Asymptomatic Arrhythmias in Patients With Symptomatic Paroxysmal Atrial Fibrillation and Paroxysmal Supraventricular Tachycardia

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Background Paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia are recognized clinically when patients seek treatment for symptoms due to recurrent arrhythmias; atrial fibrillation also increases the risk of stroke. The frequency with which asymptomatic arrhythmias occur in patients with these arrhythmias is unknown.

Methods and Results Twenty-two patients with paroxysmal atrial fibrillation (n=8) or paroxysmal supraventricular tachycardia (n=14) were studied for 29 days with two different ambulatory ECG-monitoring techniques to measure the relative frequency of asymptomatic and symptomatic arrhythmias. All class I antiarrhythmic drugs, calcium channel blockers, β-blockers, and digitalis was withheld. Sustained asymptomatic arrhythmia events (defined as lasting at least 30 seconds) were documented using continuous ambulatory ECG monitoring once weekly for a total of 5 of the 29 study days; symptomatic arrhythmia events were documented using transtelephonic ECG monitoring for all 29 days of the study. In the group of patients with paroxysmal atrial fibrillation, asymptomatic arrhythmia events occurred significantly more frequently than symptomatic arrhythmia events; the mean rates, expressed as events/100 d/patient (95% confidence interval), were 62.5 (40.4, 87.3) and 5.2 (2.7, 9.0) (P<.01); the ratio of the mean rates was 12.1 (5.8, 26.4). In contrast, in the group of patients with paroxysmal supraventricular tachycardia, asymptomatic arrhythmia events were significantly less frequent than symptomatic arrhythmia events; the mean rates were 0.0 (0.0, 5.3) and 7.4 (5.0, 10.6) (P=.02). The ratio of the mean rates was 0.0 (0.0, 0.8).

Conclusions In a group of patients with paroxysmal atrial fibrillation, sustained asymptomatic atrial fibrillation occurs far more frequently than symptomatic arrhythmia. However, it is not known whether asymptomatic atrial fibrillation is a potential risk factor for stroke even when patients are not having symptomatic arrhythmias. (Circulation. 1994;89:224-227.)

Key Words • arrhythmias • tachycardia • fibrillation, atrial • tachycardia, supraventricular

P aroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia are common arrhythmias that may be treated with antiarrhythmic drugs when patients have symptoms. Patients who are affected with these disorders have sinus rhythm that is punctuated by episodic recurrences of their arrhythmias. The sequence of these recurrent arrhythmia events can be described in mathematical terms as a "stochastic process," which is a series of events occurring in time in accordance with probabilistic laws.1 In this study, we used methods developed to study stochastic processes to estimate the average rate of asymptomatic arrhythmia events in groups of patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia.

Methods

The study sample consisted of 22 ambulatory outpatients (7 men and 15 women with mean±SD age of 47±17 years) who were being followed in the Clinical Research Unit Arrhythmia Clinic because they had a paroxysmal supraventricular arhythmia.2 Eight of these patients had paroxysmal atrial fibrillation defined by the following ECG criteria: (1) a mean rate >120 beats per minute, (2) QRS morphology during tachycardia that is either normal or functional bundle branch block, (3) a grossly irregular ventricular rhythm, (4) the absence of P waves or the presence of fibrillatory waves in the baseline when P waves had been recorded during periods of sinus rhythm, and (5) episodic occurrence. There were 5 men and 3 women with mean±SD age of 54±19 years in the paroxysmal atrial fibrillation group. A total of 5 of the patients had some associated heart or lung disease, including 3 with valvular heart disease, 1 with hypertension, 1 with premature ventricular beats, 1 with left bundle branch block, 1 with chronic obstructive lung disease, and 1 with a history of partial pneumonectomy. None of the patients with paroxysmal atrial fibrillation had the Wolff-Parkinson-White syndrome.

Fourteen subjects had paroxysmal supraventricular tachycardia identified by ECG criteria: (1) a mean rate >120 beats per minute, (2) QRS morphology during tachycardia that is either normal or functional bundle branch block, (3) <0.02-second variation in successive RR intervals, (4) no evidence of atrioventricular dissociation, and (5) episodic occurrence. The mechanism of the arrhythmia was atrioventricular nodal reentry in 1 patient, atrioventricular reentry in 3, and unknown in 10. There were 2 men and 12 women with mean±SD age of 42±13 years in the paroxysmal supraventricular tachycardia group. A total of 5 of the patients had associated heart or lung disease, including 1 with valvular heart disease, 1 with hypertension, 2 with asthma, and 1 with chronic bronchitis. The Wolf-Parkinson-White syndrome was present in 2 of the patients with paroxysmal supraventricular tachycardia.
Methods

Recording Methods

The study period for each patient lasted 29 days, during which all class I antiarrhythmic drugs, calcium channel blockers, β-adrenergic blockers, and digoxin were withheld, except verapamil was used in some patients with paroxysmal supraventricular tachycardia for acute treatment of symptomatic tachycardias; none of the patients had ever used a class III antiarrhythmic drug. During this entire period, patients used a portable monitor (Cardiooobeper Memory Monitor; Survival Technology, Bethesda, Md) to record their ECG when they had symptoms of tachycardia and to transmit the ECG to us using a toll-free telephone number. ECGs were received by a 24-hour-a-day automatic answering device, and we called patients back daily (7 days per week) if they transmitted ECGs. These ECGs were archived in laboratory log books. All patients were in sinus rhythm on the first day of the study.

We also used 24-hour continuous ambulatory ECG monitors (QuikTrak; Zymed Medical Instrumentation, Camarillo, Calif) to record arrhythmias during the study period. These monitors recorded ECG leads V₁ and V₅. These continuous recordings were done on the first day of the study period and then once weekly for the next 4 weeks for a total of five recordings in 29 days. In this way, all patients had 29 days in which symptomatic arrhythmias were recorded with the Cardiobeep and 5 days in which asymptomatic arrhythmias were also recorded using the continuous recorders. If the patient had a symptomatic arrhythmia while wearing the continuous recorder, we asked him or her first to push the event marker button on the continuous recorder and second to record the ECG with the Cardiobeep. Continuous ambulatory ECG recordings were analyzed using a Zymed Model 1610 system. All arrhythmias lasting 5 or more beats were written on chart paper at 25 mm/s for review by a cardiologist who coded them in the following way:

1. A “sustained” asymptomatic event was defined as an arrhythmia lasting at least 30 seconds recorded by 24-hour continuous monitors in the absence of symptoms. This definition is arbitrary and based on the way “sustained” is often defined in the study of ventricular tachycardia by electrophysiological techniques. For a patient with an asymptomatic event of any length, sinus rhythm was considered “restored” after 5 consecutive sinus beats.

2. A “sustained” symptomatic event was defined as an episode of paroxysmal atrial fibrillation or paroxysmal supraventricular tachycardia that was documented using the Cardiobeep. Events that were recognized and documented by the event marker on the 24-hour continuous ECG monitor but not documented by Cardiobeep were excluded from analysis; that is, these latter events were not considered either symptomatic or asymptomatic.

3. When a patient had a symptomatic (recorded by Cardiobeep) arrhythmia event, any symptomatic or asymptomatic event recorded within 1 hour of the termination was considered part of the preceding symptomatic event.

Data Analysis

The comparisons of average rates of asymptomatic and symptomatic arrhythmia events in the group of 8 patients with paroxysmal atrial fibrillation and the 14 patients with paroxysmal supraventricular tachycardia were based on theoretical properties of renewal processes, stochastic point processes in which the time intervals between successive point events are independent random variables with a common distribution. It has been shown previously that recurrences of symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia typically behave as a Poisson process, a renewal process in which the interevent times are exponentially distributed and the number of events in a time interval of length t has a Poisson distribution with mean λt where λ is the rate of occurrence. To study the average rate of symptomatic (asym-
monitoring in each patient; 30 sustained symptomatic arrhythmia events were recorded in 29 days of transtelephonic ECG monitoring. The mean rate of this arrhythmia was 0.0 (0.0, 5.3) events/100 d/patient for asymptomatic events and 7.4 (5.0, 10.6) for symptomatic events ($P=0.02$); thus, asymptomatic events were less frequent than symptomatic events. The ratio of the mean rates was 0.0 (0.0, 0.8); thus, asymptomatic events were at most about 80% as frequent as symptomatic events.

**Discussion**

This study is important because it shows that in a group of patients with symptomatic paroxysmal atrial fibrillation, sustained asymptomatic atrial fibrillation occurred 12.1-fold as often as sustained symptomatic atrial fibrillation. The 95% confidence interval for this estimate indicated that the asymptomatic rate was at least 5.8-fold the symptomatic rate.

In another group of patients with a different arrhythmia, paroxysmal supraventricular tachycardia, asymptomatic and symptomatic arrhythmias behaved quite differently. In this group of patients, sustained asymptomatic paroxysmal supraventricular tachycardia was never recorded during the study, and the estimated ratio of the mean rates (asymptomatic to symptomatic) therefore was 0.0; the 95% confidence interval showed that this ratio was at most 0.8. Thus, in the group of patients with paroxysmal supraventricular tachycardia, sustained asymptomatic arrhythmias occurred much less often than symptomatic arrhythmias. This behavior was in sharp contrast with the behavior of paroxysmal atrial fibrillation, in which asymptomatic events occurred many times more frequently than symptomatic events.

Like many clinical investigations, this study raised more questions than it answered. For example, is “sustained” atrial fibrillation lasting 30 seconds really clinically important? We defined 30 seconds as a “sustained” arrhythmia because ventricular tachycardia induced by programmed stimulation is defined this way.3,4 From the point of view of using antiarrhythmic drugs to improve a patient's sense of well-being, asymptomatic atrial fibrillation is not a clinical problem that merits attention. If, however, such an arrhythmia increases the risk of stroke, then it could be an important clinical problem. In the Framingham Heart Study, chronic atrial fibrillation was associated with a substantially increased risk of stroke.7,8 In the Stroke Prevention in Atrial Fibrillation study, the risk of stroke was not significantly different between patients who had intermittent atrial fibrillation and patients who were permanently in atrial fibrillation; and in the Boston Area Anticoagulation Trial for Atrial Fibrillation, the percent of patients with intermittent atrial fibrillation was approximately equal in patients with and without stroke (13% versus 17%, $P=NS$).9 Unfortunately, the risk of stroke from asymptomatic atrial fibrillation compared with these other types of atrial fibrillation is simply not known.

Another interesting question is, “How does antiarrhythmic drug therapy affect asymptomatic atrial fibrillation?” How does “successful” control of symptomatic paroxysmal atrial fibrillation affect the occurrence of asymptomatic atrial fibrillation? Does it eliminate asymptomatic events, or does it increase the frequency of them by slowing the ventricular rate during recurrent arrhythmias and converting symptomatic events into asymptomatic events? This issue is important for clinicians. Some authors have recommended that patients with atrial fibrillation discontinue anticoagulation 3 or 4 weeks after successful cardioversion as if successful antiarrhythmic therapy were successful antiembolic therapy.11,12 If asymptomatic atrial fibrillation poses a continuing risk of stroke in such patients, discontinuing anticoagulation may be inappropriate.

**Study Limitations and Clinical Implications**

In conducting this study, we combined observations from individual patients with a particular arrhythmia to estimate the average frequency with which asymptomatic and symptomatic arrhythmias occurred in a group of patients with that arrhythmia. We took advantage of an important feature of renewal processes: if a large number of events are contributed from many different individuals, the resulting sequence of events is a Poisson process, even if the individual processes are not. The characteristics of each individual process cannot be inferred from the combined process. In this study, we cannot infer anything about the relative frequency of asymptomatic and symptomatic arrhythmias in individual patients; in different patients with atrial fibrillation, the asymptomatic and symptomatic events may occur with very different relative frequencies. However, studying the stochastic processes formed by the successive occurrences of asymptomatic and symptomatic paroxysmal arrhythmias in an individual patient is extremely difficult because many events of both types must be recorded from each patient.5 It should also be noted that the number of patients reported here is small, and these patients may not be representative of samples of patients with these arrhythmias who could be selected in other clinical settings.

It is our current clinical recommendation that antiarrhythmic drug therapy is most appropriate for control of symptoms due to recurrent arrhythmias and that anticoagulation therapy with warfarin or aspirin is the only proven method to reduce the risk of stroke in patients with atrial fibrillation.13 The value of continuous ambulatory ECG monitoring in the clinical management of patients with paroxysmal atrial fibrillation is unknown because we do not know how much atrial fibrillation is required to confer an increased risk of stroke, and we do not know how much arrhythmia-free recording must be done to establish that the risk of stroke is absent or substantially reduced. However, understanding the effect of antiarrhythmic drug therapy on symptomatic and asymptomatic paroxysmal atrial fibrillation requires further study.

**Acknowledgments**

This work was supported in part by grant RO1-HL-40392 from the National Heart, Lung, and Blood Institute, Bethesda, Md, and by grant MO1-RR30 from the National Center for Research Resources, National Institutes of Health, Bethesda, Md.

**Appendix**

For the $i$th patient ($i=1,2,\ldots,n$), suppose that symptomatic and asymptomatic events occur according to independent Poisson processes $[N_{s}(t), t>0]$ and $[N_{a}(t), t>0]$ with intensities (or rates) $\lambda_{s}$ and $\lambda_{a}$, respectively. For example, if the fourth patient experiences one symptomatic event every 20 days, on
average, so that the intensity $\lambda_n$ is 0.05 event per day, and if $N_n(29)$ represents the number of symptomatic events experienced by this patient in an observation period of $t=29$ days, then the assumption that the events constitute a Poisson process implies that $N_n(29)$ has a Poisson distribution with mean $\lambda_n t = 1.45$; that is:

$$P[N_n(29) = x] = e^{-\lambda_n t}(\lambda_n t)^x/x!, x = 0, 1, 2, \ldots$$

If the symptomatic processes $[N_i(t), t > 0], i = 1, 2, \ldots, n$ are superimposed, the resulting process, $[N_n(t), t > 0]$ is also a Poisson process and its intensity is $\Sigma \lambda_n$. For moderately large $n$, $[N_n(t), t > 0]$ is approximately a Poisson process even if the superimposed processes are not themselves Poisson processes. Similarly, the superposition of the asymptomatic processes $[N_i(0), t > 0], i = 1, 2, \ldots, n$ yields a Poisson process $N_n(t)$ with intensity $\Sigma \lambda_i$.

The $n$ symptomatic processes have all been observed for a period of 29 days so that $N_n(29)$, the total number of symptomatic events that occur among the $n$ patients in 29 days, has a Poisson distribution with mean $29 \Sigma \lambda_n$. Similarly, $N_n(5)$, the total number of asymptomatic events that occur among the $n$ patients in 5 days, has a Poisson distribution with mean $5 \Sigma \lambda_n$.

For any Poisson-distributed random variable $X$ with mean $\mu$, an exact confidence interval for $\mu$ based on the observation $X = x$ can be characterized as follows. In a test at a significance level $\alpha$ of the hypothesis $H_0: \mu = \mu_0$ against the alternative $H_1: \mu \neq \mu_0$, the observation $x$ is said to be consistent with $H_0$ if it leads to acceptance of $H_0$. A 100$(1-\alpha)%$ confidence interval for $\mu$ consists of those values of $\mu$ with which the observation $x$ is consistent; that is, the confidence interval is given by $(\mu_L, \mu_U)$ where $\mu_L$ and $\mu_U$ are defined by:

$$\sum_{x=0}^{\infty} e^{-\mu}_x \frac{\mu^x}{x!} = \alpha/2$$

and

$$\sum_{x=0}^{\infty} e^{-\mu}_x \frac{\mu^x}{x!} = (1-\alpha)/2$$

Thus, the observed values of the random variables $N_n(29)$ and $N_n(5)$ can be used to construct confidence intervals for the parameters $29 \Sigma \lambda_n$ and $5 \Sigma \lambda_n$ and, consequently, for the average intensities $\lambda_n = (\Sigma \lambda_n)/n$ and $\lambda_i = (\Sigma \lambda_i)/n$.

A test of the equality of $\lambda_i$ and $\lambda_n$ and a confidence interval for their ratio can be obtained from the following well known result: if $X_1$ and $X_2$ are independent, Poisson-distributed random variables with means $\mu_1$ and $\mu_2$, respectively, then conditional on $X_1 = x_1$, $X_2 = x_2$ has a binomial distribution with parameters $m$ and $p = \mu_1/\mu_2$. Thus, if $N_n(5)+N_n(29)=m$, $N_n(5)$ has a binomial distribution with parameters $m$ and $p = [1 + (29/5) \lambda_i/\lambda_n]^{-1}$. The equality of $\lambda_i$ and $\lambda_n$ can be tested with the binomial test of $H_0: p = [1 - (29/5) \lambda_i/\lambda_n]^{-1}$.

A confidence interval for the ratio $\lambda_i/\lambda_n$ can be obtained by first constructing a confidence interval for $p = [1 + (29/5) \lambda_i/\lambda_n]^{-1}$. Using an argument analogous to the one used for Poisson random variables, a 100$(1-\alpha)%$ confidence interval for $p$ is given by $(\hat{p}, \bar{p})$ where $\hat{p}$ and $\bar{p}$ are defined by:

$$\sum_{k=0}^{\infty} \frac{n!}{k!(n-k)!} p^k(1-p)^{n-k} = \alpha/2$$

and

$$\sum_{k=0}^{\infty} \frac{n!}{k!(n-k)!} \bar{p}^k(1-\bar{p})^{n-k} = \alpha/2$$

By monotonicity, the inequality $\hat{p} < p < \bar{p}$ is equal to the inequality

$$(1-\bar{p})/(29/5) \bar{p} < \lambda_i/\lambda_n < (1-\hat{p})/(29/5) \hat{p}$$

Thus, $[(1-\bar{p})/(29/5) \bar{p}, (1-\hat{p})/(29/5) \hat{p}]$ is a 100$(1-\alpha)%$ confidence interval for $\lambda_i/\lambda_n$.

References

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Circulation. 1994;89:224-227
doi: 10.1161/01.CIR.89.1.224

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