Spontaneous Occurrence of Symptomatic Paroxysmal Atrial Fibrillation and Paroxysmal Supraventricular Tachycardia in Untreated Patients

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Background. Ambulatory outpatients (n=150) with a history of paroxysmal supraventricular arrhythmia were studied to establish the characteristics of the first recurrence of symptomatic tachycardia (time to first recurrence, heart rate during tachycardia, and observed rhythm that was regular versus irregular) when no antiarrhythmic drug was being taken. Baseline variables were examined to assess their impact on time to first recurrence: index arrhythmia (paroxysmal atrial fibrillation [n=37] versus paroxysmal supraventricular tachycardia [n=113]), age (mean±SD, 43.3±16.1 years), female sex (n=71), or presence of other heart or lung disease (n=53).

Methods and Results. Transtelephonic monitoring of the ECG was used to document the rhythm during recurrences of symptomatic tachycardia. Time to first recurrence of symptomatic tachycardia and heart rate during tachycardia were measured, the observed rhythm was classified as irregular (consistent with paroxysmal atrial fibrillation) or regular (consistent with paroxysmal supraventricular tachycardia), and the hour of recurrence was recorded. Advancing age was significantly associated with a decreasing time to first recurrence (p<0.001); the estimated increase in the hazard function was 25% with each 10 years of advancing age. After the effect of age was adjusted for, neither the classification of arrhythmia (p>0.2), presence of other heart or lung disease (p>0.8), nor sex (p>0.9) was significantly associated with time to first recurrence. Among patients with paroxysmal supraventricular tachycardia, 6.5% had atrial fibrillation recorded at the next symptomatic arrhythmia; among patients with paroxysmal atrial fibrillation, 11.8% had a regular tachycardia recorded at the next symptomatic arrhythmia. There was a circadian pattern to the hour of occurrence of paroxysmal supraventricular tachycardia but not paroxysmal atrial fibrillation.

Conclusions. Age is more important than other clinical variables, including the ECG classification of a paroxysmal supraventricular arrhythmia in predicting the occurrence of symptomatic arrhythmias. Arrhythmias documented by ECG during symptoms are often different from the arrhythmia documented at the time of referral, which may confound interpretation of antiarrhythmic drug effects. (Circulation 1993;87:1114–1122)

Key Words • fibrillation, atrial • circadian rhythm • electrocardiography • tachycardia, paroxysmal • tachycardia, supraventricular • Wolff-Parkinson-White syndrome

Paroxysmal supraventricular arrhythmias are frustrating disorders for patients and physicians. Their sporadic and transient nature may result in delayed diagnosis and difficulty in assessing antiarrhythmic drug effects. These arrhythmias can be classified by ECG criteria and by electrophysiological criteria obtained with intracardiac recording and programmed electrical stimulation, but little is known about the value of these classifications in predicting differences in the occurrence of the arrhythmias. The purpose of this study, therefore, was to assess the impact of arrhythmia classification and other clinical variables on the spontaneous occurrence of paroxysmal supraventricular arrhythmias in untreated patients.

Methods

Patient Sample

We studied a consecutive series of 150 patients (79 men and 71 women) referred to the Clinical Research Unit Arrhythmia Clinic between 1980 and 1991 who met ECG criteria for paroxysmal supraventricular tachycardia or paroxysmal atrial fibrillation and who underwent an observation period during which they received no antiarrhythmic drug treatment. The ECG criteria for paroxysmal supraventricular tachycardia were a ventric-
ular rhythm with a rate >120 beats per minute, a QRS morphology during tachycardia that was either normal or functional bundle branch block, <20 msec variation in successive RR intervals, no evidence of atrioventricular dissociation, and episodic occurrence. The ECG criteria for paroxysmal atrial fibrillation were a grossly irregular ventricular rhythm, a QRS morphology during arrhythmia that was either normal or functional bundle branch block, the absence of identifiable P waves when they had been obvious on ECGs during sinus rhythm, and episodic occurrence. On the basis of these criteria, the “index arrhythmia” for each patient was classified as either paroxysmal supraventricular tachycardia or paroxysmal atrial fibrillation.

Other information obtained at the time of referral included demographic variables, a description of any other heart or lung disease present, and the results of electrophysiology studies when they were available. In addition to their paroxysmal supraventricular arrhythmia, 53 patients had at least one other heart or lung disease, including 18 with valvular heart disease, 17 with hypertension, and seven with chronic obstructive lung disease (Table 1). Twenty-four of the patients (all with paroxysmal supraventricular tachycardia) had an ECG recorded during sinus rhythm that showed a short PR interval and a delta wave on the QRS complex consistent with the Wolff-Parkinson-White syndrome. None of the patients could reliably trigger his or her arrhythmia by any specific activity, beverage, or food.

Fifty-six of the patients with paroxysmal supraventricular tachycardia underwent electrophysiology study with intracardiac recording and programmed stimulation to establish the mechanism of their arrhythmia; these electrophysiology studies were done for clinical indications rather than for research purposes. On the basis of the results of the electrophysiology studies, paroxysmal supraventricular tachycardia was subclassi-
24 hours of these ECG transmissions, we contacted the patients and asked them to describe their episode, including the clock time that it began. Notes of these telephone contacts and representative samples of the observed arrhythmia were archived in laboratory log books.

The tachycardia-free period was measured as the time interval from the start of the drug-free observation period to the first documented symptomatic tachycardia. ECG rhythm strips recorded during symptomatic arrhythmias were used to calculate heart rate and to compare the observed rhythm with the index arrhythmia. In patients whose index arrhythmia was paroxysmal supraventricular tachycardia, the observed rhythm was considered concordant with the index rhythm if it was regular and discordant if it was irregular (consistent with atrial fibrillation). In patients whose index arrhythmia was paroxysmal atrial fibrillation, the observed rhythm was considered concordant with the index rhythm if it was irregular and discordant if it was regular (resembling paroxysmal supraventricular tachycardia and consistent with atrial flutter or an atrial tachycardia).

This protocol was approved by the Duke University Medical Center Committee on Clinical Investigations. All patients gave informed consent before participation.

Data Analysis

There were three outcome variables of interest: 1) the length of time in days from the beginning of the drug-free observation period to the first recurrence of paroxysmal supraventricular arrhythmia; 2) the heart rate during that arrhythmia; and 3) the time of day that the arrhythmia occurred. Primary analyses assessed the effects of age, sex, and the presence of other heart or lung disease on these outcome variables and compared the distributions of the outcome variables between the patients whose index arrhythmia was paroxysmal supraventricular tachycardia and those whose index arrhythmia was paroxysmal atrial fibrillation.

Secondary analyses compared the distributions of recurrence time and heart rate during arrhythmia within three classifications of the patients whose index arrhythmia was paroxysmal supraventricular tachycardia: 1) patients with and without the Wolff-Parkinson-White syndrome, 2) patients with electrophysiology studies whose arrhythmia mechanism was atrioventricular reentry and those whose mechanism was atrioventricular nodal reentry, and 3) patients whose mechanism was atrioventricular reentry with conduction over an accessory pathway in both antegrade and retrograde directions and those with conduction only in the retrograde direction.

We used the Kaplan-Meier product-limit method to estimate and to illustrate graphically the proportion of patients remaining free of arrhythmia on each day of the drug-free observation period. The proportional-hazards model was used to assess the effect of age on the recurrence-time distribution and to compare the recurrence-time distributions between subgroups of patients with and without adjustment for potential confounders (age, sex, and the presence of other heart or lung disease). The magnitude of these effects is expressed in terms of the hazard ratio (HR), the constant ratio of two proportional-hazard functions representing instantaneous risks of arrhythmic recurrences. Since recurrences of paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation behave, in general, like Poisson processes, this HR is equivalent to the ratio of the frequency with which these arrhythmias occur during long follow-up periods.

For the patients who experienced a symptomatic episode of paroxysmal supraventricular arrhythmia, comparisons of heart rate during arrhythmia between subgroups were made with two-sample t tests; linear regression models were used to adjust these comparisons for potential confounders. The confidence intervals for proportions are exact binomial confidence intervals.

The time of day that the episode occurred was categorized into six 4-hour intervals beginning at midnight to determine whether distribution of the time of episode was consistent with a discrete uniform distribution, implying a constant risk of episode throughout the day. This categorization was also used to analyze the relation of time of episode to age, sex, and the presence of other heart or lung disease. The consistency of the higher risk of other heart and lung disease in atrial fibrillation compared with supraventricular tachycardia across these 4-hour intervals was evaluated with the χ² statistic for testing the homogeneity of the odds ratios.

For each of the two index arrhythmias, the relative frequency of episodes within each of twelve 2-hour intervals beginning at midnight was used in a linear regression model to estimate a sinusoidal density function with a period of 24 hours:

\[ f(t) = \beta_0 + \alpha \sin(2\pi t/24 + \phi), \quad 0 \leq t < 24 \]

or, equivalently,

\[ f(t) = \beta_0 + \beta_1 \sin(2\pi t/24) + \beta_2 \cos(2\pi t/24), \quad 0 \leq t < 24 \]

The departure of this density function from the uniform density on the 24-hour interval was tested by ANOVA for the regression model; the two densities were also compared directly with each other by a single regression model containing an indicator variable for the index arrhythmia and interaction terms between this indicator and the two trigonometric terms.

Results

Length of Time to Recurrence of Supraventricular Arrhythmia

Of the 150 patients in the study population, 126 experienced a symptomatic episode of paroxysmal supraventricular arrhythmia during the drug-free observation period that was observed and documented by ECG by use of the telephone monitor system. Twenty-five percent of the patients had an episode of symptomatic tachycardia by day 4 and 50% by day 23 (Figure 1A).

Age was significantly associated with the time to a symptomatic episode (p < 0.001); the estimated increase in the hazard function associated with 10 years of advancing age was 25%. The recurrence-time distributions for the older and younger halves of the study population are illustrated in Figure 1B. Although the presence of other heart or lung disease appeared to be associated with the time to an episode (Figure 1C), this difference was not significant either before (HR = 1.16, p > 0.4) or after (HR = 1.04, p > 0.8) adjustment for the effect of age. Male sex also had no effect on the time to
a symptomatic episode, either before or after adjustment for age (HR=0.9, p>0.4 in both models).

Of the 150 patients followed during an antiarrhythmic drug-free observation period, 113 had paroxysmal supraventricular tachycardia as their index arrhythmia, and 37 had paroxysmal atrial fibrillation. The patients with atrial fibrillation were significantly older (p<0.001) and had a significantly higher prevalence of other heart or lung disease (p=0.05) than the patients whose index arrhythmia was supraventricular tachycardia (Table 1). The estimated recurrence-time distributions for the two index arrhythmias are shown in Figure 1D; atrial fibrillation as an index arrhythmia was associated with significantly shorter recurrence times (HR=1.6, p<0.03). However, the difference in the recurrence time distributions between the two groups was no longer significant after adjustment for the effect of age (HR=1.3, p>0.2). Furthermore, there was no evidence that the age effect differed between the two index arrhythmias (Figure 2).

In an analysis containing both index arrhythmias, the interaction between age and the index arrhythmia was not significant (χ²=0.3, p>0.5). In separate analyses for the two index arrhythmias, the HR for each year of advancing age was 1.02 for both.

Among the 113 patients with paroxysmal supraventricular tachycardia, 24 had short PR intervals and a delta wave on the QRS complex of the ECG recorded during sinus rhythm consistent with the Wolff-Parkinson-White syndrome. These patients were significantly younger than the 89 patients without this syndrome (mean ages, 29.5 and 43.4 years, respectively; p<0.001). However, the longer recurrence times associated with this syndrome were not significant either before (HR=0.8, p>0.3) or after (HR=0.9, p>0.8) adjustment for age.

Of the 113 patients with paroxysmal supraventricular tachycardia, 56 underwent electrophysiology studies; the mechanism of their supraventricular tachycardia
Patients with atrial fibrillation (age-adjusted HR = 1.5, p > 0.3) (Figure 3). The recurrence time distributions also showed no significant difference between those patients with conduction only in the retrograde direction and those with conduction in the antegrade direction (age-adjusted HR = 1.5, p > 0.3).

Heart Rate and Ventricular Rhythm During Observed Supraventricular Arrhythmias

Among the 126 patients who experienced a symptomatic episode of paroxysmal supraventricular arrhythmia that was observed and documented by ECG, the index arrhythmia was paroxysmal supraventricular tachycardia in 92 and atrial fibrillation in 34 (Table 2). Among the 92 patients with paroxysmal supraventricular tachycardia, the ventricular rhythm recorded during the observed arrhythmia was discordant with the index arrhythmia (i.e., it was irregular and consistent with paroxysmal atrial fibrillation) in six patients (6.5%, with 95% CI of [2.4%, 13.7%]); the mechanism of tachycardia was atrioventricular reentry in two of these six patients, atrioventricular nodal reentry in one, and unknown in three. The observed arrhythmia was concordant with the index arrhythmia (regular and consistent with paroxysmal supraventricular tachycardia) in 86 (94.5%). Among the 34 patients with paroxysmal atrial fibrillation, the ventricular rhythm recorded during the observed arrhythmia was discordant with the index arrhythmia (i.e., the rhythm was regular and consistent with paroxysmal supraventricular tachycardia) in four (11.8%, with 95% CI of [3.3%, 27.4%]); it was concordant (irregular and consistent with paroxysmal atrial fibrillation) in 30 (88.2%). Age was significantly correlated with heart rate during observed arrhythmia (r = -0.34, p < 0.001), heart rate decreasing with advancing age. Although the mean heart rate was lower in patients with other heart or lung disease than in those without other heart or lung disease (mean heart rates, 168.3 and 182.8 beats per minute, respectively), the difference was not significant either before (p = 0.08) or after (p > 0.5) adjustment for age. The difference in heart rate during observed arrhythmia for men and women (mean, 173.6 and 182.8 beats per minute, respectively) was not significant.

In a comparison of heart rates of observed arrhythmias that were concordant with the index arrhythmia (i.e., regular ventricular rhythm when the index arrhythmia was paroxysmal supraventricular tachycardia and irregular ventricular rhythm when the index arrhythmia was atrial fibrillation), the mean heart rate during regular ventricular rhythms was significantly greater than the mean heart rate during irregular ventricular rhythms (age-adjusted mean heart rates, 196.0 and 135.5 beats per minute, respectively; p < 0.001) (Table 2).

In the patients whose index arrhythmia was paroxysmal supraventricular tachycardia, the mean heart rate during an observed episode with a regular ventricular rhythm was significantly greater than that during an episode with an irregular ventricular rhythm (age-adjusted mean heart rates, 197.4 and 135.9 beats per
minute, respectively; \( p<0.001 \). Similarly, in patients whose index arrhythmia was atrial fibrillation, the mean heart rate during an observed episode with a regular ventricular rhythm was substantially greater than that during an observed episode with an irregular ventricular rhythm (age-adjusted mean heart rates, 165.0 and 131.9 beats per minute, respectively), but the difference was not significant (\( p=0.07 \)).

There were no significant differences in the comparisons of age-adjusted mean heart rates during observed supraventricular arrhythmias between those with and without the Wolff-Parkinson-White syndrome (205.4 and 195.4 beats per minute, respectively; \( p>0.3 \)), those with atrioventricular reentry compared with those with atrioventricular nodal reentry (198.9 and 204.3 beats per minute, respectively; \( p>0.6 \)), or those with and without conduction in the antegrade direction over an accessory pathway (200.5 and 199.7 beats per minute, respectively; \( p>0.9 \)).

Circadian Distribution of Observed Supraventricular Arrhythmias

Among the 126 patients who experienced a symptomatic episode of paroxysmal supraventricular arrhythmia, 124 were able to recognize the time that their arrhythmia began: nine (7.3%) between midnight and 4 AM, 17 (13.7%) between 4 AM and 8 AM, 21 (16.9%) between 8 AM and noon, 23 (18.6%) between noon and 4 PM, 32 (25.8%) between 4 PM and 8 PM, and 22 (17.7%) between 8 PM and midnight. This distribution differed significantly from the discrete uniform distribution \( (X^2=13.8, p<0.02) \); thus, the risk of episode was not constant throughout the day. There were no significant relations between these six time intervals and either age \( (F_{5.118}=0.74, p>0.5) \) or sex \( (X^2=2.70, p>0.7) \), but the presence of other heart or lung disease did vary significantly among the six intervals \( (X^2=12.4, p<0.03) \), ranging from a prevalence of 14.3% among the patients whose episodes occurred between 8 AM and noon to a

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bpm, Beats per minute; PSVT, paroxysmal supraventricular tachycardia; PAF, paroxysmal atrial fibrillation.
prevalence of 55.6% among those whose episodes occurred between midnight and 4 AM. Based on the relative frequency of episodes in twelve 2-hour intervals beginning at midnight, the estimated sinusoidal density function for the time of episode in paroxysmal supraventricular tachycardia was

$$f(t) = 0.0417 - 0.0195 \sin(2\pi t/24) - 0.0070 \cos(2\pi t/24)$$

and this density was significantly different from the uniform density ($F_{29}=9.08, p<0.01$). The maximum incidence of episode in paroxysmal supraventricular tachycardia (the maximum of the density function) occurs at approximately 6 PM; the incidence there is 2.75 times the minimum incidence at 6 AM (Figure 4). The corresponding density for the time of episode in atrial fibrillation was

$$f(t) = 0.0417 + 0.0018 \sin(2\pi t/24) - 0.0089 \cos(2\pi t/24)$$

but this density was not significantly different from the uniform density ($F_{29}=1.60, p>0.2$). Furthermore, these two density functions were significantly different from each other ($F_{1,18}=4.61, p<0.03$) and there was no evidence that the difference was attributable to the effect of other heart and lung disease, because the higher risk of other heart and lung disease associated with atrial fibrillation was consistent across the six 4-hour intervals ($\chi^2=3.01, p>0.7$).

Discussion

This study reports several important new insights into the spontaneous occurrence of symptomatic paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation. We found that among the many factors that could influence the occurrence of these arrhythmias, age was most important. Older patients had symptomatic recurrences of their arrhythmias significantly sooner after beginning a drug-free observation period. Symptomatic arrhythmias also occurred sooner in the subgroup of patients with paroxysmal atrial fibrillation than in those having paroxysmal supraventricular tachycardia, but age differences in the subgroups accounted for this apparent effect of arrhythmia mechanism. There was a substantial discordance between the diagnosis of the index arrhythmia made at the start of the study and the arrhythmia observed during the study. We found differences in heart rates among observed arrhythmias, regular tachycardias being uniformly faster than irregular tachycardias. In addition, we found no evidence for a sinusoidal circadian pattern in the occurrence of paroxysmal atrial fibrillation, in contrast to the sinusoidal density function that described the circadian occurrence of paroxysmal supraventricular tachycardia.

Length of Time to the Occurrence of Supraventricular Arrhythmia

In our study of untreated patients who were known to have paroxysmal supraventricular arrhythmias, the patient's age was the clinical characteristic most closely associated with the tachycardia-free period. We found that 10 years of age was associated with a 25% increase in the hazard function. This suggests that a 30-year increase in age would be associated with a doubling of the frequency of arrhythmia episodes. Since our study was cross-sectional rather than longitudinal, we do not know whether the age effect represents arrhythmia progression in individual patients, a cohort effect, or a distinctive referral pattern in our population. If it represents a longitudinal effect, then young patients with paroxysmal supraventricular arrhythmias can expect to experience more frequent arrhythmias as they get older. Confirmation that this is indeed a longitudinal effect would provide some rationale for early intervention with radiofrequency ablation in patients with paroxysmal supraventricular tachycardia.

Paroxysmal atrial fibrillation was associated with shorter tachycardia-free periods than paroxysmal supraventricular tachycardia, but this difference was attributable to the differences in age between the two groups. Moreover, the specific mechanism of the paroxysmal supraventricular tachycardia determined by electrophysiology study (atrioventricular nodal reentry versus atrioventricular reentry) failed to influence significantly the length of time to the occurrence of arrhythmia.

Heart Rate and Ventricular Rhythm During Supraventricular Arrhythmia

Observations from electrophysiology laboratories and from ambulatory monitoring laboratories have shown that paroxysmal supraventricular tachycardia sometimes precipitates atrial fibrillation.11-15 In most of these studies, patients were instrumented with catheters or were taking antiarrhythmic drugs, either of which might have contributed to the change in rhythm. Our present study provides a useful estimate of how often this transition may occur spontaneously in untreated patients. In our patients known to have paroxysmal supraventricular tachycardia, 6.5% had atrial fibrillation recorded at the time of their next symptomatic tachycardia. The true percentage might be even higher than...
our estimate, since our ECG monitor sampled only 30 seconds of tachycardia that lasted for several minutes to several hours. Conversely, among patients known to have paroxysmal atrial fibrillation, 11.8% had a regular tachycardia, most likely atrial flutter.

This discordance between the index arrhythmia and the observed arrhythmia had an important impact on the heart rate during observed tachycardia: regular rhythms were substantially faster than irregular rhythms in all comparisons (Table 2). The magnitude of these differences for both index arrhythmias is large enough to be clinically important in the interpretation of antiarrhythmic drug effects. For example, a patient known to have paroxysmal atrial fibrillation with a mean ventricular rate of 130 beats per minute would have about one chance in nine of having a regular tachycardia with ventricular rate of 165 beats per minutes with his next episode of tachycardia if he were receiving no antiarrhythmic drug. If he were receiving an antiarrhythmic drug, this new, faster rhythm might be interpreted as a "proarrhythmic" drug effect and lead to an inappropriate adjustment in drug therapy. In a clinical trial of an antiarrhythmic drug, such an observation might be misinterpreted as an adverse event attributable to investigational drug therapy. In addition, implantable cardioverter defibrillators that are programmed to a rate cut-off that distinguishes atrial fibrillation from ventricular arrhythmias may try to convert atrial flutter because the rate of this rhythm exceeds the programmed rate for ventricular arrhythmia intervention.16

Circadian Distribution of the Occurrence of Supraventricular Arrhythmia

Our finding of a circadian distribution of occurrence of paroxysmal supraventricular tachycardia is consistent with our previous report of such a pattern in a smaller sample of patients.5 We did not, however, observe a circadian distribution in our patients with paroxysmal atrial fibrillation. Coumel et al17 suggested that a substantial number of patients with paroxysmal atrial fibrillation have episodes induced by high vagal tone and that atrial fibrillation occurs at night in such patients. We found no increased incidence of symptomatic atrial fibrillation at night and thus cannot confirm Coumel's hypothesis that increased vagal tone contributes to a large number of episodes of atrial fibrillation.

Limitations

Because our study was designed to assess the symptomatic occurrence of supraventricular arrhythmias, our conclusions do not apply to the occurrence of asymptomatic supraventricular arrhythmias. It is the symptomatic supraventricular arrhythmias that are the focus of patients' complaints and physicians' therapeutic interventions. Additionally, clinical trials of antiarrhythmic drugs have used the prevention of symptomatic, not asymptomatic, recurrences of supraventricular arrhythmias as end points.18,19

The use of continuous ambulatory monitoring to detect all recurrences of supraventricular arrhythmias, both symptomatic and asymptomatic, might have demonstrated results different from ours. However, continuous ambulatory monitoring techniques are not practical in the clinical management of patients with paroxysmal supraventricular arrhythmias, treating asymptomatic arrhythmias is not a common practice, and recent clinical trials of antiarrhythmic drug therapy for these arrhythmias have not used continuous ambulatory monitoring to assess outcome.18-21

Another limitation of the study is that the effect of advancing age on reducing the time to recurrence could have been caused by improved compliance among older patients. Although we have no direct measure of compliance, it is our impression that compliance among our patients was high regardless of age.

Clinical Implications

Our findings suggest that the type of paroxysmal supraventricular arrhythmia and the specific mechanism of the arrhythmia are less important in predicting the frequency with which an arrhythmia recurs than is the age of the patient. This information should be considered in both the management of individual patients and the design of antiarrhythmic drug trials. The presence of a circadian distribution of tachycardia in patients with paroxysmal supraventricular tachycardia and the absence of such a distribution in paroxysmal atrial fibrillation may have implications for the administration of antiarrhythmic drugs to these two groups of patients.

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