Distribution of fast heart rate episodes during paroxysmal atrial fibrillation

K Hnatkova, F D Murgatroyd, C A Alferness, A J Camm, M Malik

Abstract

***Objective*—To investigate the defibrillator waiting time (time between the recognition of atrial fibrillation and the actual shock) by studying paroxysmal atrial fibrillation episodes with RR intervals shorter than a certain limit (that is, episodes during which defibrillation should not be attempted).**

***Methods*—Long term 24 hour Holter recordings from a digoxin *v* placebo cross-over study in patients with paroxysmal atrial fibrillation were analysed. In all, 23 recordings with atrial fibrillation episodes of at least 1000 ventricular cycles and with < 20% Holter artefacts or noise were used (11 recorded on placebo and 12 on digoxin). For each recording, the mean ("mean waiting time") and maximum ("maximum waiting time") duration of continuous sections of atrial fibrillation episodes with all RR intervals shorter than a certain threshold were evaluated, ranging the threshold from 400 to 1000 ms in 10 ms steps. For each threshold, the mean and maximum waiting times were compared between recordings on placebo and on digoxin.**

***Results*—Both the mean and maximum waiting times increased exponentially with increasing threshold. Practically acceptable mean waiting times less than one minute were observed with thresholds below 600 ms. There were no significant differences in mean waiting times and maximum waiting times between recordings on placebo and digoxin, and only a trend towards shorter waiting times on digoxin.**

***Conclusions*—Introduction of a minimum RR interval threshold required to deliver atrial defibrillation leads to practically acceptable delays between atrial fibrillation recognition and the actual shock. These delays are not prolonged by digoxin treatment.**

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Keywords: atrial defibrillator; shock delivery; ventricular proarrhythmia; digoxin

Department of Cardiological Sciences, St George's Hospital Medical School, London, UK
K Hnatkova
F D Murgatroyd
A J Camm
M Malik

InControl Inc, Redmond, Washington, USA
C A Alferness

Correspondence to:
Dr Katerina Hnatkova, Department of Cardiological Sciences, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK.
email: k.hnatkova@sghms.ac.uk

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Very low atrial defibrillation thresholds can be achieved by the use biphasic shocks delivered between a pair of high surface area transvenous leads arranged in a "biatrial" configuration (for example, right atrium to coronary sinus). Such thresholds are of the order of 5 J for chronic and resistant atrial fibrillation, and 2 J or lower for paroxysmal atrial fibrillation.[1–3] These data make an implantable atrial defibrillator practically feasible. In contrast to the ventricular implantable cardioverter defibrillators, the use of such an atrial device on a stand alone basis depends critically on its safety, in particular with respect to the propensity of atrial defibrillation shocks to trigger ventricular tachyarrhythmias.[4]

Animal studies indicate that, in order to avoid ventricular proarrhythmia, atrial defibrillation shocks must be synchronised to the QRS complex and delivered following RR intervals that do not exceed a minimum, which was found to be around 300 ms, although it seems that a longer RR interval threshold may improve the safety of an atrial defibrillator.[5–7] Thus a stand alone atrial defibrillator will need to monitor successive RR intervals and deliver a shock only after an RR interval exceeding a given duration. At the same time, as a proportion of atrial fibrillation episodes spontaneously terminate after a short period of time, an atrial defibrillator is likely to be programmed only to deliver treatment after confirmed atrial fibrillation has been present for a minimum duration.[8] Thus programming the atrial defibrillator to deliver treatment only after an RR interval longer than a certain threshold will introduce a delay between the recognition of atrial fibrillation and the actual shock. This delay is termed here "the defibrillator waiting time." While it is obvious that programming an unreasonably long RR interval threshold (say one second) may lead to an unacceptably long defibrillator waiting time, the duration of waiting times for realistic RR interval thresholds has never been investigated in a systematic fashion and the consequences of programming the RR interval threshold to "safe" values of 500 or 600 ms are not known.

Moreover, the effect of drugs used in patients with atrial fibrillation on the defibrillator waiting time are not known.[9 10] Digoxin is often used in patients with paroxysmal atrial fibrillation, and it is likely that a proportion of patients with atrial defibrillators will be digitalised.[11 12] As digoxin is known to slow the ventricular rate in chronic atrial fibrillation, it can be hypothesised that this slower ventricular rate will become more regular and this will, paradoxically, increase the defibrillator waiting time.

With all these problems in mind, we investigated the differences in duration of episodes of atrial fibrillation with RR intervals shorter than a given limit—that is, episodes during which a defibrillation shock should not be delivered (episodes simulating the defibrillator waiting

Table 1 Study data

(A) Distribution of noise in all atrial fibrillation (AF) episodes

Duration of noise in AF episode	*Number of episodes*	*Proportion of all episodes*
0%	18	27.3%
1–5%	36	54.5%
6–10%	3	4.5%
11–15%	5	7.6%
15–20%	4	6.1%

(B) Proportion of correct RR intervals in AF episodes and the median duration of all corresponding AF episodes

Number of correct RR intervals in the episode (×1000)	*Proportion of all AF episodes*	*Median duration of AF episodes (min)*
1–1.5	16.7%	11.0
1.5–2.5	16.7%	17.9
2.5–5	27.3%	29.3
5–10	15.2%	58.2
>10	24.2%	269.0

Median rather than the mean, which can skew the result owing to a few exceptionally long AF episodes.

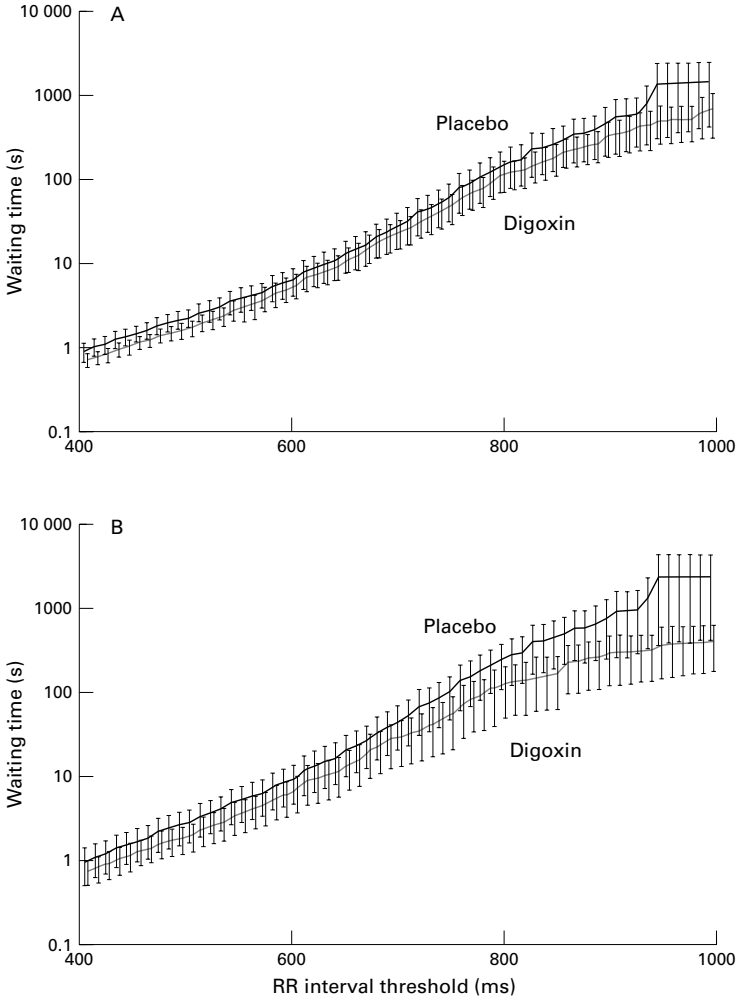

Figure 1 Mean waiting times—that is, mean durations of atrial fibrillation sections with RR intervals shorter than a given threshold (x axis). Vertical axes use a logarithmic scale in seconds, the dashed lines correspond to 1 s, 1 min, and 1 h waiting times. The mean waiting times were averaged separately in recordings made on placebo and on digoxin. The averages and standard errors used in the graphs were obtained from the mean waiting times in individual tapes rather than from individual atrial fibrillation episodes. Panel A illustrates the results from pooled data, panel B shows the results from case controlled data (see the text for details).

time)—in patients receiving treatment with digoxin or placebo. Episodes of atrial fibrillation were selected from 24 hour Holter tapes recorded in patients with paroxysmal atrial fibrillation during a randomised crossover trial of placebo and digoxin.

Methods

DATA AND RECORDINGS

The study population consisted of a subset of patients who had been recruited in the multicentre CRAFT 1 study, which investigated the effects of different types of pharmacological treatment on paroxysmal atrial fibrillation.[13] In brief, the CRAFT study enrolled 43 patients selected from a registry of patients with frequent episodes of paroxysmal atrial fibrillation (18 women, mean (SD) age 58.2 (11.2) years, treated hypertension in 5%, angina in 7%, history of myocardial infarction in 5%, clinical heart failure in 5%). All patients had echocardiography: mean left atrial diameter was 3.27 (0.62) cm, minor valve abnormality (calcification without stenosis and/or mitral valve prolapse with no more than trivial regurgitation) was seen in 24%, significant valve abnormality in 9%, and left ventricular hypertrophy in 12%. All patients underwent 24 hour ambulatory Holter monitoring (two channel recordings of leads II and modified CM5) during each phase of a double blind crossover trial when digoxin and placebo were given in a random order. Digoxin dose was initially based on estimated renal function and then adjusted to achieve therapeutic plasma levels, after which monitoring began. The median digoxin dose was 375 μg/day; the mean (SD) plasma concentration (central laboratory assessment using fluorescence polarisation immunoassay) was 1.01 (0.27) μg/l. For the purposes of this study, all 86 Holter recordings were available. Recordings containing only atrial fibrillation or only sinus rhythm episodes were excluded from the analysis, as were recordings which were of too poor quality to allow useful analysis. Episodes of atrial fibrillation were identified by a previously validated semiautomated method.[14] In brief, each recording was subjected to an analysis and manual editing using a commercial Holter system (Laser Holter System 8000, Marquette Medical Systems, Milwaukee, Wisconsin, USA). The precise timing of each episode of atrial fibrillation and sinus rhythm was determined by visual inspection on a full small scale printout of the total recording, and marked using a digitising board. These data were matched with the corresponding beats in a conventional RR interval file generated by Holter analysis. A composite file was created, listing the rhythm of each beat, RR interval duration, and the marker of noise in every RR interval. The file also listed the real time of each beat and the QRS complex morphology. The validation study of this method showed that the onset and termination of each atrial fibrillation episode can be identified within the Holter beat file with a precision of ±1 cardiac cycle.[14]

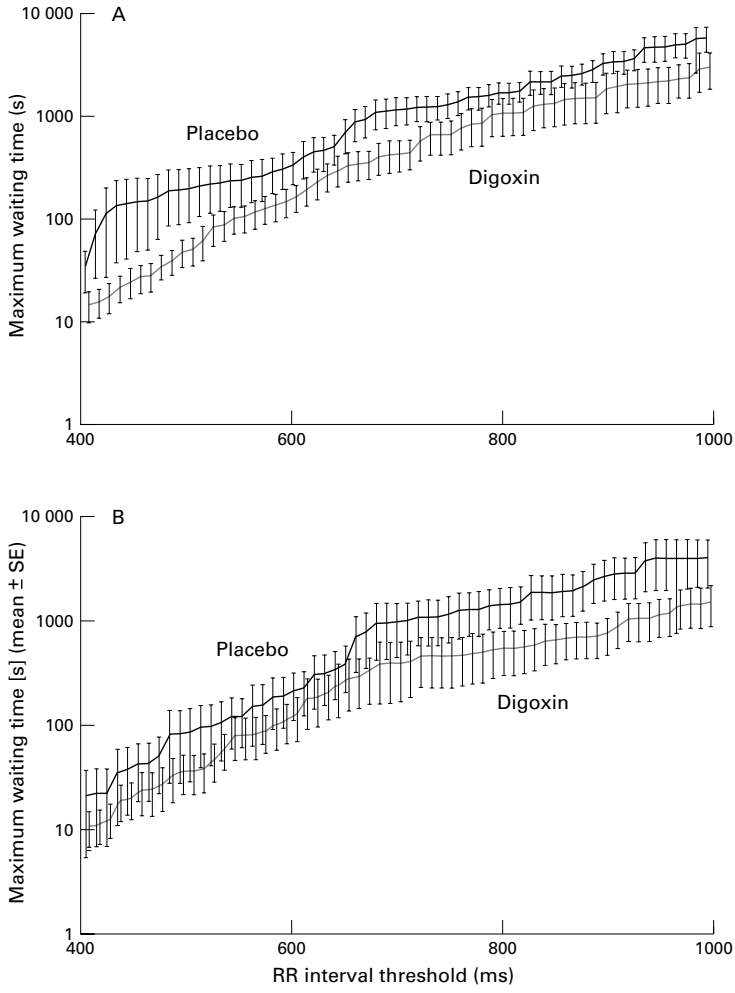

Figure 2 Maximum waiting times—that is, maximum durations of atrial fibrillation sections with RR intervals shorter than a given threshold (x axis). Details and layout as in fig 1.

DATA ANALYSIS

For each atrial fibrillation episode, its total duration, number of correct RR intervals without noise, and the proportion of noise and recording artefacts were calculated. For the purposes of this investigation, only recordings which contained atrial fibrillation episodes of at least 1000 ventricular cycles and which were polluted by less than 20% of noise or Holter artefact qualified for further analysis.

Each episode of at least 1000 RR intervals was converted into a sequence of correct RR intervals after noise exclusion. These sequences of correct RR intervals will be further termed "atrial fibrillation series." This approach was based on the assumption that during all atrial fibrillation episodes the ventricular cycles create an almost Poisson process.[15] In practical terms this assumption means that the exclusion of intervals invalid due to noise or Holter artefact does not change the statistical properties of atrial fibrillation series.

For each tape, the mean and maximum duration of continuous sections of atrial fibrillation series with all RR intervals shorter than a given threshold were computed. In this analysis, the value of the threshold varied from 400 to 1000 ms in 10 ms steps. The duration of sections of atrial fibrillation series with RR intervals shorter than the threshold modelled the treatment waiting times of an atrial defibrillator programmed to shock only after an RR interval exceeding the given threshold. The mean and the maximum duration of continuous atrial fibrillation sections with RR intervals shorter than a threshold is further termed "*mean waiting time*," and "*maximum waiting time*" corresponding to that threshold, respectively.

For each threshold, the mean and maximum waiting times were evaluated for each tape, and averaged for (1) all placebo and all digoxin recordings (pooled data), and (2) for all placebo and all digoxin recordings obtained in those patients for whom both the placebo and the digoxin recording were eligible for this study (case controlled data).

For both the pooled data and the case controlled data the mean and maximum waiting times of different thresholds were compared between digoxin and placebo using a non-parametric Mann-Whitney test. An in house software package was written for the data analysis and statistical comparisons. The programming of statistical tests reflected precisely their mathematical theory and no errors due to simplifying assumptions were introduced. Probability (p) values $\leqslant 0.05$ were taken as the level of statistical significance.

Results

Of all the Holter tapes available, 23 recordings (12 on digoxin and 11 on placebo) made in 16 patients (mean (SD) age 59.0 (10.9) years, nine males, seven females) satisfied the selection criteria. In six patients (59.5 (4.3) years, three males, three females) both recordings on placebo and digoxin were eligible for the analysis and constituted the case controlled data. There were no significant differences in the characteristics of the patients with eligible recordings and the total CRAFT 1 population.

In all, the study investigated 66 atrial fibrillation episodes. The mean (SD) duration of qualifying episodes was 119.6 (228.8) minutes (median 31.7 minutes). The shortest episode lasted 7.5 minutes, and the longest 23 hours. Table 1 summarises the quality of qualifying recordings. Part A shows the distribution of Holter recognition noise in analysed atrial fibrillation episodes, part B lists the distribution of RR intervals involved in the analysis. Median durations of atrial fibrillation episodes are skewed (the distribution of atrial fibrillation episode durations is highly non-normal).

Figure 1 shows the values of the mean waiting times. There were no significant differences in mean waiting times between placebo and digoxin, either in pooled or in case controlled data. Figure 2 shows the corresponding results for the maximum waiting times. As with the mean waiting time, there were no systematic statistical differences between the maximum waiting times on placebo and digoxin. Generally there was a trend towards a decrease in both mean and maximum waiting times on digoxin but the differences did not reach statistical significance.

Both the mean and maximum waiting times increased practically exponentially with the threshold of minimum RR interval. (Note that the graphs in figs 1 and 2 have nearly a linear form while using a logarithmic scale on the vertical axis.) Setting the minimum RR interval threshold to 500–600 ms leads to mean waiting times of ⩽ 10 s and maximum waiting times of ⩽ 3 min, which seems to be acceptable for practical purposes. Attempting to set the RR interval threshold to larger values (for example, 800 ms) leads to less acceptable waiting times (maximum waiting time approaching 1 h).

Discussion

The risk of ventricular proarrhythmia from atrial defibrillation shocks arises if the current is delivered to a portion of the ventricular myocardium at a time of its vulnerability. The right atrium–coronary sinus lead configuration reduces both the total current delivery and the proportion reaching the ventricles, but it is still likely that a shock delivered during the ventricle's vulnerable period could stimulate sufficient myocardium to initiate an arrhythmia. The vulnerable period generally falls within the latter portion of the T wave, corresponding at a cellular level to the relative refractory period of the myocytes, and at a macroscopic level to an interval when the ventricle is inhomogeneously excitable. Generally, shocks that are synchronised to the R wave are incapable of proarrhythmia. However, at short cycle lengths the R wave may begin at a time when part of the ventricular myocardium is still only partially excitable. Thus in extensive sheep experiments ventricular fibrillation was occasionally seen following correctly synchronised atrial defibrillation shocks, but this risk was confined to shocks that followed RR intervals of less than 300 ms.[6] It is therefore mandatory that the implantable atrial defibrillator delivers shocks that are both synchronised and follow RR intervals of 300 ms plus a safety margin.

In this study, we found that the maximum waiting time (time before an RR interval occurred that was exceeded the preset threshold) increased almost exponentially with that preset threshold, from under 10s with a threshold of 400 ms to about three minutes with a threshold of 600 ms, and to several tens of minutes with a threshold of 800 ms. The mean and the maximum waiting times in atrial fibrillation episodes recorded on placebo were not significantly different from those found in atrial fibrillation episodes recorded on digoxin. At thresholds that are likely to be clinically used, namely between 500 and 600 ms, the mean waiting time was under 10 s irrespective of treatment.

Although this study was not aimed at evaluating effects of digoxin other than the influence on defibrillator waiting time, some comments might be made on this subject. Unfortunately, the data on the potential benefit of digoxin are restricted to the reduction of resting ventricular rate in patients with chronic atrial fibrillation and a modest inotropic effect. The use of the drug in atrial fibrillation undoubtedly remains a controversial subject.[16] There is no evidence of a primary antiarrhythmic action, and it has even been proposed that the vagotonic action of digitalis is proarrhythmic in the atrium.[17] Our observations do not support a general marked decrease in ventricular rate in qualifying episodes of paroxysmal atrial fibrillation, which is in agreement with previously published studies.[18 19] Long RR intervals within paroxysmal atrial fibrillation episodes do not appear more frequently on digoxin. However, it has to be recognised that the design of our study was not well suited to a comprehensive evaluation of the effects of digoxin. To analyse the defibrillator waiting time properly, we had to exclude short atrial fibrillation episodes and analysed only episodes of at least 1000 RR intervals, which might not be representative. Also, this study was sufficiently powered to examine the effects of waiting times on RR interval threshold but not necessarily powered enough to depict minute differences in ventricular rate and RR interval distribution in recordings on placebo and digoxin.

CONCLUSION

In patients with paroxysmal atrial fibrillation, programming an automatic atrial defibrillator to deliver treatment only after a sufficiently long "safe" RR interval constitutes a delay between the recognition of atrial fibrillation the treatment. This "waiting time" increases exponentially with the duration of the target safe RR interval. Practically acceptable delays shorter than one to three minutes correspond to safe RR thresholds of around 500 to 600 ms. These delays are not significantly affected by digoxin treatment. The thresholds between 500 and 600 ms are well within the safety margin of published experimental data and might be proposed for eventual programming of automatic atrial defibrillators.

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