Symptoms of Atrial Fibrillation in Patients With and Without Subsequent Permanent Atrial Fibrillation Based on a Retrospective Questionnaire Survey

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SUMMARY

The aim of the present study was to determine whether symptoms of atrial fibrillation (AF) differ between patients with and without subsequent permanent AF. Sixty-four patients (68 ± 10 years old, 45 males) were recruited. AF follow-up was started at the age of 61 ± 10 years and accomplished in a median period of 4.9 years (396 person-years). Permanent AF, defined as lasting > 180 days, developed in 17 patients (14 males) (43 per 1000 person-years). The AF follow-up period was longer in the permanent AF group than in the non-permanent AF group (median, 9.8 versus 4.2 years, $P < 0.001$). For baseline characteristics, hypertension was less frequent in the permanent AF group than in the nonpermanent AF group (18% versus 45%, $P < 0.05$). A retrospective questionnaire survey regarding initial AF symptoms was conducted. The severity of AF symptoms by a 4-grade scale was significantly milder in the permanent AF group than in the nonpermanent AF group ($P < 0.05$). Cox proportional hazards model analysis revealed that the severity of initial AF symptoms was related to the subsequent development of permanent AF (hazard ratio 0.46 per grade, 95% confidence interval 0.23 - 0.93, $P < 0.05$), but age, gender, hypertension, diabetes mellitus, organic heart disease, and left atrial dimension were not. The permanent AF-free rate was significantly lower in 33 patients with mild symptoms than in 31 patients with severe symptoms (log-rank test, $P < 0.05$). These results point to an inconspicuous feature in the development of permanent AF. (Int Heart J 2010; 51: 242-246)

Key words: Arrhythmia, Heart failure, Hypertension, Susceptibility

The severity of symptoms is quite an important factor for determining the prognosis of patients with organic heart disease. The New York Heart Association classification of cardiac performance is clearly related to subsequent cardiac events. Syncope is a risk factor for sudden cardiac death in patients with a Brugada-type electrocardiogram. As a consequence, symptoms affect the treatment of such diseases. Atrial fibrillation (AF) causes variable symptoms, from mild which are subclinical, to severe requiring emergency care. Very slightly symptomatic AF is allowed and left; by contrast, severely symptomatic AF requires intensive therapies to restore or maintain sinus rhythm. AF usually occurs in a paroxysmal or persistent form, and then develops into a permanent form when the feasibility of restoring sinus rhythm becomes extremely low.^{1,2)} We believe that patients' perceptions of their symptoms may be associated with the course of AF. To clarify whether the symptoms of AF differ between patients with and without subsequent development of permanent AF, a retrospective questionnaire survey was carried out.

METHODS

Ethical issues: The study was conducted in accordance with

Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol and written subject information were reviewed and approved by the ethics committee of Tokyo Medical and Dental University. Sixty-four patients (68 ± 10 years old, 45 males) provided written informed consent prior to entry; 3 other patients who refused were not included.

Study patients: Patients were selected from hospital files beforehand and recruited between May and November 2008. AF follow-up was started at the age of 61 ± 10 years and accomplished in a period of 4.9 (2.4, 8.9) [median (first and third quartiles)] years (396 person-years). Permanent AF was defined as AF lasting > 180 days and confirmed by consecutive ECG recordings and medical charts. Permanent AF developed in 17 of the 64 patients during the follow-up (43 per 1000 person-years). Onset of permanent AF was at the start of AF follow-up in 2 patients and overall after a follow-up period of 4.2 (1.9, 5.1) years, which was similar to the full length of 47 patients without permanent AF [4.2 (1.9, 6.2) years, $P = 0.78$]. The full AF follow-up period was significantly longer in the permanent AF group [9.8 (8.2, 12.4) years] than in the non-permanent AF group ($P < 0.001$). Mean age at entry and gender were not significantly different between the groups (permanent AF group, 71 ± 8 years old, 14 males; non-permanent AF group, 66 ± 11 years old, 31 males; $P = 0.11$, $P = 0.20$, re-

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Received for publication November 30, 2009.

Revised and accepted April 5, 2010.

spectively).

Patient characteristics at the start of AF follow-up in both groups as well as at the development of permanent AF in the permanent AF group or at entry in the non-permanent AF group were checked. These included age, hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, cardiomyopathy, valvular heart disease, heart failure, sick sinus syndrome, atrioventricular block, cerebrovascular disease, and CHADS₂ score.¹⁾ Valvular heart disease was identified by a history of valvular surgery or by echocardiography demonstrating significant stenosis or regurgitation of any valve that was more severe than mild. Heart failure was defined as the presence of symptoms such as dyspnea, fatigue, and peripheral edema necessitating diuretics or vasodilator therapy.

Laboratory findings were checked in regard to the start of AF follow-up as well as to the development of permanent AF in the permanent AF group or at entry in the non-permanent AF group. A temporal difference of less than 1 year was allowed. Heart rate during AF and left atrial dimension by echocardiography irrespective of the contemporary rhythm were evaluated.

Treatments for AF until the development of permanent AF in the permanent AF group, or until entry in the non-permanent AF group were examined. These included drugs for rhythm and rate control, renin-angiotensin system (RAS) inhibitors (angiotensin converting enzyme inhibitors and angiotensin receptor blockers), and pulmonary vein isolation by radiofrequency catheter ablation.

Questionnaire survey: We interviewed the patients before or after a regular medical examination using a questionnaire regarding the symptoms of initial episodes of AF. Flash-back period, severity, and frequency on a 4-grade scale were included. Severity was selected from: #1, asymptomatic; #2, discomfort with keeping usual activity; #3, laboring/restricted on stairs; #4, requiring acute care; and frequency from: #1, ≤ 3 times/year; #2, ≤ 1 time/month; #3, ≤ 1 time/week; #4, > 1 time/week.

Statistical analysis: Data are expressed as the mean $\pm$ SD or median (first and third quartiles). Differences in representative values were tested by Student's *t*-test or the Mann-Whitney *U*

test, and those in frequencies by the chi-square test, Fisher exact probability test, or Mann-Whitney *U* test. Permanent AF relative risk was estimated for age, gender (male), hypertension, diabetes mellitus, organic heart disease including valvular heart disease, ischemic heart disease and cardiomyopathy, heart failure, left atrial dimension at the start of AF follow-up, and severity of the initial AF symptoms using the Cox proportional hazards model. Permanent AF-free survival was assessed in regard to severity of the initial AF symptoms with a log-rank test (Kaplan-Meier method). The starting point was set at the first day of AF follow-up and the endpoint at the first day of permanent AF. A *P* value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics: The clinical characteristics of the patients are listed in Table I. Mean age was similar between the groups both at the start of AF follow-up and at the development of permanent AF in the permanent AF group or at entry in the non-permanent AF group. At the start of AF follow-up, the frequencies of underlying diseases were not significantly different between the groups except for hypertension, with the frequency of the permanent AF group being about 40% that of the non-permanent AF group (18% versus 45%, *P* < 0.05). The incidence of hypertension increased thereafter, maintaining the proportion between the permanent AF group at the development of permanent AF and the non-permanent AF group at entry (24% versus 64%, *P* < 0.01). The incidence of other underlying diseases remained unchanged or increased, but there was no significant difference between the permanent AF group at the development of permanent AF and the non-permanent AF group at entry. The CHADS₂ score was not significantly different between the groups at the start of AF follow-up, but was significantly lower in the permanent AF group at the development of permanent AF compared to the non-permanent AF group at entry [0 (0, 1) versus 1 (1, 2), *P* < 0.05].

Laboratory findings: The laboratory findings are shown in Ta-

Table I. Clinical Characteristics of Patients

	Permanent AF group (<i>n</i> = 17)				Non-permanent AF group (<i>n</i> = 47)	
	Start of AF follow-up	<i>P</i> [*]	Development of permanent AF	<i>P</i> [†]	Start of AF follow-up	Entry
Age, years	61.0 $\pm$ 9.2	0.94	65.1 $\pm$ 9.7	0.67	61.6 $\pm$ 10.7	66.4 $\pm$ 10.8
Hypertension, %	17.6	0.048	23.5	0.004	44.7	63.8
Diabetes mellitus, %	11.8	0.89	11.8	0.81	6.4	8.5
Dyslipidemia, %	17.6	0.32	35.3	0.83	27.7	38.3
Ischemic heart disease, %	11.8	0.89	11.8	0.55	6.4	14.9
Cardiomyopathy, %	11.8	0.73	11.8	0.73	10.6	10.6
Valvular heart disease, %	11.8	0.81	17.6	0.60	8.5	19.1
Heart failure, %	11.8	0.64	11.8	0.39	12.8	19.1
Sick sinus syndrome, %	0	0.39	0	0.10	6.4	14.9
Atrioventricular block, %	5.9	0.27	5.9	0.27	0	0
Cerebrovascular disease, %	17.6	0.19	17.6	0.82	6.4	12.8
CHADS ₂ score	0 (0, 1)	0.69	0 (0, 1)	0.049	0 (0, 1)	1 (1, 2)

Data are mean $\pm$ SD or frequency or median (first and third quartiles). AF indicates atrial fibrillation. ^{*}, [†] Versus non-permanent AF group, start of AF follow-up and entry, respectively.

Table II. Laboratory Findings

	Permanent AF group				Non-permanent AF group	
	Start of AF follow-up	<i>P</i> [*]	Development of permanent AF	<i>P</i> [†]	Start of AF follow-up	Entry
Heart rate during AF/minute	83 ± 23 (<i>n</i> = 9)	0.24	85 (80, 91) (<i>n</i> = 17)	0.99	93 ± 22 (<i>n</i> = 25)	83 (77, 95) (<i>n</i> = 22)
Left atrial dimension, mm	39 (39, 45) (<i>n</i> = 7)	0.48	46 ± 6 (<i>n</i> = 11)	0.015	40 (36, 43) (<i>n</i> = 35)	40 ± 6 (<i>n</i> = 30)

Data are mean ± SD or median (first and third quartiles). AF indicates atrial fibrillation. ^{*},[†] Versus non-permanent AF group, start of AF follow-up and entry, respectively.

Table III. Treatments for Atrial Fibrillation

	Permanent AF group [*] (<i>n</i> = 17)	Non-permanent AF group (<i>n</i> = 47)	<i>P</i>
Rhythm control drugs, %	70.6	76.6	0.62
Rate control drugs, %	52.9	61.7	0.53
RAS inhibitors, %	11.8	51.1	0.005
Pulmonary vein isolation, %	0	14.9	0.10

Data are frequency. AF indicates atrial fibrillation; and RAS, renin-angiotensin system. ^{*}Before development of permanent AF.

Table IV. Summary of Questionnaire Results Regarding Initial Episodes of Atrial Fibrillation

	Permanent AF group (<i>n</i> = 17)				Non-permanent AF group (<i>n</i> = 47)				<i>P</i>
Flash-back period, years	10 (8, 18)				7 (4, 10)				0.004
Severity	#1	#2	#3	#4	#1	#2	#3	#4	0.022
%	23.5	47.1	23.5	5.9	8.5	36.2	25.5	29.8	
Frequency	#1	#2	#3	#4	#1	#2	#3	#4	0.89
%	61.5	0.0	0.0	38.5	52.3	6.8	11.4	29.5	

Data are median (first and third quartiles) or frequency. AF indicates atrial fibrillation.

ble II. Neither electrocardiographic nor echocardiographic data were complete among the patients. At the start of AF follow-up, heart rate during AF and left atrial dimension were not significantly different between the groups. Thereafter, heart rate during AF remained similar between the groups. Meanwhile, left atrial dimension was significantly larger in the permanent AF group at the development of permanent AF (46 ± 6 mm) than in the non-permanent AF group at entry (40 ± 6 mm) ($P < 0.05$).

Treatments for AF: Treatments for AF until permanent AF development and in the non-permanent AF group are summarized in Table III. Drugs both for rhythm control and for rate control were used comparably in the 2 groups. RAS inhibitors with a minimum duration of 84 days were less frequently administered in the permanent AF group than in the non-permanent AF group (12% versus 51%, $P < 0.01$). Pulmonary vein isolation had been performed solely in the non-permanent AF group, without a significant difference.

Questionnaire results: The questionnaire results are summarized in Table IV. The flash-back period of the initial episodes of AF was significantly longer in the permanent AF group [10 (8, 18) years] than in the non-permanent AF group [7 (4, 10) years] ($P < 0.01$). The severity of the initial AF episodes was

milder in the permanent AF group than in the non-permanent AF group ($P < 0.05$). In particular, the mildest grade (#1) was chosen by 24% of the permanent AF group and 9% of the non-permanent AF group; in contrast, the severest grade (#4) was chosen by 6% of the permanent AF group and 30% of the non-permanent AF group. On the other hand, the frequency of initial AF episodes was not significantly different between the groups.

Cox proportional hazards analysis: The relative risks of permanent AF drawn from all patients are listed in Table V (upper left). Multivariate Cox proportional hazards model revealed that the severity of the initial AF symptoms was an exclusive factor significantly related to the subsequent development of permanent AF (hazard ratio 0.46 per grade, 95% confidence interval 0.23 - 0.93, $P < 0.05$). Age, gender (male), hypertension, diabetes mellitus, organic heart disease, and heart failure were not significantly related to subsequent permanent AF. The echocardiographic data at the start of AF follow-up were disproportionate between the permanent and non-permanent AF groups (7/17 versus 35/47, $P < 0.05$). When we confined patients to those with the initial echocardiographic data (Table V, lower left), the severity of the initial AF symptoms was marginally related to the subsequent permanent AF (hazard ratio

Table V. Hazard Ratio of Permanent Atrial Fibrillation

	All patients		With censored patients (< 3 years) removed	
	Hazard ratio (95% CI)	<i>P</i>	Hazard ratio (95% CI)	<i>P</i>
All patients	<i>n</i> = 64		<i>n</i> = 45	
Age, per year	1.00 (0.93 - 1.07)	0.98	1.00 (0.93 - 1.08)	0.99
Gender (male)	0.80 (0.16 - 3.91)	0.78	0.82 (0.16 - 4.19)	0.81
Hypertension	0.61 (0.12 - 3.06)	0.55	0.85 (0.17 - 4.16)	0.84
Diabetes mellitus	3.13 (0.46 - 21.2)	0.24	2.86 (0.38 - 21.6)	0.31
Organic heart disease	0.88 (0.19 - 4.05)	0.87	1.06 (0.20 - 5.78)	0.94
Heart failure	2.29 (0.37 - 14.3)	0.38	2.43 (0.35 - 17.0)	0.37
Severity of symptoms, per grade	0.46 (0.23 - 0.93)	0.031	0.43 (0.21 - 0.89)	0.023
Patients with echocardiographic data	<i>n</i> = 42		<i>n</i> = 28	
Left atrial dimension, per mm	1.12 (0.95 - 1.33)	0.17	1.17 (0.96 - 1.42)	0.11
Severity of symptoms, per grade	0.36 (0.12 - 1.07)	0.065	0.30 (0.088 - 0.995)	0.049

CI indicates confidence interval.

Figure. Permanent atrial fibrillation-free survival curves stratified by severity of the initial episodes of atrial fibrillation drawn from all patients (A) and from those with censored cases (< 3 years) removed (B). Vertical axis shows the event-free rate at follow-up; horizontal axis, follow-up period. AF indicates atrial fibrillation. * Log-rank test.

0.36 per grade, 95% confidence interval 0.12 - 1.07, $P = 0.07$), but left atrial dimension was not. Exclusion of censored patients with a follow-up period shorter than 3 years ($n = 19$) (Table V, right) hardly changed these results, except that the severity of initial AF symptoms after confinement to patients with echocardiographic data resumed significance ($P < 0.05$).

Kaplan-Meier analysis: When we divided the patients based on the severity of initial AF symptoms, the permanent AF-free rate in 33 patients with mild (#1 and #2) symptoms was significantly lower than in 31 patients with severe (#3 and #4) symptoms (log-rank test, $P < 0.05$) (Figure A). The exclusion of pa-

tients with a censored time shorter than 3 years ($n = 19$) did not change this result (Figure B).

DISCUSSION

Major findings: Patients who developed permanent AF remembered relatively mild initial AF symptoms in this study. This is in accordance with common clinical observations that permanent AF often develops insidiously.

Whether AF is paroxysmal or not is important for the

strategy of AF treatment,³⁾ and the presence of sinus rhythm is a possible factor of survival even though rhythm control therapy by current anti-arrhythmic drugs has no benefit over rate control therapy.⁴⁾ Factors related to the development of permanent AF have been reported.^{2,5-7)} A number of recent studies^{3,8-11)} have associated AF and its treatment with quality-of-life issues. To the best of our knowledge, however, the symptoms of AF have as yet not been shown as being related to the development of permanent AF.

From the perspective of the patients and medical staff, it may be possible that in patients hardly tolerating AF, efforts are made for early conversion to sinus rhythm, and no prolonged episodes of AF are allowed. In patients with minimal symptoms, rate-control may be adopted and, as a consequence, the duration of AF will be long.

Patient characteristics: The association of the non-permanent form of AF with the more frequent hypertension (Table I) may suggest intolerance of AF in hypertensive patients. Additionally, the concomitant use of antihypertensive agents including RAS inhibitors may have interfered with the development of permanent AF.

The incidence of heart failure was not different between the groups either initially or at the development of permanent AF. However, concurrent latent progression of heart failure at the development of permanent AF is suggested by the larger left atrial dimension than at entry in the non-permanent AF group.

Reason for milder symptoms in the permanent AF group: There are several possible explanations concerning why patients with subsequent permanent AF had milder symptoms. Firstly, an enlarged left atrium in the permanent AF group may have buffered against pulmonary congestion such as in a setting of chronic mitral disturbances. Secondly, conceivable advanced degeneration in the atrium may have caused slow ventricular responses in a very acute phase of AF in the permanent AF group, resulting in relatively mild symptoms. Both of these may seem reasonable possibilities at least at the development of permanent AF, but are uncertain at the start of AF follow-up according to the results of echocardiography. Lastly, patient susceptibility may have affected the severity of the symptoms as well as the subsequent course of AF.

Other possible factors: Age, myocardial infarction, valvular disease, and left atrial dimension were reported as independent factors for early development of permanent AF.²⁾ The lack of dependency of subsequent permanent AF on these factors might be attributed to the study population, follow-up duration, and sample size. Mean age at the start of AF follow-up was slightly older, the frequency of organic heart disease was low and even mild cases were included, the follow-up period was short, and the sample size was small. Furthermore, echocardiographic data at the start of AF follow-up were minor, especially in the permanent AF group.

Study limitations: The retrospective design and the small number of patients limit our conclusions. The long flash-back period might have affected the patients' memories, especially concerning the frequency of AF episodes. Nonetheless, the pa-

tients were thought to have decided how to respond regarding their disease on the basis of its severity, which made us believe that the symptoms registered well in their minds.

Conclusion: This retrospective questionnaire survey demonstrated that mild rather than severe symptoms preceded the development of permanent AF and highlighted its relative inconspicuousness.

ACKNOWLEDGMENTS

The authors are grateful to the subjects for their participation.

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