

## Early repolarization and risk of lone atrial fibrillation

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## Abstract

**Introduction:** Early repolarization syndrome is a recently proposed condition characterized by early repolarization pattern in the electrocardiogram and ventricular fibrillation in the absent of structural heart abnormalities. Although  
5 some studies have suggested that early repolarization is associated with frequency of atrial fibrillation, the association of early repolarization with atrial fibrillation is not well known.

**Hypothesis:** Early repolarization indicates the substrate for atrial fibrillation in addition to that for ventricular fibrillation.

10 **Method:** This study included 79 patients (57 men [72%]; age, 45±12 years) aged less than 60 years who had paroxysmal lone atrial fibrillation and 395 age- and sex-matched healthy controls (patient: control ratio, 1:5). Patients who had structural heart disease, hypertension, diabetes, hyperthyroidism, history of successful resuscitation, or Brugada type electrocardiogram were excluded.  
15 Electrocardiograms recorded during sinus rhythm were compared between patients with atrial fibrillation and healthy controls.

**Results:** Early repolarization in the inferior and/or lateral leads was more common in patients with atrial fibrillation (25%) than controls (10%) (P=0.001). The location and magnitude of early repolarization were similar between the two  
20 groups. Other electrocardiographic measurements were not different between the two groups. Among patients with atrial fibrillation, there was no difference in clinical characteristics including age at atrial fibrillation development, sex, and body mass index between patients with early repolarization and those without early repolarization. Electrocardiographic measurements were not different  
25 between patients with early repolarization and those without early repolarization.

**Conclusion:** Early repolarization was associated with lone atrial fibrillation. Early repolarization may indicate increased susceptibility to atrial fibrillation.

*Key words: arrhythmia; electrocardiogram; early repolarization; atrial fibrillation; electrophysiology*

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## Introduction

Early repolarization is a common electrocardiographic finding, which is characterized by elevation of the J point in the inferior and/or lateral leads, and has generally been considered benign for decades. However, recent studies have indicated that early repolarization is associated with an increased risk of idiopathic ventricular fibrillation and sudden death.<sup>1-4</sup> Furthermore, early repolarization increases the risk of arrhythmia events in other cardiac diseases such as long QT syndrome, short QT syndrome, Brugada syndrome, vasospastic angina, myocardial infarction, and non-ischemic cardiomyopathies.<sup>5-14</sup> The recent evidence has suggested that early repolarization indicates the substrate for ventricular tachyarrhythmias; however, the association of early repolarization with risk of atrial fibrillation is not well known. Atrial fibrillation is the most common cardiac arrhythmia in clinical practice, and is often associated with various pathophysiologies such as structural heart disease, advanced age, and hypertension.<sup>15</sup> However, atrial fibrillation can also develop in individuals without any pathogenic conditions, defined as lone atrial fibrillation.<sup>16</sup> Here, we tested the hypothesis that early repolarization indicates the arrhythmogenic substrate for atrial fibrillation.

## 20 Methods

### Study population

Institutional review board approval was obtained. This study included 79 patients aged less than 60 years who were diagnosed with lone atrial fibrillation in our institution between 1999 and 2015 and 395 age- and sex-matched healthy controls. Atrial fibrillation was diagnosed by 12-lead electrocardiograms (ECGs)

in all patients. We reviewed medical records of all patients with atrial fibrillation in our institution. To identify patients with lone atrial fibrillation, patients who were  $\geq 60$  years old and those who had structural heart disease, obesity (body mass index  $>30$  kg/m<sup>2</sup>), hypertension, diabetes, hyperthyroidism, and/or history of successful resuscitation were excluded. Patients with Brugada type ECG, bundle-branch block, intraventricular conduction delay, left ventricular hypertrophy, and/or abnormal QT intervals (corrected QT interval with Bazett's formula  $<360$  ms or  $\geq 440$  ms) in the electrocardiograms were also excluded. The absence of structural heart disease was confirmed by noninvasive studies such as detailed interview, physical examination, 12-lead ECG, and echocardiography in all patients. Control subjects were selected from 86,068 consecutive electrocardiograms stored in the electrocardiogram database in Niigata University Medical and Dental Hospital. Control subjects with cardiovascular disease and/or medication use were excluded. Control subjects with Brugada type ECG, bundle-branch block, intraventricular conduction delay, and/or abnormal QT intervals in the electrocardiograms were also excluded.

### **ECG analysis**

We evaluated ECGs recorded in the absence of antiarrhythmic drugs during sinus rhythm in all study subjects. Early repolarization was defined as the presence of a positive J wave, which is a slurring or notch at the QRS terminal which is  $\geq 0.1$  mV or more above the isoelectric line in  $\geq 2$  contiguous leads (Figure). The J wave location was classified as inferior (II, III, and aVF), lateral (I, aVL, and V4 to V6), or both. All ECGs were manually evaluated separately by two independent cardiologists who were blinded to the patient status (atrial fibrillation or control).

The cases in dispute were resolved by agreement. In addition to analysis of early repolarization, we measured ECG characteristics including heart rate and conduction intervals manually using magnifying lens and calipers.

## 5 **Data Analysis**

Data were expressed as the mean  $\pm$  SD or number (percentage). Differences in parameters between patients with lone atrial fibrillation and control subjects were analyzed using Student's *t*-test for continuous variables and by the Fisher exact test for categorical variables. The statistical analyses were performed with the  
10 SPSS version 24 (IBM Inc., Armonk, NY). A two-sided  $P < 0.05$  was considered statistically significant.

## **Results**

### **Comparisons between patients with lone atrial fibrillation and controls**

15 The clinical and ECG characteristics in 79 patients with lone atrial fibrillation and 395 age- and sex-matched controls are shown in Table 1. Patients with lone atrial fibrillation included 57 men (72%), and a mean age was  $45 \pm 12$  years. No atrial fibrillation patient had a history of resuscitation. Control group included 395  
20 healthy individuals who were matched to patients with atrial fibrillation based on gender and age (patient: control ratio, 1:5). Early repolarization was more common in patients with atrial fibrillation (25%) than controls (10%). The other ECG parameters were not different between two groups. Among subjects with early repolarization, the location and magnitude of early repolarization were similar between patients with atrial fibrillation and controls (Table2).

### **ECG characteristics and early repolarization in patients with atrial fibrillation**

Among patients with lone atrial fibrillation, there was no difference in clinical characteristics including age at atrial fibrillation development, sex, body mass index, and ECG measurements between patients with early repolarization and those without early repolarization (Table 3). P-wave duration measured during sinus rhythm was also similar between the two groups.

### **Discussion**

This study demonstrated that early repolarization was more common in patients aged less than 60 years with lone atrial fibrillation than healthy controls. There was no difference in other clinical and electrocardiographic characteristics between two groups. Early repolarization may indicate the substrate for atrial fibrillation in addition to that for ventricular fibrillation.

Early repolarization is a common electrocardiographic finding, which is observed in 3% to 13% in the general population in previous studies as well as healthy controls of this study.<sup>3, 17-19</sup> However, early repolarization has recently been emerging as a risk factor of ventricular tachyarrhythmias.<sup>5-12, 14</sup> Furthermore, there has been increasing evidence that early repolarization is also linked to the risk of atrial tachyarrhythmias.<sup>8,20,21</sup> In previous studies, 23% with early repolarization syndrome also have atrial fibrillation.<sup>21</sup> The prevalence of atrial fibrillation is high in subjects with early repolarization compared to that in the general population.<sup>20</sup> In this study including patients with lone atrial fibrillation and age- and sex-matched controls, early repolarization was also associated with atrial fibrillation, although the association has not been found in other studies.<sup>22,23</sup>

A population study in Finland did not find an association of early repolarization with atrial fibrillation.<sup>23</sup> In the study, atrial fibrillation was diagnosed only when the patients visited to the hospital because of atrial fibrillation, and the incidence of atrial fibrillation may be underestimated. In another case-control study, the control  
5 group was composed of patients diagnosed with supraventricular tachyarrhythmia excluding atrial fibrillation or atrial flutter, nonspecific palpitation, or neutrally-mediated syncope. In our study, control group was composed of healthy subjects who had no medical history. The discrepancy between our study and the previous ones may be due to the differences in the study methods and  
10 the control populations.

Although the precise mechanism by which early repolarization increases arrhythmia susceptibility is unknown, genetic basis of early repolarization syndrome has recently been reported.<sup>24</sup> Causative genes of early repolarization syndrome encode ion channels including sodium, calcium, and potassium  
15 channels.<sup>24</sup> Given the affected protein is present in ventricular and atrial myocardium, the repolarization abnormalities of the atrial and ventricular may be potentially related. Interestingly, all of the causative genes of early repolarization syndrome have also been associated with atrial fibrillation.<sup>24, 25</sup> There may be common genetic background for atrial fibrillation and ventricular fibrillation related  
20 to early repolarization.

Atrial fibrillation is the most common sustained arrhythmia observed in clinical practice, with a lifetime risk of 1 in 6 for people 40 years or older, even in the absence of heart disease.<sup>26</sup> Atrial fibrillation increases risks of ischemic stroke, heart failure, and all-cause mortality. Because of the high prevalence and serious  
25 complications, atrial fibrillation is a significant public health problem. There are



multiple risk factors for atrial fibrillation, and atherosclerotic risk factors such as age, male gender, hypertension, obesity, type II diabetes, dyslipidemia, and metabolic syndrome are implicated as prominent risk factors.<sup>26-28</sup> Furthermore, electrocardiographic abnormalities including abnormal P wave measurements, left ventricular hypertrophy, ST-segment abnormality, high-frequency premature complexes are also associated with the risk of atrial fibrillation.<sup>29-31</sup> In this study, we demonstrated that early repolarization is an additional electrocardiographic risk factor for atrial fibrillation. Physician's awareness about these risk factors may be important to prevent complications of atrial fibrillation.

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### **Conclusion**

Our study found that the prevalence of early repolarization is high in patients with lone atrial fibrillation. Early repolarization may indicate increased susceptibility to atrial fibrillation.

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### Figure legends

J wave was defined as a notch or slurring at the QRS terminal that was 0.1 mV above the isoelectric line. Arrows indicate early repolarization in lead II in patients with atrial fibrillation.

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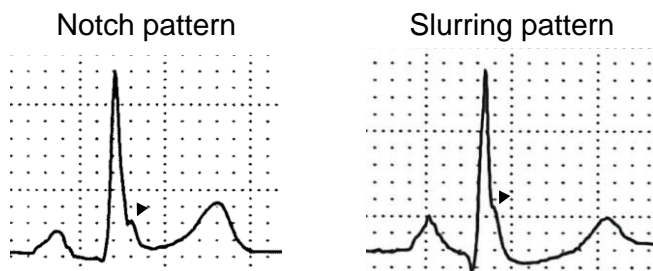
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**Figure.** Examples of early repolarization.



J wave was defined as a notch or slurring at the QRS terminal that was 0.1 mV above the isoelectric line. Arrows indicate early repolarization in lead II in patients with atrial

5 fibrillation.

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Table 1. Comparisons of electrocardiograms between patients with lone AF and controls

	Lone AF (N=79)	Control (N=395)	P value
Male sex, N (%)	57 (72)	285 (72)	—
Age, years	45±12	45±12	—
Early repolarization, N (%)	20 (25)	41 (10)	0.001
ECG parameters			
Heart rate, bpm	67±10	68±12	0.32
PR interval, ms	155±21	150±20	0.09
QRS duration, ms	99±10	7±10	0.10
QT interval, ms	378±30	375±30	0.41
Corrected QT interval, ms	397±24	397±22	0.98

AF indicated atrial fibrillation.

Table 2. Comparisons of early repolarization between patients with lone AF and controls

	Lone AF (N=20)	Control (N=41)	P value
Male sex, N (%)	16 (80.0)	35 (85.4)	0.72
Location of early repolarization, N (%)			
Inferior	13 (65.0)	25 (61.0)	1.00
Left precordial leads	3 (15.0)	6 (14.6)	1.00
High lateral	2 (10.0)	4 (9.8)	1.00
Location >1	2 (10.0)	6 (14.6)	1.00
J point elevation			
>0.1mV	14 (70.0)	33 (80.5)	0.52
>0.2mV	6 (30.0)	8 (19.5)	0.52

AF indicated atrial fibrillation.

Table 3. Comparisons of electrocardiograms between AF patients with early repolarization and AF patients without early repolarization

	With early repolarization (N=20)	Without early repolarization (N=59)	P value
Male sex, N (%)	16 (80)	41 (70)	0.56
Age at AF development, years	43±12	42±12	0.80
Body mass index	23±4	24±4	0.69
ECG parameters			
Heart rate, bpm	67±11	67±10	1.00
PR interval, ms	150±23	156±21	0.31
QRS duration, ms	102±10	98±10	0.12
QT interval, ms	386±29	375±30	0.16
Corrected QT interval, ms	402±25	396±24	0.38
P wave duration*, ms	92±14	94±16	0.46

\*P wave duration during sinus rhythm was measured in leads II and III. AF indicated atrial fibrillation.