



Clinical and electrocardiographic characteristics for prediction of new-onset atrial fibrillation in asymptomatic patients with atrial premature complexes☆

Sung Il Im^{1,2}, Dong Hyun Park^{1,3}, Bong Joon Kim, Kyoung Im Cho, Hyun Su Kim, Jung Ho Heo^{*}

Division of Cardiology, Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan 602-702, Republic of Korea

ARTICLE INFO

Article history:

Received 16 January 2018

Received in revised form 21 April 2018

Accepted 9 May 2018

Available online xxxx

Keywords:

Atrial premature complex

New onset atrial fibrillation

Electrocardiographic characteristics

Clinical outcomes

ABSTRACT

Backgrounds: Identification of precursors of atrial fibrillation (AF) may lead to early detection and prevent associated morbidity and mortality. Atrial premature complexes (APCs) are commonly seen in healthy subjects. However, there was limited data about the clinical and electrocardiographic (ECG) characteristics for prediction of new-onset AF in asymptomatic patients with APCs in the long-term follow up.

Methods: The Kosin University (No. 2014-02-04) 24-h holter monitoring, echocardiography, ECG database were reviewed from 2008 to 2016 to identify new-onset AF in patients with APCs. We analyzed demographic and clinical features and the nature of the APCs by ECG according to new-onset AF in those patients.

Results: Among 652 patients who underwent 24-h holter monitoring, 226 (34.4%) patients had new-onset AF. There was no difference of the baseline characteristics between new-onset AF group and non-AF group. In univariate analysis, hypertension (HTN), renal failure (CRF), high APC burdens, fastest APC running heart rate (HR), minimal HR, left ventricular ejection fraction (LVEF), left atrial volume index, peak mitral flow velocity of the early rapid filling wave and tricuspid regurgitation grade were significantly associated with new-onset AF. In multivariate analysis, higher APCs burden ($P = 0.047$), higher fastest APCs running HR ($P = 0.034$) and lower minimal HR ($P = 0.025$) were independent risk factors for new-onset AF in asymptomatic patients with APCs.

Conclusion: Higher APCs burden, higher fastest APCs running HR and lower minimal HR were associated with new-onset AF in asymptomatic patients with APCs in the long-term follow up.

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1. Introduction

Atrial fibrillation (AF) is the most common clinically significant arrhythmia in clinical practice. AF is associated with increased morbidity and mortality that primarily occur as a result of complications, such as thromboembolic events and heart failure [1]. However, AF is often asymptomatic and frequently diagnosed for the first time on admission for stroke treatment.

AF has been considered as one disease generally. However, it may actually represent the final pathway of multiple different

pathophysiological mechanisms. The understanding of these mechanisms and the identification of clinical predictors of AF may be the key to more customized therapeutic strategies development [2].

Atrial premature complex (APC) is frequently observed in clinical practice, especially in healthy subjects and often considered a benign condition [3]. However, previous study reported that APC serve as acute triggers for AF and frequent APCs have been reported to be associated with an increased risk of new occurrence of AF and adverse cardiovascular events [4]. APC count was found to predict AF independent of the other markers. APCs have been shown to be critical to AF pathogenesis and AF ablation is largely built on the premise that triggers or APCs arising in pulmonary veins initiate AF [5]. However, although shown to trigger paroxysmal AF, they are at present, considered innocuous. Therefore, if APC-related AF is found to be a distinct mechanistic phenotype, this may be a group particularly amenable to APC suppression for effective AF prevention or treatment [6,7].

There was limited data about the clinical and electrocardiographic (ECG) characteristics for prediction of new-onset AF in asymptomatic patients with APCs in the long-term follow up. This study has been designed to confirm previous findings looking to better analyze an

☆ Conflicts of interest: The authors have no conflicts of interest.

^{*} Corresponding author at: Division of Cardiology, Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan 602-702, Republic of Korea.

E-mail address: duggymdc@gmail.com (J.H. Heo).

¹ The first two authors contributed equally to this paper.

² This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

³ This author performed preliminary analyses.

asymptomatic population and to evaluate the clinical and ECG characteristics for prediction of new-onset AF in patients with APCs.

2. Methods

2.1. Study populations

We retrospectively reviewed the medical records of 1110 patients who underwent 24 h holter monitoring at Kosin university gospel hospital from January 2008 to November 2016.

Inclusion criteria included patients with/without APCs. Patients with a history of APC documented by a standard ECG or Holter-ECG were enrolled.

Exclusion criteria included a history of persistent AF (PeAF), chronic AF, cardiomyopathy, or valvular or congenital heart disease; hepatic or renal disease (known chronic liver disease or AST > 3 times than normal range, more advanced chronic kidney disease or stage 3); an acute cardiovascular or cerebrovascular event within the preceding 3 months; any major trauma or surgery within the preceding 3 months; hyperthyroidism; uncontrolled hypertension; malignancy; connective tissue disease; or any acute or chronic inflammatory disease; ischemic heart disease.

Finally, 652 consecutive patients (mean age; 66.8 ± 15.3 years, 49.4% male) at Kosin university gospel hospital from January 2008 to November 2016 were enrolled. And all patients were monitored to evaluate clinical and ECG characteristics for prediction of new-onset AF in asymptomatic patients with APCs during follow-up. Symptom evaluation was determined by reviewing the cardiology records, created by cardiologist. The baseline characteristics of the patients are presented in Table 1.

2.2. Data collection

After ECG and chest X-ray, cardiovascular status was evaluated for each patient using echocardiography, an exercise test, 24-h Holter recordings, and blood laboratory data from the initial visit, as determined

by the attending physicians. From the database, the following information was collected: (1) patient data, including sex, age, height, and weight; (2) cardiovascular risk factors, including hypertension (use of antihypertensive agents, systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure 90 mm Hg on admission) and diabetes mellitus (use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin $\geq 6.5\%$); (3) cardiovascular disease status, including structural heart disease, congestive heart failure, or a history of a disabling cerebral infarction or transient ischemic attack (TIA); and (4) use of medication. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

2.3. Definitions of atrial fibrillation and atrial arrhythmia

In the present study, paroxysmal AF (PAF) at the initial visit was defined as sinus rhythm on ECG and previous diagnosis of PAF by referring physicians. Patients whose AF was estimated to continue for ≥ 7 days after the initial visit were considered to have persistent AF (PeAF) originally and were excluded from the analysis. Chronic AF was defined as an ongoing long-term episode. Asymptomatic AF was defined as AF documented on 12 lead ECG during a visit, in the absence of any new symptoms such as palpitations, tachycardia, fatigue, malaise, shortness of breath on exertion, dyspnea, chest pain, syncope, or pre-syncope related to AF or other illnesses. During the follow-up period, the onset of AF was defined as the first time in which all ECGs indicated AF after ≥ 3 consecutive ECGs at intervals of ≥ 1 week after the initial examination [8]. When an ECG could not be obtained thrice during the period, the physicians made a clinical judgment regarding the onset time of AF progression. We calculated the CHADS₂ score (congestive heart failure, hypertension, age ≥ 75 years], diabetes mellitus; 1 point each, and history of stroke or TIA; 2 points). The CHA₂DS₂-VASc score was also determined, which also includes vascular disease (previous myocardial infarction, complex aortic plaque, and peripheral artery disease [PAD]), age 65–74 [9]. HAS-BLED score was calculated (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly – 1 point each). Atrial arrhythmia during follow-up was defined as atrial premature complex, atrial tachycardia, atrial flutter.

2.4. Definition of electrocardiographic characteristics

We defined the electrocardiographic characteristics following:

APC burden (%) was APC rate/total heart rate during 24 h. APC couplet (n) APC isolated (n) was the number of APCs during 24 h. Longest APC run (beats) was the longest sustainable APC rates. Fastest APC run heart rate (BPM) was heart rate of shortest R-R intervals of APCs. Average heart rate (BPM) was average heart rate including sinus rhythm and APC. Maximal heart rate (BPM) was fastest heart rate including sinus rhythm and APC. Minimal heart rate (BPM) was slowest heart rate including sinus rhythm and APC.

2.5. Clinical endpoints

The primary clinical endpoint was new onset AF in patients with asymptomatic APCs and the secondary endpoint was to analyze the electrocardiographic characteristics of 24 hours holter monitoring and to find out the independent predictor for new onset AF in patients with asymptomatic APCs in the long follow-up.

2.6. Transthoracic echocardiography

All enrolled subjects underwent 2-dimensional transthoracic echocardiography (TTE). All examinations were performed using a commercially available Vivid 9™ (GE Medical System, Vingmed, Horten, Norway) ultrasound system. All recorded echocardiograms were measured and

Table 1
Baseline characteristics according to new onset AF in patients with asymptomatic APCs.

Variables	non-AF group (n = 426)	New onset AF group (n = 226)	P-value
Age (years)	70.4 $\pm$ 14.7	68.8 $\pm$ 12.6	0.185
Gender (Male, %)	205 (48.1)	105 (46.5)	0.742
DM (%)	79 (18.5)	53 (23.5)	0.152
HTN (%)	137 (32.1)	101 (44.7)	0.002
CAD (%)	93 (21.8)	47 (20.8)	0.841
CHF (%)	58 (13.6)	31 (13.9)	0.451
Stroke (%)	32 (7.5)	28 (12.4)	0.046
COPD (%)	13 (3.1)	11 (4.9)	0.275
CRF (%)	37 (8.8)	20 (8.8)	1.000
CHA ₂ DS ₂ VASc	1.9 $\pm$ 1.7	2.4 $\pm$ 1.8	0.003
HAS BLED score	0.4 $\pm$ 0.4	0.7 $\pm$ 0.4	0.011
<i>Medication</i>			
Beta-blocker (%)	99 (23.5)	36 (16.0)	0.026
CCB (%)	54 (12.8)	28 (12.4)	0.894
ARB & ACEi (%)	40 (10.5)	26 (10.6)	0.158
Aspirin	167 (39.7)	77 (34.2)	0.201
<i>Echocardiographic findings</i>			
LVEF	63.1 $\pm$ 13.3	58.1 $\pm$ 13.7	<0.001
LAVI	24.1 $\pm$ 6.6	34.5 $\pm$ 19.2	0.001
E velocity	0.7 $\pm$ 0.2	0.9 $\pm$ 0.3	<0.001
TR grade	1.2 $\pm$ 0.4	1.4 $\pm$ 0.6	0.001

Values are mean $\pm$ SD (range). AF indicates atrial fibrillation; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; ACEi, angiotensin converting enzyme inhibitor; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; E, peak mitral flow velocity of the early rapid filling wave; TR, tricuspid regurgitation.

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