Circadian variation of symptomatic paroxysmal atrial fibrillation

Data from almost 10 000 episodes

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Aims To determine the circadian rhythm of paroxysmal atrial fibrillation in a very large outpatient population.

Methods and Results We reviewed all emergency telephone calls received in Shahal (a medical service covering 44 000 subscribers), from 1987 to 1997. Patients were included if new-onset atrial fibrillation was recorded. During this study period, 9989 episodes of paroxysmal atrial fibrillation were recorded. The time of onset was not uniformly distributed throughout the 24 h period. Instead, the distribution of arrhythmic episodes showed a double peak, with a significant increase in the number of episodes in the morning and a second rise in the evening \((P<0.001)\). A non-uniform weekly distribution of events was also noted, with substantially fewer episodes on Saturdays \((P<0.001)\). Finally, more arrhythmias occurred during the last months of each year \((P<0.001)\).

Conclusions The onset of paroxysmal atrial fibrillation does not occur randomly. The large patient population in the present study suggests that the circadian rhythm of paroxysmal atrial fibrillation is similar to that described for other cardiovascular diseases, with clustering of events in the morning and (to a lesser degree) late in the evening. Weekly and yearly circadian patterns are also prominent. (Eur Heart J 1999; 20: 1429–1434)

Key Words: Atrial fibrillation, circadian rhythm, circadian variation.

See page 1369 for the Editorial comment on this article

Introduction

Circadian periodicity has been demonstrated for various cardiovascular syndromes, including sudden death and acute myocardial ischaemia or infarction\(^1\)\(^-\)\(^3\). In all these cardiovascular syndromes, an increased number of events occur early in the morning, and to a lesser degree, late in the evening\(^4\). This consistent circadian pattern has been asecribed to the increased sympathetic activity that exists in the early morning hours\(^4\).

Data on the time of onset and circadian rhythm of paroxysmal atrial fibrillation is limited to a few studies involving relatively small numbers of patients (from 37 to 726 patients)\(^5\)\(^-\)\(^8\). We present data on the time of onset of arrhythmic symptoms in more than 3000 patients with close to 10 000 episodes of paroxysmal atrial fibrillation.

Methods

We reviewed computerized data from ‘Shahal’, a medical service that covers 44 000 subscribers. As previously described\(^9\)\(^-\)\(^12\), Shahal consists of a central operations centre, managed by intensive care nurses, from which mobile intensive care units are dispatched. All mobile units are staffed by physicians and paramedics. Each applicant is personally interviewed by a physician when subscribing to Shahal and his medical record (including a 12-lead ECG) is stored in a central computer and is continuously updated. All members carry a cardiobeeper (Meridian Medical Technologies Inc. Washington DC, U.S.A.) for transtelephonic transmission of a three-lead (I, II, III) or a 12-lead ECG.


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Whenever a subscriber calls the centre, his medical file is immediately displayed on a computer screen. After obtaining all the necessary facts from the file and the transtelephonic ECG, the centre’s nurse may either: (a) dispatch a mobile intensive care unit; (b) consult the physician present at the centre or (c) provide the patient with appropriate medical or behavioral instructions. The nurse’s actions and decisions are based on written protocols, and all details of calls, including timetables and actions carried out by the centre, are fully recorded and stored. Subscribers are repeatedly encouraged to contact Shahal without delay whenever any new symptoms occur.[9]

For the present study, we reviewed the data of all emergency telephone calls received in Shahal between July 1987 and June 1997. Patients were included if atrial fibrillation was recorded by transtelephonic ECG. Patients with a history of chronic atrial fibrillation were excluded. Patients with more than one episode of atrial fibrillation were repeatedly entered into the study. However, only the first of all episodes reported within 24 h were evaluated.

**Statistical analysis**

The distribution of the number of paroxysmal atrial fibrillation episodes occurring during 24 h was tested with a chi-square test for goodness of fit to the uniform distribution. Comparison of the distribution of paroxysmal atrial fibrillation episodes between groups was performed by the non-parametric Kolmogorov–Smirnov test. Comparison between the groups of patients was done by chi-square test for discrete variables and t-test for continuous variables. A \( P \) value of <0·05 was considered significant.

**Results**

**Patient characteristics**

Paroxysmal atrial fibrillation occurred in 3343 patients (age=74·3 ± 12 years, 56% males) during the study period. The vast majority of patients had organic heart disease (mainly coronary heart disease) (Table 1). Data on the interval between onset of symptoms and the decision to call for medical assistance was available for 1334 (40%) patients reporting the most recent 3483 consecutive episodes of atrial fibrillation. Although the final patients were comparable to the whole patient cohort in regard to age, history of coronary disease, smoking, hypertension or diabetes, they were more likely to be females or to be prescribed beta-blockers and less likely to receive antiarrhythmic drugs. The cumulative interval between onset of symptoms and the transtelephonic ECG transmission showed that new-onset atrial fibrillation was \( \leq 1 \) h for 2185 (63%) episodes, \( \leq 2 \) h for 2472 (71%) episodes and \( \leq 3 \) h for 2629 (75%) episodes of atrial fibrillation. Thus, only 25% of episodes (for whom the duration of symptoms was recorded) lasted more than 3 h before symptoms related to paroxysmal atrial fibrillation were reported.

**Time of onset of paroxysmal atrial fibrillation**

During the study period (10 years), 9989 episodes of paroxysmal atrial fibrillation were recorded. The time of onset of atrial fibrillation was not uniformly distributed throughout the 24 h period. Instead, the distribution of episodic atrial fibrillation showed a double peak, with a significant increase in the number of episodes in the morning and a second rise in the evening (\( P<0·001 \), Fig. 1). A very similar pattern, with non-uniform distribution of events (early-morning and evening peaks) was observed among patients with a duration of symptoms known to be 3 h or less (Fig. 1B and C).

**Weekly and yearly circadian rhythm**

A non-uniform distribution of events was noted during the week (\( P<0·001 \), Fig. 2): episodic atrial fibrillation was significantly more common on Sundays and substantially less common on Saturdays (1·16 times and 0·84 times the daily average of the remaining 6 days of the week, respectively). The non-uniform distribution was also evident among patients with a duration of symptoms known to be 3 h or less (Fig. 2B). The number of episodes of paroxysmal atrial fibrillation was not

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**Table 1 Characteristics of 3343 patients who experienced 9989 episodes of paroxysmal atrial fibrillation during the study period**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient characteristics (n=3343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71 ± 12 years</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>56%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47%</td>
</tr>
<tr>
<td>Smokers</td>
<td>9%</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
</tr>
<tr>
<td>Old myocardial infarction</td>
<td>41%</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>23%</td>
</tr>
<tr>
<td>History of heart surgery</td>
<td>16%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>25%</td>
</tr>
<tr>
<td>History of PAF</td>
<td>53%</td>
</tr>
<tr>
<td>No heart disease*</td>
<td>4%</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>20%</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>24%</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>20%</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>31%</td>
</tr>
<tr>
<td>Tranquilizers</td>
<td>14%</td>
</tr>
</tbody>
</table>

*The definition of no heart disease includes absence of arterial hypertension.*

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uniformly distributed throughout the year ($P<0.001$, Fig. 3). Instead, the distribution of episodic atrial fibrillation showed a significant increase in the number of episodes towards the end of the year (autumn and winter).

Subgroup analysis

We found no difference in the pattern of distribution of paroxysms of atrial fibrillation between males and females. Also, similar circadian rhythms were observed among diabetics, among patients with a history of coronary disease and among patients with atrial fibrillation in the absence of heart disease. Six-hour and 4 h block times were also plotted against the type of medication received at the time of the arrhythmic event. The diurnal rhythm of atrial fibrillation was not blunted by drug therapy (including beta-blockers).

Discussion

The present study demonstrates a circadian pattern of symptomatic, out-of-hospital, paroxysmal atrial fibrillation, in a very large number of patients: Almost 10 000 episodes of atrial fibrillation, in 3343 patients (mainly patients with organic heart disease), were reviewed. In our large patient cohort, significantly more episodes of atrial fibrillation occurred in the morning (and to a lesser degree late in the evening) than during the afternoon and late night hours (Fig. 1). This diurnal
variation is similar to that reported previously for other cardiovascular syndromes, including out-of-hospital sudden death\cite{2}, stroke\cite{13}, and myocardial infarction\cite{1} or ischaemia\cite{3,14-18}. Interestingly, significantly fewer episodes of paroxysmal atrial fibrillation occurred during Saturdays (day of rest in Israel). Finally, a yearly circadian pattern was also noted. During the 10 years of the study, more arrhythmic episodes were noted during the late months of each year. The non-uniform weekly and yearly circadian pattern has not been described for paroxysmal atrial fibrillation. Interestingly, a similar seasonal pattern (with significantly fewer events during

Figure 2 Weekly distribution of episodes of paroxysmal atrial fibrillation for the whole study cohort (9989 arrhythmic episodes) (panel A) and for the 2629 episodes for which the duration of symptoms was known to be 3 h or less (panel B). The horizontal axis shows the day of the week (Sun=Sunday, Mon=Monday, Tue=Tuesday, etc.).

Figure 3 Yearly distribution of episodic atrial fibrillation. Data from 9989 arrhythmic episodes recorded over 10 years. The horizontal axis shows the month of the year (Jan=January, Feb=February, Mar=March, etc.).

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the summer) was recently described for acute myocardial infarction\cite{19} and for acute cardiogenic pulmonary oedema\cite{20}.

**Previous studies**

Four studies have attempted to determine the daily circadian rhythm of paroxysmal atrial fibrillation\cite{5-8}. These studies, however, included substantially fewer patients than the present one, and only three of them included more than 100 patients\cite{6-8}. First, a Finnish group\cite{6} detected a circadian rhythm similar to the one found in the present study. In the Finnish study, which included 130 patients, the majority of episodes started between 0600 h and 1200 h or between 1800 h and 0000 h. Subsequently, an Italian group\cite{7} reported the time of onset of atrial fibrillation in 726 patients. These investigators also reported an uneven distribution of events. However, the majority of arrhythmias in the Italian study occurred at night (between 2100 h and 0200 h). Finally, a Japanese study\cite{8} analysed the time of onset of atrial fibrillation in 151 patients with no organic heart disease. In contrast to all other studies (including the present one), the Japanese study used Holter recordings — rather than presentation with symptoms — to estimate the onset of atrial fibrillation. Again, a non-even, double-peak distribution of events was noted: this time, most episodes occurred between 1200 h and 1500 h or at night (between 2000 h and 0000 h). The differences in the timing of the events observed in previous studies could be related to inadequate patient population size. This further emphasizes the importance of the very large number of arrhythmias (almost 10 000 episodes of atrial fibrillation) included in the present study. Lastly, the tendency of paroxysmal atrial fibrillation to occur at certain hours of the day may suggest that antiarrhythmic regimens should attempt to achieve maximal effects at the time of maximal chances of arrhythmias.

**Limitations**

Our study cohort includes mainly patients with underlying heart disease, many of whom received antiarrhythmic drugs in an uncontrolled fashion. Limitations inherent to retrospective studies apply to our present report. In addition, our study shares the flaw of most previous studies\cite{5-7}, in that the time of onset of the arrhythmia was derived from the time of a telephone call reporting symptoms. Thus, our data relate only to symptomatic arrhythmias. Also, our results overestimate the time of onset of atrial fibrillation by the sum of the time lag between the onset of the arrhythmia and the appearance of symptoms and the interlude between the onset of symptoms and decision to call for medical help.

The magnitude of the delay between the onset of symptoms and the decision to call for medical help was known for only 40% of patients (the most recent arrhythmic episodes included in our study, representing 35% of all arrhythmic episodes in the study cohort). However, even this figure, which represents 3140 episodes of atrial fibrillation, is more than three times larger than the total number of episodes reported in all previous studies together\cite{6-8}. Patients for whom the duration of symptoms was known differed from the rest in several clinical variables (including gender and use of medications). However, these variables did not affect the circadian pattern of paroxysmal atrial fibrillation in our study.

The correlation between the initiation of the arrhythmia and the onset of symptoms in our patients is less clear. Based on data from ambulatory electrocardiographic monitoring, Page et al\cite{21} reported that for each symptomatic episode of atrial fibrillation, at least six episodes of ‘sustained atrial fibrillation’ occur without symptoms. It should be noted, however, that the definition of sustained atrial fibrillation used by Page et al included arrhythmias lasting ‘30 s or more.’ The clinical significance of such a definition is questionable. More relevant to our observations are the data reported by Yamashita et al\cite{8}. These investigators reported that 29% of episodes of atrial fibrillation ‘lasting 1 min or more’, were accompanied by symptoms. However, whenever symptoms occurred, the symptomatology started within 30 min of the onset of arrhythmia in the majority (79%) of patients\cite{8}. This suggests that the interlude between the onset of arrhythmia and symptoms in our patients was not very long.

**Conclusion**

The onset of paroxysmal atrial fibrillation does not occur randomly. All studies (of 100 patients or more) looking at this phenomenon concluded that paroxysmal atrial fibrillation exhibits circadian variation. The very large patient population in the present study strongly suggest that the circadian rhythm of symptomatic paroxysmal atrial fibrillation is similar to that described for other cardiovascular diseases, with clustering of the majority of symptomatic events early in the morning and (to a lesser degree) late in the evening. Weekly and yearly circadian patterns are also prominent.

**References**


