The role of atrial ectopics in initiating paroxysmal atrial fibrillation


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Aims To characterize the nature and timing of atrial ectopics preceding clinical episodes of paroxysmal atrial fibrillation.

Methods and Results Holter recordings (n=177, 60 patients, 58% male, mean age 61·7 ± 11·5 years) were performed on patients with paroxysmal atrial fibrillation. These were subjected to standard analysis and recordings containing atrial fibrillation episodes suitable for analysis were identified (n=74). Beat interval files differentiating sinus rhythm from atrial fibrillation were generated and atrial ectopics were identified. Atrial ectopics preceding atrial fibrillation were found to be more frequent (5·07 ± 7·39 min⁻¹) and more premature (ratio of coupling interval to that of surrounding sinus cycles=0·56 ± 0·08) compared to ectopics occurring remote from atrial fibrillation episodes (frequency=3·60 ± 7·32 min⁻¹, prematurity ratio=0·60 ± 0·10, P=2 × 10⁻⁷). Atrial ectopic coupling interval frequency histograms were generated and analysed visually and by an automated statistically based test. Many ectopics were seen to occur at one coupling interval in 27 recordings (in eight this occurred only preceding atrial fibrillation onset, while in a further 19 cases this was also seen remote from atrial fibrillation onset). Overall 45% of ectopics preceding atrial fibrillation episodes occurred in isolation, 13% as part of a bigeminal rhythm, 22% as couplets and 20% as runs. This pattern did not differ from that seen remote from atrial fibrillation episodes.

Conclusion Paroxysmal atrial fibrillation is preceded by ectopics of a fixed coupling interval in a significant proportion of patients. If, as seems likely, this is a marker of ‘focally mediated’ atrial fibrillation, then Holter techniques may provide a useful screening tool with which to identify patients suitable for fuller electrophysiological assessment.

Key Words: Atrial fibrillation, computerized analysis, arrhythmia mechanisms, atrial ectopic beats.

Introduction

Paroxysmal atrial fibrillation is associated with numerous predisposing conditions, such as hypertension, previous myocardial infarction, and congestive cardiac failure[1]. However, up to half of patients suffering from paroxysmal atrial fibrillation have no apparent underlying cardiac pathology, as do 20% of those with persistent or permanent atrial fibrillation[2]. Therefore, primary arrhythmic mechanisms are probably important in the genesis of atrial fibrillation.

Other tachycardias[3–5] and atrial premature beats[6–8] trigger the onset of atrial fibrillation, which is then maintained by random multiple wavelet re-entry[9,10]. Although some patients with atrial fibrillation paroxysms have an underlying focal atrial tachycardia[11,12] or other initiating tachycardia[3–5], systematic evaluation suggests such cases are not too frequent[13]. The autonomic nervous system plays a role in atrial fibrillation initiation[14], with some patients suffering atrial fibrillation episodes at times of high vagal or, more rarely, high adrenergic tone. While such patients are seen in clinical practice, systematic evaluation reveals that consistent patterns of tachycardic or bradycardic onset are difficult to document[15]. The potential of an ectopic to initiate an atrial fibrillation episode is also influenced by haemodynamic factors which cause atrial stretch, myocardial ischaemia and pre-existing intra-atrial conduction inhomogeneity. Such
mechanisms are probably only important in a minority of cases.

We hypothesized that the initiation of atrial fibrillation was determined by the coupling interval of atrial ectopics preceding atrial fibrillation onset. This hypothesis was tested by systematic comparisons of ectopics occurring prior to atrial fibrillation onset and those remote from tachycardia. The average coupling interval of ectopics which did or did not precede atrial fibrillation onset was considered and the distribution of atrial ectopic coupling intervals was characterized. Atrial ectopics which occurred at a single coupling interval were hypothesized to have the same origin. Thus the feasibility of detecting atrial fibrillation initiated by a single atrial focus, so-called ‘focal atrial fibrillation’, through assessment of ventricular coupling intervals on Holter recordings was investigated.

Methods

Holter recordings utilized for this analysis were recorded as part of two multicentre randomized controlled trials. The CRAFT-1 trial compared the efficacy of digoxin vs placebo, and the CRAFT-2 trial atenolol vs disopyramide, both with a Holter recording during each arm of the study. Therapy allocation during Holter recording is known, but analysis by treatment did not affect the observations of this study and thus all analysis is based on pooled data. The inclusion criteria for the trials were paroxysmal atrial fibrillation symptomatic enough to warrant treatment and absence of severe cardiac disease likely to result in persistent atrial fibrillation during the following months. Paroxysmal atrial fibrillation was defined as recurrent attacks of generally self-terminating episodes of atrial fibrillation with electrocardiographic documentation on at least one occasion. Those who had suffered a recent myocardial infarction (<3 months) were not eligible, and all patients were assessed clinically and had 12 lead electrocardiography and echocardiography. Most echocardiograms showed no evidence of significant structural heart disease with a normal sized left atrium, but approximately 14% had significant left ventricular hypertrophy and 10% had significant valve dysfunction.

Twenty-four hour Holter tapes (Laser Holter XP, Marquette Medical Systems, Milwaukee, U.S.A.) recorded two channels: lead II and a modified CM5 lead. Each Holter was converted to a digitized format and subjected to routine processing and manual editing on commercial equipment (Marquette Laser Holter System 8000, Marquette Medical Systems, Milwaukee, U.S.A.). Paroxysmal atrial fibrillation was defined as episodes of irregular ventricular rhythm without discernible P wave activity lasting ≥3 ventricular cycles. Recordings without an onset of atrial fibrillation or with less than 18 h of analysable data were excluded from analysis. All other recordings were printed on paper (1 min per line, 60 lines per page), and the onset and termination of each atrial fibrillation episode marked by an operator on a digitizing board using a previously described technique.

Cardiac rhythm was classified into sinus rhythm, atrial fibrillation or uninterpretable (i.e. noise and Holter artefact). Sinus rhythm included any rhythm that was essentially sinus, eventually containing other transient arrhythmias that were not atrial fibrillation, such as sinus tachycardia or multiple atrial premature beats. Areas of atrial flutter were, however, excluded. The episode classifications were combined with the standard Holter beatstream to give a stream of RR intervals, distinguishing atrial fibrillation from sinus rhythm on a beat-to-beat basis. Ventricular premature complexes were infrequent and excluded, along with the preceding and following interval.

Reliable assessment of P wave morphology is not feasible in analogue Holter recordings due to low signal-to-noise ratio. Therefore, atrial ectopics within the sinus rhythm episodes were defined as cardiac cycles with an abnormally short RR interval and normal QRS morphology. For each beat, the ratio between the preceding RR interval and the median of the preceding 10 RR intervals was calculated. If this ratio was <0.8, the beat was assumed to be an atrial ectopic (the limitations of this method in general and of the arbitrary threshold chosen are discussed later).

It was hypothesized that phenomena important to the onset of paroxysmal atrial fibrillation may only be seen immediately prior to atrial fibrillation onset. In order to examine this, four zones were distinguished in each recording (see Fig. 1). These were (1) the episodes of atrial fibrillation themselves, (2) periods of sinus rhythm preceding an atrial fibrillation episode, (3) periods of sinus rhythm following atrial fibrillation episodes and (4) sinus rhythm remote from atrial fibrillation episodes. Thus the zones of interest were zone 2 (sinus rhythm preceding atrial fibrillation onset) and zone 4 (sinus rhythm remote from atrial fibrillation onset). The duration of zones 2 and 3 was set at 1 min (i.e. all sinus rhythm which preceded atrial fibrillation by 1 min belonged to zone 2, while that which was neither within 1 min of atrial fibrillation termination nor within 1 min of atrial fibrillation onset belonged to zone 4). In addition to the primary cut-off of 1 min, analyses were repeated with secondary cut-offs of 2 and 5 min. Note that individual recordings may have had multiple analysable atrial fibrillation episodes, in which case the data from temporally separated periods of the same zone were pooled. Only zones containing <20% of Holter recognition noise were considered. Zones of category 2, relating to atrial fibrillation episodes of <5 ventricular beats, were excluded. All analysis was performed using an in-house developed software package.

The relative frequency (ectopics per minute) and the mean prematurity index of ectopics was determined. The prematurity index was calculated as the ratio between the coupling interval of the ectopic and the mean coupling interval of the previous 10 beats. The relative frequency and mean prematurity index of ectopics during the period preceding atrial fibrillation (zone 2) was...
statistically compared to those of sinus rhythm remote from atrial fibrillation (zone 4).

Histograms of the relative frequency of the coupling intervals of atrial ectopics were constructed for zones 2 and 4 of each recording.

On visual inspection, some histograms exhibited distinct, narrow peaks. Such narrow maxima represent frequent ectopics of the same coupling interval. We hypothesized that these represented ectopics of the same origin. To study the importance of such ectopics for atrial fibrillation initiation, the histograms of all recordings were classified into three patterns: Pattern A=distinct narrow maxima in zone 2 but not zone 4. Pattern B=distinct narrow maxima in both zones 2 and 4. Pattern C=no significant maxima present. Some of the recordings showed maxima in zone 4 but not in zone 2, and these were classified as pattern C.

To perform this classification without operator bias, an automated test was developed. This tested that the peak occurred at coupling intervals <600 ms, was sharp and contained a moderate proportion of all ectopics. The precise methodology of this test is described in the appendix.

Finally, each atrial ectopic was classified as: belonging to a run (≥3) of ectopics, an atrial couplet, a bigeminal rhythm (two or more pairs of short and non-short cycles) or as solitary. The proportion of all ectopics belonging to each of these classes was compared between tapes showing different patterns of ectopic distribution, as described in the preceding paragraph.

All statistical comparisons were made using a paired Wilcoxon test unless otherwise stated. A P value <0.05 was considered statistically significant.

Results

The CRAFT trials generated a total of 177 Holter recordings. These were from 60 patients (mean age 61.7 ± 11.5 years, range 33 to 81, 35 male), with the participation of some patients in both trials. Application of the criteria specified for this study selected 71, 74 and 74 recordings for zone cut-offs (the duration period preceding and following atrial fibrillation) of 1, 2 and 5 min, respectively, which were from 38 different patients. The total number of atrial fibrillation episodes was 783 (range of episodes per recording 1 to 73, median 2), 596 (range 1 to 54, median 2) and 363 (range 1 to 25, median 2), respectively.

Ectopics were more frequent prior to atrial fibrillation, with the largest absolute difference seen with a zone cut-off of 1 min (Table 1). This suggests a progressive increase in ectopics before atrial fibrillation. Ectopics immediately prior to atrial fibrillation were significantly more premature than those remote from atrial fibrillation (Table 1). The difference in the means was 3% to 4%, corresponding to an absolute shortening of about 32 ms (given that the mean heart rate at onset was 65 beats . min⁻¹), and was very variable, as demonstrated by the wide standard deviation.

<table>
<thead>
<tr>
<th>Mean prematurity index</th>
<th>Number of ectopics (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSR 0.55 ± 0.08</td>
<td>6.78 ± 8.60</td>
</tr>
<tr>
<td>RSR 0.59 ± 0.09</td>
<td>3.95 ± 7.62</td>
</tr>
<tr>
<td>P value 2 × 10⁻¹¹</td>
<td>3 × 10⁻¹¹</td>
</tr>
<tr>
<td>PSR 0.56 ± 0.08</td>
<td>5.07 ± 7.39</td>
</tr>
<tr>
<td>RSR 0.60 ± 0.10</td>
<td>3.60 ± 7.32</td>
</tr>
<tr>
<td>P value 2 × 10⁻⁻³</td>
<td>5 × 10⁻⁻²</td>
</tr>
<tr>
<td>PSR 0.58 ± 0.08</td>
<td>4.42 ± 7.27</td>
</tr>
<tr>
<td>RSR 0.61 ± 0.09</td>
<td>3.92 ± 8.10</td>
</tr>
<tr>
<td>P value 3 × 10⁻⁻¹⁴</td>
<td>1 × 10⁻⁻⁴</td>
</tr>
</tbody>
</table>

Figure 1 Visual representation of the classification of a segment of Holter recording performed in this study. The solid black line is the plot of heart rate change with time. Two episodes of atrial fibrillation associated with a rise in heart rate are shown. The zones are shown along the bottom, with zone 1 representing atrial fibrillation, and zones 2–4 sinus rhythm. Zone 2 is the sinus rhythm immediately preceding atrial fibrillation onset, and zone 3 that immediately after atrial fibrillation termination. Zone 4 is sinus rhythm remote from atrial fibrillation. Analyses in this study are of zone 2 and zone 4.
The frequency histograms of the coupling intervals’ ectopic beats often had a skewed broad distribution appearance without distinct peaks (pattern C, Fig. 2). The analysis of distinct peaks was performed with the zone cut-off of 2 min. Eight recordings (seven patients) had distinct peaks in the frequency histogram of the sinus rhythm preceding atrial fibrillation but not remote from atrial fibrillation (pattern A), 13 exhibited peaks in both zones of sinus rhythm (pattern B) and 53 in neither (pattern C). Where there was more than one recording from individual patients, there was agreement of pattern assignment between recordings in 75% of cases (18 of 24). Fourteen of 38 patients had pattern A or B in one or more recording. Recordings demonstrating distinct histogram maxima (i.e. of pattern A or B) had a greater number of ectopics prior to atrial fibrillation than did those without any maxima (pattern C). For pattern A (distinct peak only prior to atrial fibrillation onset) the median number of ectopics before atrial fibrillation was 95, while pattern B histograms contained a median of 168 ectopics prior to atrial fibrillation onset (P=0.046). In contrast, pattern C (no detectable maxima) recordings only had a median of nine ectopics before atrial fibrillation onset (P=2×10⁻⁵ vs combination of A and B patterns).

The proportion of all ectopics occurring in isolation, as part of bigeminy, as couplets or as runs is shown in Table 2. There was a trend for patients with patterns A or C to have more complex arrhythmias (i.e. couplets or runs) than patients with pattern B. All groups showed a non-significant increase in couplets, while runs of atrial ectopics decreased. This observation must be interpreted in the light of the data acquisition method. If runs of ectopics degenerated into atrial fibrillation then the atrial tachycardia at the beginning of the atrial fibrillation would probably be classified by the observer within the atrial fibrillation itself. Either definite sinus beats between tachycardia and atrial fibrillation, or a clearly identifiable atrial tachycardia (good registration of P waves or relatively slow rate) would be required for this methodological issue not to arise.

**Discussion**

**Findings of present study**

This study has demonstrated that the characteristics of atrial ectopics preceding the onset of atrial fibrillation differ from those of ectopics occurring at other times. Atrial ectopics were more frequent and on average more premature prior to atrial fibrillation onset. However, the difference in prematurity between ectopics prior to and remote from atrial fibrillation was small and of uncertain significance in provoking atrial fibrillation.

In some patients, atrial ectopics are more likely to occur at certain coupling intervals. One fifth of all recordings showed predominance of one atrial ectopic coupling interval both before atrial fibrillation onset and remote from atrial fibrillation, while in a further 10% the predominance was demonstrated prior to atrial fibrillation onset only. It is likely that ectopics occurring at the same coupling interval arise from the same source. Hence, evidence for atrial ectopics from a single focus being linked to the initiation of atrial fibrillation is present in one third of recordings. Importantly, detection of this phenomenon by our statistically based method is dependent upon sufficient ectopics being present and the median number of ectopics prior to atrial fibrillation was much lower in those recordings which did not demonstrate the phenomenon (pattern C). Thus, the figure of one third is an under-estimate—when counted as the proportion demonstrating the phenomenon in one or more recording, either pattern A or B was seen in 37% of patients.

In all patients a large proportion of all ectopics were not isolated but occurred as part of an arrhythmia sequence. There was, however, no increase in the complexity of atrial arrhythmias before atrial fibrillation onset. There were also no significant differences in the complexity of atrial arrhythmia dependent upon the presence or absence of a putative dominant atrial ectopic focus.

**Relation to previous studies**

The higher frequency of atrial ectopics before atrial fibrillation onset is in line with our previous report of a progressive increase in ectopics over the final 2 min prior to atrial fibrillation onset and the high frequency of ectopic beats before atrial fibrillation onset reported by others. The higher frequency of ectopic beats may reflect enhanced automaticity per se, or may be mediated by fluctuations in autonomic balance or increased atrial stretch related to posture or activity. The onset of arrhythmias such as automatic atrial tachycardia and torsades de pointes in the long QT syndrome may be initiated by raised catecholamine levels but the importance in triggering atrial ectopics is unknown. Certainly ventricular ectopic beats tend to be suppressed by exercise, a cause of sympathetic activation and vagal withdrawal.

Previous publications suggested that the degree of prematurity of atrial ectopics is critical to the atrial fibrillation initiation, at striking variance with the findings of this study. Killip and Gault reported that the ectopics which reinitiated atrial fibrillation following successful cardioversion had a mean prematurity index of 0·48 vs 0·65 of others. This is a difference of 0·17, compared with a difference of 0·04 in our study. Capucci et al. also reported that the coupling interval of the ectopic initiating atrial fibrillation was much shorter than that seen in ectopics unrelated to atrial fibrillation onset. Although it cannot be certain that study populations were directly comparable, we conceptually favour a critical role for the timing, site of origin, and nature of the ectopic focus rather than the degree of prematurity. Other re-entrant arrhythmias are
Figure 2  Representative histograms to illustrate the differing distributions. The coupling interval of ectopics (in ms) is given on the x-axis, with the y-axis indicating the proportion of all ectopics that occur at that coupling interval. The heavy line is the histogram for ectopics occurring during the 2 min preceding atrial fibrillation (i.e. in zone 2, see Fig. 1), and the thin line for ectopics remote from atrial fibrillation (zone 4). (a) Pattern A — a recording with many ectopics of a similar coupling interval before atrial fibrillation onset, but not remote from atrial fibrillation onset. (b) Pattern B — a large number of ectopics of approximately the same coupling interval both prior to and remote from atrial fibrillation onset. (c) Pattern C — a random distribution of ectopics.
The major limitation of this study is that atrial events were inferred from ventricular activity. As the conduction time of intra-atrial, His-Purkinje and in particular intra-atrioventricular nodal tissues between an ectopic focus are unlikely to be constant, a certain imprecision is introduced. Of particular concern is that non-conducted atrial ectopics and some of those provoking Wenckebach behaviour of the AV node cannot be identified. In terms of a screening test, however, utilization of ventricular timing is an advantage as R wave detection is robust against the effects of noise and is widely implemented in commercial systems.

It is likely that the ectopies of the same cycle length originate predominantly from a single focus, but this is a further potential imprecision of the technique used.

The optimal cut-off between beat to beat variability of sinus rhythm and long cycle length ectopics has not been precisely determined, but probably lies in the range of 70% to 85% of the median [33]. The threshold of 80% chosen in this study is an arbitrary level arrived at following investigation of several threshold duration ratios, each of which causes misclassifications in both directions (false positives where a sinus beat is very premature and false negative where atrial ectopics are late-coupled). In practice, we found that even a threshold of 95% gave similar results. This study used histograms of absolute coupling intervals rather than the prematurity index based ones. Histograms of prematurity index values were investigated in a pilot stage, but were found to be of inferior discriminatory power.

Conclusions

Paroxysmal atrial fibrillation is preceded by atrial ectopics of a fixed coupling interval in a significant proportion of cases. In some patients it is likely that these ectopics represent the focus for so-called ‘focal atrial fibrillation’, while in others, it represents an initiating trigger for multiple wavelet re-entry atrial fibrillation. In both situations, however, a clear target for ablation with the hope of reducing atrial fibrillation frequency is identifiable non-invasively. We believe that Holter techniques based upon these principles may provide a useful screening method for identifying patients who warrant fuller electrophysiological assessment. This study demonstrated no clinically important change in the prematurity of atrial ectopics or in the complexity of atrial premature beats arrhythmias before atrial fibrillation onset.

Funded in part by the British Heart Foundation.

Appendix

The automated method developed to perform user independent distribution classification used the parameters below. For clarity, three different terms are used: all ectopics (all short RR intervals, as defined in the text), the distribution peak (the region of the histogram within which there is a rise and then a decline in the frequency of ectopics) and the spike or maxima (the

<table>
<thead>
<tr>
<th>Rhythm remote from atrial fibrillation</th>
<th>A (n=8)</th>
<th>B (n=13)</th>
<th>C (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary ectopics</td>
<td>45 ± 31%</td>
<td>63 ± 19%</td>
<td>55 ± 26%</td>
</tr>
<tr>
<td>Atrial couplet</td>
<td>15 ± 10%</td>
<td>12 ± 12%</td>
<td>15 ± 13%</td>
</tr>
<tr>
<td>Run of atrial ectopics</td>
<td>30 ± 24%</td>
<td>14 ± 9%</td>
<td>27 ± 24%</td>
</tr>
<tr>
<td>Atrial bigeminy</td>
<td>11 ± 21%</td>
<td>10 ± 12%</td>
<td>5 ± 10%</td>
</tr>
<tr>
<td>Rhythm prior to atrial fibrillation</td>
<td>47 ± 24%</td>
<td>57 ± 23%</td>
<td>56 ± 33%</td>
</tr>
<tr>
<td>Solitary ectopics</td>
<td>21 ± 13%</td>
<td>16 ± 12%</td>
<td>18 ± 23%</td>
</tr>
<tr>
<td>Atrial couplet</td>
<td>25 ± 23%</td>
<td>12 ± 10%</td>
<td>18 ± 25%</td>
</tr>
<tr>
<td>Atrial bigeminy</td>
<td>7 ± 6%</td>
<td>15 ± 17%</td>
<td>6 ± 10%</td>
</tr>
</tbody>
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narrow area of the distribution with the highest number of ectopics).

- Peak at coupling intervals <600 ms.
- Ectopics within the peak comprised ≥7.5% of all ectopics for rhythm remote from atrial fibrillation (zone 4), and ≥10% for rhythm preceding atrial fibrillation (zone 2).
- Ectopics within the spike of the distribution were >40% of all ectopics within that distribution (>60% for very sharp narrow peaks).
- Maxima were required to be sharply peaked. This was tested by calculating the kurtosis of the distribution, which is a standard statistical test of sharpness of distributions.
- The width of the spike had to exceed 15 ms.
- Finally, if spike was present in both histograms, then the difference between the coupling intervals of the spikes was considered to ensure that they represented the same ectopic focus.

References


