reduction, the sample size was 740 and 700 patients, respectively (Figure 5).

Discussion

The new generation of pacemakers with extended monitoring capabilities allows one to measure AT burden accurately and potentially evaluate the efficacy of anti-arrhythmic interventions. AT burden has recently been used as a surrogate endpoint for clinical outcome in studies testing AT therapies in patients with implantable devices.11–17 Our analysis was designed to characterize AT burden variability in patients with brady–tachy syndrome, to give estimates of sample size for future studies using burden as an endpoint, and to allow interpretation of currently published data.

AT recurrences

All the patients in this analysis had a significant history of AT, with atrial fibrillation being the main atrial arrhythmia in 87% of patients. Despite this inclusion criterion, a large percentage of patients did not have AT recurrences during the study periods. This observation has also been reported in other studies with similar inclusion criteria.13,16 DDDR pacing and/or changes in the anti-arrhythmic drugs after pacemaker implantation may have prevented AT recurrences in an undetermined number of patients.

AT burden inter-patient variability

We found that there is high variability of AT burden as a function of time for a given patient. The variability
depends upon the number of patients with episodes in the study design. The results also suggest that sample size burden, and whether it is a parallel arm or crossover the duration of the study, the anticipated change in burden, between the ON and the OFF arms depends on the number of patients with episodes in the follow-up period and the variability of burden. The greater the number of patients with episodes, the smaller the sample size. In our data, the number of patients with AT episodes increased with longer study duration. Therefore, this effect should result in a smaller sample size with a 12 month vs. a 6 month study duration. On the other hand, the larger the variability, the greater the sample size. Our data showed that both the intra-patient and inter-patient variability increased as the duration of follow-up increased and this should result in a greater sample size with a 12 month vs. a 6 month study duration. Since these two factors have opposing effects on sample size as study duration increases, the overall sample size will depend on the magnitude of each effect and the statistical test performed. For the crossover design, the magnitude of the intra-patient variability effect was more pronounced as the duration of the follow-up increased, resulting in an increase in sample size. In contrast, for a parallel study design, the effect of the increase in the number of patients with AT episodes predominates, resulting in a smaller sample size as the duration of follow-up increases.

AT burden reduction in patients without any episodes during the follow-up period cannot be established. As a consequence, the inclusion of these patients reduces the power of studies. When only patients with at least one AT episode in the first month study period were included in our analysis, a significant reduction in sample size was observed. The sample size was about 700–740 patients for a parallel design and between 100 and 160 patients for a crossover design, depending on the follow-up duration. However, the number of implanted patients required should be doubled as, in our population, only half of the patients had at least one episode in the first month post-implant and therefore half of the patients would be excluded. Nevertheless, a study with this inclusion criterion would require about 60–70% fewer patients than a study design that uses all implanted patients for data analysis.

Sample size evaluations

This study demonstrates that the sample sizes required to measure strategies for rhythm control are lower than those required for studies using clinical endpoints such as mortality and stroke. For example, there is sufficient power to detect a 30% reduction in AT burden with a sample size of 400 patients in a crossover study, whereas about 3000 patients would be required in a parallel study design. Our method does not make any assumption about the AT burden distribution as we did not attempt to parameterize it. Rather the observed AT burden distribution was used in our analysis in order to simulate what would be expected during a clinical trial involving bradycardia pacemaker recipients with a clinical history of AT.

Our analysis indicates that the number of patients required to demonstrate a significant difference in AT burden, between the ON and the OFF arms depends on the duration of the study, the anticipated change in burden, and whether it is a parallel arm or crossover study design. The results also suggest that sample size depends upon the number of patients with episodes in the follow-up period and the variability of burden. The greater the number of patients with episodes, the smaller the sample size. In our data, the number of patients with AT episodes increased with longer study duration. Therefore, this effect should result in a smaller sample size with a 12 month vs. a 6 month study duration. On the other hand, the larger the variability, the greater the sample size. Our data showed that both the intra-patient and inter-patient variability increased as the duration of follow-up increased and this should result in a greater sample size with a 12 month vs. a 6 month study duration. Since these two factors have opposing effects on sample size as study duration increases, the overall sample size will depend on the magnitude of each effect and the statistical test performed. For the crossover design, the magnitude of the intra-patient variability effect was more pronounced as the duration of the follow-up increased, resulting in an increase in sample size. In contrast, for a parallel study design, the effect of the increase in the number of patients with AT episodes predominates, resulting in a smaller sample size as the duration of follow-up increases.

Non-pharmacological therapies impact on AT burden: interpretation of published trials data

Several trials have tested non-pharmacological atrial therapies efficacy in patients with bradycardia and atrial fibrillation by measuring AT burden together with other endpoints. Carlson et al. showed that overdrive atrial pacing decreases the percentage of days with AT-related symptoms. Ricci et al. showed that a consistent atrial pacing algorithm reduces AT recurrences. Preliminary results of the Aspect study show that three prevention pacing algorithms reduce symptomatic AT episode frequency in septal-paced patients. Convergence of these studies in finding evidence of pacing algorithm impact on AT surrogate endpoints may suggest that these therapies do have a role in AT prevention. Until now, this hypothesis has been challenged by the fact that these and other studies failed to show a significant reduction of AT burden. Our analysis shows that the
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previously mentioned studies did not have the statistical power to detect a reduction of AT burden.

Study limitations

Our results should be limited to patients with brady-tachy syndrome; nevertheless similar distributions have been observed in intra-cardiac device indicated patients with a history of AT13 and therefore sample size estimates may be similar in such a patient population.

Another limitation of this study is that, in all the patients, therapies were enabled throughout the study. This may not represent a control population in whom therapies would be disabled and the goal would be to demonstrate a reduction in burden when therapies are enabled.

AT therapies were assumed to reduce the patients’ AT burden by a certain percentage in all patients, thus our results may be affected by hypothesizing that not all patients are responders. Therapies were also assumed to affect patients immediately and for the entire study period; any time-dependent remodelling or carry-over effects were ignored.

Conclusion

In our population of patients paced for the brady–tachy form of SND and prior AT history, AT burden was characterized by specific features: first, it had a skewed distribution; secondly, many patients had no recurrences within the 13 month post-implant follow-up period; and finally, AT burden was associated with high intra-patient variability. The influence of time-related burden fluctuations could be of paramount importance when evaluating rhythm control strategies in crossover study designs: in many patients, burden variability could in fact hide the burden reduction induced by the experimental therapy.

To evaluate a therapy that reduces AT burden by 30% would require about 400 patients for a crossover design and 3000 patients for a parallel study design with a total follow-up duration of 12 months. For crossover studies, a 6 month follow-up would require fewer patients than would a 12 month, probably due to the increase in variability with longer follow-up duration. For parallel studies, sample size decreases as the follow-up period increases, probably because the number of patients with AT episodes increases with longer study duration. Sample size estimates can be significantly reduced by only including patients who have at least one AT episode during the first month post-implant.

Acknowledgements

The authors thank Rita Ianni, Fabiola Zanna, Daniela Fabrizi, Tiziana de Santo, and Jodi Koehler, for expert assistance in data management and statistical analysis, and Rahul Mehra, Francesco deSeta, Massimiliano Pepe, and Francesco Miraglia for valuable suggestions and contributions.

Appendix


References


