Progressive Nature of Paroxysmal Atrial Fibrillation

— Observations From a 14-Year Follow-up Study —

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Atrial fibrillation (AF) is believed to occur first as paroxysmal, then be gradually perpetuated, and finally become chronic as the end result. However, this presumed clinical course has not been well confirmed. To construct a therapeutic strategy for AF, the long-term view of its clinical course is needed for decision making, because treatment will vary according to the clinical history of each patient. In the Framingham Study, 55–64-year-old male patients with AF have a long mean life period of 12.6 years, although it can be worse than for patients with chronic AF, the latter being the end result of paroxysmal AF and chronic AF, the latter being the end result. However, this presumed clinical course has not been well confirmed, because the progression of the arrhythmia is much more gradual than the follow-up periods of many previous studies.

To construct a therapeutic strategy for AF, the long-term view of its clinical course is needed for decision making, because treatment will vary according to the clinical history of each patient. In the Framingham Study, 55–64-year-old male patients with AF have a long mean life period of 12.6 years, although it can be worse than for patients with sinus rhythm. These observations strengthen the importance of understanding the long-term outcome of AF.

Recent mega-trials, including the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study and the Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) Study, have investigated the clinical course of AF prospectively, and thus proposed important clues to constructing the treatment strategy for AF. However, the AFFIRM results were derived from a composite patient population of paroxysmal AF and chronic AF, the latter being the end result of paroxysmal AF and the RACE Study only included patients after electrical cardioversion of persistent AF. Therefore, the clinical course of paroxysmal AF from its onset is still unknown and the purpose of the present study was to define the clinical course of paroxysmal AF from its onset to its presumed end result of chronic AF, taking a long-term perspective.

Methods

Study Population

We researched our database of 24-h ambulatory electrocardiogram (ECG) recordings to identify patients with paroxysmal AF (PAF). Patients were enrolled if they had visited the hospital for the first time during the period from May 1961 to September 1999 and their first episode of PAF and its recurrence were documented at the hospital. The recurrence of PAF was ascertained by 12-lead ECG at the monthly visit and/or 24-h ambulatory ECG monitoring obtained during the period from January 1997 to December 2002. All the patients with recurrent PAF were generally followed up monthly and treated with antiarrhythmic drugs, which were changed as required by the attending physicians when they assessed the prescribed drugs as ineffective.

Data Collection

All patient data were entered into a computerized database: gender, age, date of PAF onset, date of chronic AF development, fractional shortening (FS), left atrial dimension (LAD), histories of defibrillation, medication, congestive heart failure, heart surgery and hypertension, the presence of diabetes, and underlying structural heart diseases including angina pectoris, myocardial infarction, dilated cardiomyopathy, hypertrophic cardiomyopathy, valvular diseases and others. The onset of PAF was defined clinically according to the patients’ symptoms together with ECG documentation or only the ECG when AF was recorded incidentally.
Chronic AF was defined clinically when defibrillation of PAF was unsuccessful (permanent AF) or AF was continuously observed for more than 6 months (persistent AF). FS and LAD were recorded by echocardiography, as near to the onset of PAF as possible. Valvular diseases were also identified by echocardiography by the following criteria: mitral/atrial regurgitation ≥ grade 3, mitral valve area <2.0 cm² and/or atrial valve area <1.5 cm².

Statistical Analysis

Statistical analysis was performed with StatView 5.0 (SAS Institute Inc, Cary, NC, USA). Parametric data are expressed as mean ± SD. Survival curves were estimated by the Kaplan-Meier product-limit method and compared by means of Mantel (log-rank) test. The effect of prognostic factors on chronic AF development was evaluated with Cox models. We tested the following covariates: age (years), gender (female, male), FS (%), LAD (mm), history of defibrillation (yes, no), history of congestive heart failure (yes, no), heart surgery (yes, no), history of hypertension (yes, no), angina pectoris (yes, no), myocardial infarction (yes, no), hypertrophic cardiomyopathy (yes, no), and valvular disease (yes, no). All p values were two-tailed and values of <0.05 were considered statistically significant. All confidence intervals (CI) were calculated to the 95th percentile.

Results

Baseline Characteristics of the Study Population

From our database we identified 171 patients who had visited hospital at the time of presumed PAF onset and had been followed thereafter. The main baseline characteristics of the population are shown in Table 1. The mean duration of follow-up was 14.1±8.1 years; 27% of the patients were women and approximately 50% of the patients had no underlying structural heart disease (‘lone PAF’). The mean age at onset of PAF was 58.3±11.8 years old and no difference was observed between the absence and presence of structural heart diseases (Fig 1).

Antiarrhythmic Therapy

During the follow-up period, the drugs were changed as
necessary according to the judgment of the attending physicians and Table 2 outlines the drugs used for the prevention of PAF. Vaughan Williams class 1 antiarrhythmic drugs were frequently used, which was considered as a tendency of Japanese physicians,\(^{10}\) and a class 3 drug (amiodarone) was administered in only 1 patient (0.6%). Defibrillation by direct current shock was undertaken in 52.6% of the patients (Table 1).

Development Into Chronic AF

Fig 2A shows the time-course of the ratio of patients in whom sinus rhythm was maintained without developing chronic AF during the follow-up period. In each panel, year zero indicates the presumed onset of paroxysmal AF. Paroxysmal AF developed into its chronic form with overall annual ratio of 5.5% per year (A). In patients with structural heart diseases, prevalence of sinus rhythm was significantly lower than those without structural heart diseases (*p*<0.05, B). Patients with cardiomyopathy and myocardial infarction were significantly more likely to develop chronic AF (*p*<0.05, C).

Fig 2. Ratio of patients in whom sinus rhythm was maintained without developing chronic AF during the follow-up period. In each panel, year zero indicates the presumed onset of paroxysmal AF. Paroxysmal AF developed into its chronic form with overall annual ratio of 5.5% per year (A). In patients with structural heart diseases, prevalence of sinus rhythm was significantly lower than those without structural heart diseases (*p*<0.05, B). Patients with cardiomyopathy and myocardial infarction were significantly more likely to develop chronic AF (*p*<0.05, C).

Effects of Drugs

The effects of drugs on maintaining sinus rhythm were evaluated by adding the variables to the Cox proportional hazard model. Even after their addition, the significant independent variables for early progression to chronic AF were unaltered, and a history of hypertension or heart failure remained insignificant. Among the drugs investigated, digitalis, calcium channel blocker, \(\text{\&}\) channel blocker and angiotensin-converting enzyme inhibitor did not affect the progression to chronic AF, whereas angiotensin-receptor blocker showed a tendency to prevent chronic AF development (HR 0.36, 95% CI 0.17–0.74, \(p=0.048\)). However, this finding might be inconclusive because of the relatively short follow-up period and the small population of patients (12 patients).

Discussion

The major findings of this long-term study were as follows. (1) Paroxysmal AF developed into its chronic form with an overall incidence of 5.5% per year in Japanese, and (2) aging, an enlarged left atrium, myocardial infarction and valvular diseases were independent risk factors for early development into chronic AF.

The recent AFFIRM\(^6\) and RACE\(^7\) studies have presented the clinical course of AF by investigating a large number of patients prospectively in the US and Europe.\(^6,7\) In the
AFFIRM Study, the prevalence of sinus rhythm in the rhythm-control group at follow-up was 82.4%, 73.3%, and 62.6% at 1, 3, and 5 years, respectively, and the RACE Study reported the prevalence as 39% at the end of a follow-up period of 2.3±0.6 years. However, patients included in those studies had various types of AF and therefore the results might be different from the present study, which concentrated on the clinical course from the onset of PAF. Moreover, the mean follow-up time of the present study was 14.1 years, which is markedly longer than either the AFFIRM Study (3.5 years) or the RACE Study (2.3 years).

The present study, though retrospective, is the first to report the long-term clinical course of PAF after its apparent onset. From a long-term perspective, surprisingly, most cases of PAF gradually but eventually developed into chronic AF with an overall annual ratio of 5.5%. Aging, an enlarged left atrium, myocardial infarction and valvular disease significantly increased the development ratio. Unfortunately, most cases of PAF were not curable and developed into chronic AF irrespective of rhythm control therapy. However, it should be noted that the present results were obtained in Japanese clinical situations. In Japan, Vaughan Williams class 3 antiarrhythmic drugs are not permitted for prevention of PAF by the health insurance except for cases complicated by hypertrophic cardiomyopathy. In the present study, therefore, almost all the cases were treated with class 1 antiarrhythmic drugs and from a short-term viewpoint, the antiarrhythmic treatment was relatively effective; the prevalence of sinus rhythm as 95.3%, 81.7%, 70.9% at 1, 3, and 5 years after PAF onset, respectively. However, the higher prevalences in the present study could be partially related to the younger population (mean 58.3±11.8 years at PAF onset) than in the previous studies (eg, mean 69.7±9.0 years and 68±8 years at entry in the AFFIRM Study and the RACE Study, respectively).

In addition, we should point out another characteristic of the present study: the prevalence of patients without structural heart disease was higher than in the US or Europe; however, this is also the character of Japanese patients with PAF, and relatively good efficacy has been observed in a short-term study reported in Japan. Actually, the Japanese Antiarrhythmics Long-Term Study-2 (JALT-2) followed-up Japanese patients with PAF for a mean period of 463 days, and reported that PAF progressed to its chronic form in 10.9% of the patients (8.6% per year) under antiarrhythmic treatment. Those short-term results are in accordance with the present report.

From the long-term perspective, however, our study has revealed for the first time that the prevalence of sinus rhythm without development into chronic AF was quite low, 42.9% and 23.8%, at 10 and 15 years, respectively. Consequently, at 20 years after PAF onset, sinus rhythm was maintained in only 10.6% of the patients and development into chronic AF was observed in the remaining 89.4%. Although many class 1 antiarrhythmic drugs have been reported to be effective for maintaining sinus rhythm, this is not the case in the long-term prevention of AF. The inconsistency in efficacy between short- and long-term effects suggests the importance of the recent concept of electrical and structural remodeling. In the short-term, PAF could be suppressed by antiarrhythmic drugs, but might not be prevented completely and this incompleteness of the conventional antiarrhythmic therapy might promote remodeling and make the AF more refractory. These possibilities are supported, in part, by the existence of asymptomatic PAF which is more common than expected although it partially alleviated by the use of antiarrhythmic drugs.

Previous investigators have shown ischemic heart disease and valvular disease as independent risk factors for AF and aging and increased left atrial size have been also identified as important risk factors. In accordance with those previous reports, our study, using multivariate analysis, revealed that these 4 factors were significant predictors of early chronic AF development. In contrast, although congestive heart failure, hypertension and diabetes were identified as significant risk factors in the Framingham Study, these factors were not significant perpetuators of AF in the present study. However, inclusion of left atrial dimension as a variable in our study may account for this inconsistency. The hazards of congestive heart failure, hypertension, and diabetes as risk factors for chronic AF development can be explained by an enlarged left atrium, which is an independent risk factor. Similarly, although patients with dilated or hypertrophic cardiomyopathy...
developed chronic AF significantly earlier than those without structural heart diseases, these were not independently significant factors in multivariate analysis, suggesting that the cardiomyopathy might also perpetuate the AF through enlargement of the left atrium.\(^6\)

We have 2 controversial strategies for the treatment of AF: one is cardioversion followed by treatment with antiarrhythmic drugs (rhythm control), and the other is controlling heart rate while allowing the AF to persist (rate control). Initial therapy for AF is often directed toward rhythm control\(^5\) because of fewer possible symptoms and better quality of life under the treatment.\(^6\) However, the AFFIRM, RACE and Strategies of Treatment of Atrial Fibrillation (STAF) studies revealed that the rhythm-control strategy offers no survival advantage over the rate-control strategy and has potential disadvantages,\(^6\)\(^,\)\(^7\)\(^,\)\(^26\) such as adverse drug effects or the need for more hospitalization.\(^2\) Another disadvantage of the rhythm-control is unawareness of asymptomatic PAF.\(^2\)\(^7\)\(^,\)\(^26\) The present results also support the limitations of the rhythm-control strategy from the longer-term viewpoint. In almost all cases PAF is a gradually progressive disease, even with apparently effective antiarrhythmic treatment, which can become poorly responsive to the treatment. This character of PAF is remarkable when patients are old, have underlying heart disease or an enlarged left atrium.

Because of the long-term observations, there are several limitations to the present results. First, because the study population was composed of only Japanese, the results cannot be extrapolated to different ethnic groups. Second, we can not deny some bias involved in the present study. Actually, the number of patients who suffered from stroke was relatively small, which might have resulted from some of the patients not being able to be followed at the hospital after the onset of severe stroke. However, at present, clinical observations for such a long period can not be gained by any other method than this retrospective one. Lastly, in Japan, as discussed, Vaughan Williams class 3 antiarrhythmic drugs are not used generally for AF prevention. Long-term results for Japanese patients using the class 3 drugs are unknown. Although limited for these reasons, the present study augments the understanding of the long-term course of PAF and the construction of a therapeutic strategy from a long-term perspective.

References


