Risk Factors for New-Onset Atrial Fibrillation During Routine Medical Checkups of Japanese Male Workers

Masahide MINAMI,¹ MD, Yasuki KOBAYASHI,¹ MD, Satoshi TOYOKAWA,¹ PhD, Kazuo INOUE,¹ MD, and Yasuo TAKESHITA,² MD

SUMMARY

The current study aimed to identify risk factors for atrial fibrillation (AF) detected during routine medical checkups of male workers in Japan. A nested case-control study was conducted using retrospective data from January 1998 to December 2006 collected at a hospital in Ishikawa Prefecture. Cases were those first diagnosed with AF with no record of AF events during the preceding 3 years. For each case, 2 controls were matched for age and time of medical checkup, randomly selected from among those who had not been diagnosed with AF during the same 3 years. Logistic regression was used to identify risk factors in the 3 years prior for new-onset AF. Sixty-nine cases and 138 controls were recruited; their average ages were 57.6 (SD 6.7) and 57.4 years (SD 6.7), respectively. In the logistic models, new-onset AF was associated with systolic blood pressure and drinking habits in the 3 years prior. (Int Heart J 2009; 50: 457-464)

Key words: Atrial fibrillation, Risk factors, Blood pressure, Drinking habits, Medical checkup

ATRIAL fibrillation (AF) is one of the major causes of cerebral infarction, thromboemboli, and heart failure.¹⁾ Risk factors for AF described in previous studies include body mass index (BMI), hypertension, left ventricular hypertrophy on an electrocardiogram (ECG), drinking habits, diabetes, a history of cardiac disease (angina, myocardial infarction, congestive heart failure, or valvular heart disease), and a family history of arrhythmias.²⁻⁷⁾ Studies in Japan have reported BMI, systolic blood pressure, fasting blood glucose level, serum levels of HbA1c, gamma-glutamyl transpeptidase (γ -GTP) and uric acid, cardiomegaly on chest roentgenography, cigarette smoking, and drinking habits as being associated with AF.⁸⁻¹⁰⁾ However, since most Japanese studies have been cross-

From the ¹ Department of Public Health, Graduate School of Medicine, University of Tokyo, Tokyo and ² Kanazawa Social Insurance Hospital, Ishikawa, Japan.

Address for correspondence: Masahide Minami, MD, Department of Public Health, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

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sectional and have not considered the temporal relationships between potential risk factors and AF onset, it has been difficult to determine any causal relationships from them.⁸⁻¹⁰⁾ Thus, we identified individuals with new-onset AF discovered incidentally during the last of 4 consecutive annual medical checkups and examined the association between incidental AF and preexisting factors within the context of a matched case-control study.

METHODS

Study participants: Data were collected from the clinical records of routine annual medical checkups of male workers performed at a single health assessment center hospital in Ishikawa Prefecture. The study period was from January 1998 to December 2006. To render the data anonymous, all identifiable information, such as name and birth date, was deleted. Prior to initiating data collection, the study was approved by the center, using due process.

Cases consisted of male workers newly diagnosed with AF based on a routine ECG. Each of these cases had 3 prior annual checkups during which ECGs were negative for AF. In addition, cases had no ongoing or historical incidence

Figure 1. Flowchart of the process for selecting cases.

of cardiopathy, arrhythmia, or cerebral infarction and had not taken any antiarrhythmia drug. Participants who were over 78 years old and those who were not in a fasting state at the time of their checkup were excluded (Figure 1).

Controls, which were matched for age and time period (people who had check-ups within one month before to one month after the time of being newly diagnosed with AF) were randomly selected from those never diagnosed with AF over the same 4 yearly evaluations as cases; as with the cases, those over 78 years old, those who had taken an antiarrhythmia drug, those not in a fasting state, and those with a history of ongoing or past cardiopathy, arrhythmia, or cerebral infarction were excluded (Figure 1). The ratio of cases to controls was set a priori at 1 to 2.

Measurement and definitions: The cases and controls were compared retrospectively in the 3 years prior in terms of BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking habits (current smoker versus nonsmoker/former smoker), Brinkman index, drinking habits, number of times drinking per week, alcohol consumption per day and per week, laboratory data, and the existence or absence of cardiomegaly. Cardiomegaly was defined as a cardiothoracic ratio exceeding 50% on chest roentgenography.

Laboratory data: We determined the serum levels of the following, as mandated by law during checkups for workers: total cholesterol (TCH), triglycerides (TG), HDL cholesterol (HDL-C), aspartate amino transferase (AST), alanine amino transferase (ALT), gamma-glutamyl transpeptidase (γ -GTP), uric acid (UA), fasting plasma glucose (FPG), red blood cell count (RBC), and hemoglobin (Hb). Laboratory tests were performed at a laboratory firm that conducts accuracy management.

Data analysis: Initially, bivariate analysis was performed using nonpaired *t*-tests to identify variables for which the means were statistically different between cases and controls in the 3 years before new-onset AF. In order to assess the extent of collinearity, values of variance inflation factors (VIF) greater than 2.5 were used as criteria for exclusion of independent variables for regression models.¹¹⁾ Models included those variables that differed between cases and controls in the 3 years before new-onset AF, and we added those factors that had been reported in previously published literature as being associated with AF. The statistical package SAS (version 9.1.3) was used for data analysis, and a *P* value < 0.05 was considered significant.

RESULTS

Bivariate analysis: We identified 69 cases of new-onset AF that included adequate data to continue data analysis. The average age of these cases was 57.6

Table I. Bivariate Analysis of Characteristics Between Cases and Controls in the 3 Years Before New-Onset AF

Variable	Cases (<i>n</i> = 69)	Controls (<i>n</i> = 138)	<i>P</i>
Age (years) [†]	57.6 ± 6.7	57.4 ± 6.7	0.883
BMI (kg/m ²)	24.2 ± 3.2	22.9 ± 2.8	0.004**
SBP (mmHg)	135.8 ± 21.0	126.7 ± 18.7	0.002**
DBP (mmHg)	82.7 ± 12.0	78.0 ± 11.7	0.007**
TCH (mg/dL)	195.7 ± 31.3	196.0 ± 28.0	0.932
TG (mg/dL)	126.6 ± 100.6	111.5 ± 59.0	0.254
HDL-C (mg/dL)	57.2 ± 15.6	56.0 ± 14.7	0.563
AST (IU/L)	26.8 ± 11.0	25.4 ± 8.1	0.349
ALT (IU/L)	24.5 ± 18.0	23.9 ± 14.6	0.824
γ-GTP (IU/L)	55.3 ± 47.1	43.8 ± 30.7	0.069
UA (mg/dL)	5.9 ± 1.2	5.8 ± 1.4	0.486
FPG (mg/dL)	105.5 ± 30.7	98.7 ± 14.2	0.084
RBC (×10 ³ /μL)	471.9 ± 34.8	473.5 ± 35.4	0.763
Hb (g/dL)	15.0 ± 1.0	14.9 ± 1.0	0.375
Cardiomegaly (chest roentgenography)	9 (13.0%)	7 (5.1%)	0.043*
Smoking habits	36 (52.2%)	65 (47.1%)	0.608
Brinkman Index	521.4 ± 452.2	460.0 ± 424.6	0.338
Drinking habits	59 (85.5%)	89 (64.5%)	0.002**
Drinking frequency (per week)	4.8 ± 2.8	3.8 ± 3.1	0.031*
Alcohol consumption (g per day)	28.9 ± 16.9	22.0 ± 19.9	0.014*
Alcohol consumption (g per week)	168.0 ± 124.3	129.4 ± 126.3	0.039*

The data are presented as the mean ± SD.

P* < 0.05, *P* < 0.01, [†] AF-onset year.

Figure 2. Distribution of alcohol consumption per week between cases and controls in the 3 years before new-onset AF.

Table II. Logistic Analysis of Factors Related to Incidence of AF

Variable	Model 1			Model 2			Model 3			Model 4		
	Odd ratio	95% C.I.		Odd ratio	95% C.I.		Odd ratio	95% C.I.		Odd ratio	95% C.I.	
Age (years)	0.998	0.949	1.051	0.994	0.945	1.045	1.000	0.951	1.051	0.996	0.948	1.047
BMI (kg/m ²)	1.110	0.981	1.261	1.117	0.988	1.267	1.110	0.982	1.259	1.113	0.986	1.262
SBP (mmHg)	1.019*	1.002	1.037	1.017*	1.000	1.035	1.017*	1.000	1.035	1.016	1.000	1.034
TCH (mg/dL)	0.999	0.988	1.010	0.998	0.987	1.009	0.998	0.987	1.009	0.998	0.987	1.009
γ -GTP (IU/L)	1.002	0.993	1.011	1.003	0.994	1.012	1.003	0.993	1.012	1.003	0.994	1.013
UA (mg/dL)	0.898	0.695	1.155	0.906	0.701	1.163	0.919	0.714	1.176	0.925	0.719	1.184
FPG (mg/dL)	1.009	0.994	1.029	1.010	0.994	1.028	1.009	0.994	1.028	1.009	0.994	1.028
Hb (g/dL)	0.889	0.623	1.262	0.882	0.618	1.251	0.893	0.628	1.263	0.889	0.624	1.259
Cardiomegaly	2.179	0.663	7.342	2.220	0.679	7.426	2.036	0.628	6.739	2.094	0.645	6.938
Brinkman Index	1.000	1.000	1.001	1.000	1.000	1.001	1.000	1.000	1.001	1.000	1.000	1.001
Drinking habits	3.209**	1.442	7.702									
Drinking frequency (per week)				1.114	0.997	1.249						
Alcohol consumption (g per day)							1.016	0.998	1.034			
Alcohol consumption (g per week)										1.002	0.999	1.005

* $P < 0.05$, ** $P < 0.01$.

years (SD, 6.7, range, 39-77). Accordingly, we selected 138 matched controls (two per case), whose average age was 57.4 years (SD, 6.7, range, 38-77) (Table I). Present illnesses consisted of hypertension (cases 19.8%, controls 17.4%), hyperlipidemia (cases 4.3%, controls 2.9%), diabetes (cases 4.3%, controls 4.3%), and gout (cases 1.4%, controls 1.4%). Past illnesses were gout (cases 4.3%, controls 1.4%), and asthma (cases 1.4%, controls 1.4%). For the comparison of laboratory data from 3 years prior to new-onset AF cases, no significant differences between cases and controls were identified in TCH, TG, HDL-C, AST, ALT, γ -GTP, UA, FPG, RBC, Hb, smoking habits, or Brinkman index. On the other hand, BMI, SBP, DBP, cardiomegaly, drinking habits, number of times drinking per week, and alcohol consumption per day and per week were significantly higher in cases than they were in controls (Table I). Distribution of alcohol consumption per week is shown for both cases and controls in Figure 2.

Logistic analysis: In the logistic model, we used the new-onset of AF as the dependent variable and entered the participant's age, BMI, SBP, and cardiomegaly at the onset of AF, as well as drinking habits (Model 1), number of times drinking per week (Model 2), alcohol consumption per day (Model 3), or alcohol consumption per week (Model 4). We also included TCH (8), γ -GTP (9,10), UA (8, 10), FPG (8, 10), Hb (10), (9) and Brinkman index (8) as independent variables because previous studies suggested they are possible risk factors.

In Model 1, with respect to independent variables measured 3 years prior, the onset of AF was associated with SBP ($P < 0.05$) or drinking habits ($P < 0.01$) (Table II). In Models 2 and 3, the onset of AF was associated with SBP ($P < 0.05$).

In Model 4, no significant variables were found. Thus, both blood pressure and drinking habits appear to be predictive factors 3 years prior to the new-onset of AF, at least among otherwise healthy male workers in Japan.

DISCUSSION

In this study of male workers in Japan who underwent annual medical checkups as part of routine health maintenance and promotion between January 1998 and December 2006, 69 cases of new-onset AF and 138 controls were identified out of approximately 244,000 records at a single health assessment center hospital. These individuals were either asymptomatic or their AF had been missed during evaluation for symptoms. A predictive variable was identified during the multivariate analysis. Blood pressure and drinking habits were the factors identified as a risk among parameters measured in the 3 years prior to AF onset.

Atrial fibrillation and drinking habits: The influence of drinking on the heart is presumed to be both short-term (acute) and long-term (chronic). Too much alcohol consumption has been reported to be a trigger for AF,¹²⁾ presumably via increased sympathetic nerve activity.¹³⁾ The short-term influence of alcohol on AF is known as Holiday Heart Syndrome.^{5,14,15)}

The Framingham study reported the long-term influence of drinking; in a follow-up study over 50 years, Djousse, *et al*⁴⁾ reported a significant increase in the prevalence of AF among those with an average of 36 grams or more of alcohol intake per day versus those with less. However, Benjamin, *et al*³⁾ argued that aging, diabetes, hypertension, congestive heart failure, and valvular disease were background factors for AF, while smoking and drinking exerted no significant influence. Meanwhile, the mechanisms behind any long-term effects of alcohol intake on the onset of AF remain unclear. In Japan, a cohort study conducted in Hisayama-cho revealed that habitual drinking was an independent risk factor in males.¹⁶⁾ The results of the current study support those findings. In addition, a weak, but not significant relationship existed between onset of AF and the amount of drinking in the current study (Table II).

Association of atrial fibrillation with BMI and cardiomegaly: Enlargement of the left atrium also appears to be associated with AF.¹⁷⁾ Several studies have identified BMI as one of the most powerful determinants of left atrium size.¹⁸⁻²⁰⁾ In this context, Wang²⁾ reported that obesity is a correctable risk factor for AF. Furthermore, cardiac enlargement on chest roentgenography was reported as associated with AF in a cross-sectional study.⁹⁾ In the Framingham study, Benjamin, *et al* reported that ECG-documented cardiac enlargement is associated with incidental AF in both men and women.³⁾ In our study, although new-onset AF was

associated with both BMI and cardiomegaly in the 3 years prior to AF-onset in bivariate analysis, statistical differences disappeared in the logistic models. The sample size of our study might be too small so that such relationships could not be detected.

Atrial fibrillation and blood pressure: Conventional beliefs hold that blood pressure is associated with AF.^{8,9,21,22)} However, other reports have failed to demonstrate such an association.¹⁰⁾ Thus, whether a true association exists independent of cardiomegaly remains unknown.

In the current study, bivariate analysis showed an association between new-onset AF and blood pressure (both SBP and DBP). In the logistic models, the onset of AF was associated with SBP. The results of our study were in concordance with conventional beliefs.

Study limitations: We limited our participants to those with no AF detected over the previous 3 years and no diseases associated with AF (cardiopathy, other arrhythmias, or cerebral infarction). Moreover, we recruited participants from a pool of workers undergoing routine medical checkups at one hospital, so caution should be taken when attempting to generalize the study results.

However, because the current study selected cases of new-onset AF as well as their matched controls using a meticulous selection process from some 244,000 records of medical checkups, the results should be valid for male workers in Japan who get regular check-ups. In order to confirm the causal relationship between AF and alcohol intake, further studies are warranted.

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