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

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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.

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

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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 ≥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.

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 ± 14.7	68.8 ± 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
CHA2DS2 VASc	1.9 ± 1.7	2.4 ± 1.8	0.003
HAS BLED score	0.4 ± 0.4	0.7 ± 0.4	0.011
Medication			
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
Echocardiographic findings			
LVEF	63.1 ± 13.3	58.1 ± 13.7	<0.001
LAVI	24.1 ± 6.6	34.5 ± 19.2	0.001
E velocity	0.7 ± 0.2	0.9 ± 0.3	<0.001
TR grade	1.2 ± 0.4	1.4 ± 0.6	0.001

Values are mean ± 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.

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 $CHADS_2$ score (congestive heart failure, hypertension, age [≥75 years], diabetes mellitus; 1 point each, and history of stroke or TIA; 2 points). The CHA_2DS_2-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

interpreted with clinical information blinded using a computerized off-line analysis station (Echopac™ 6.3.4; GE Medical System).

All measurements were derived from 3 consecutive cardiac cycles and averaged. The left ventricular (LV) dimensions, wall thicknesses and left atrial dimensions (LAD) were determined in the parasternal long-axis view with the M-mode cursor positioned just beyond the mitral leaflet tips perpendicular to the long axis of the ventricle according to the recommendations of the American Society of Echocardiography [10]. The LV ejection fraction (LVEF) was obtained via the modified biplane Simpson method from the apical 4- and 2-chamber views.

2.7. Ethics

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and the research protocol was approved by the ethics committee of Kosin university gospel hospital [11]. All patients provided written informed consent.

2.8. Statistical analysis

All continuous variables are expressed as either mean ± standard deviation (SD) or median (25th, 75th interquartile range), depending on the distribution. For continuous data, statistical differences were evaluated using Student's *t*-test or the Mann-Whitney *U* test, depending on the data distribution. Categorical variables are presented as frequencies (percent) and were analyzed using the chi-squared test. To determine whether any of the variables were independently related to new-onset AF according to APCs burden, a multivariate analysis of variables with a *P*-value < 0.05 in the univariate analysis was performed using linear logistic regression analysis. All correlations were calculated using Spearman's rank correlation test. All statistical analyses were conducted using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL, USA), and statistical significance was set at $P < 0.05$ (two-sided).

3. Results

The baseline demographics for both groups are listed in Table 1. Among 652 patients who underwent 24-hours 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, except for stroke ($P = 0.046$), CHA2DS2 VASc ($P = 0.003$), and HAS BLED score ($P = 0.011$).

For the history of medications, there was no difference between the new onset AF group and the non-AF group, except for beta-blocker (%) ($P = 0.026$) that were used more often in the new AF group than in the non-AF group.

Electrocardiographic characteristics according to new onset AF in patients with asymptomatic APCs in Table 2. APC burden was higher in patients with new onset AF. However, there was no difference in both group statistically. The number of APC couplet ($P = 0.001$), fastest APC running heart rate [HR, $P = 0.045$] was higher in patients with new onset AF. Minimal HR ($P = 0.005$) was lower in patients with new onset AF.

Hypertension, chronic renal failure (CRF), APC burden, APC fastest running HR, minimal HR, LVEF, left atrial volume index (LAVI), velocity and tricuspid regurgitation (TR) grade were associated with new onset AF in univariate analysis. In multivariate analysis, APC burden ($P = 0.047$), APC fastest running HR ($P = 0.034$) and minimal HR ($P = 0.025$) were independent risk factors for new onset AF in our study. (Table 3).

Receiver operating characteristic (ROC) curve analysis were performed to define cut-off point for new onset AF in patients with asymptomatic APCs. (A) APC burden (%) = 10.5%/24 h Holter monitoring [sensitivity = 0.972; specificity = 0.943], (B) APC burden (n) = 128 beats/24 h Holter monitoring [sensitivity = 0.994; specificity = 0.986] (Fig. 1).

Table 2
Electrocardiographic 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
APC burden (%)	16.1 ± 14.5	21.4 ± 16.2	0.349
APC couplet (n)	981 0.7 ± 163.78	1538 ± 485.3	0.001
APC isolated (n)	7298 ± 1393	8002 ± 1040	0.282
Longest APC run (beats)	106.7 ± 33.85	105.3 ± 32.3	0.253
Fastest APC run heart rate (BPM)	144.1 ± 37.9	150.4 ± 36.2	0.045
Average heart rate (BPM)	72.7 ± 15.7	72.5 ± 16.5	0.865
Maximal heart rate (BPM)	135.6 ± 34.1	139.9 ± 34.7	0.124
Minimal heart rate (BPM)	47.2 ± 13.0	44.3 ± 11.6	0.005

Values are mean ± SD (range). AF indicates atrial fibrillation; APC, atria premature complex; BPM, beats per minute.

4. Discussion

4.1. Major findings

In our study, we showed that 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, suggesting more intensive medical therapy to control APCs burden with close clinical follow-up will be required.

4.2. Electrocardiographic characteristics and new onset AF in patients with asymptomatic APCs

Previous study reported that there have been great advances in understating the pathophysiology of AF. Several studies have suggested that ectopic beats originating from the pulmonary vein (PV) initiate AF [7]. Yamane et al. reported that the number of APC significantly decreases after successful PV isolation in patient with PAF. Moreover, AF recurrences after PV isolation are associated with an increased the number of APC in that same study [12]. These findings indicate that APCs are a potent predictor of AF occurrence. In ischemic stroke patients without known AF, frequent APCs (APCs ≥70; forth quartile) are associated with a higher incidence of AF. A report of 428 patients who underwent elective 24-hour ECG monitoring has also shown that frequent atrial ectopic beats (>100 APCs/day) increases one's risk of AF development. Additionally, a study of 1260 participants (95% whites) from the Cardiovascular Health Study who underwent 24-hour ambulatory ECG monitoring demonstrated that the risk of AF increases with APC count [13]. The aforementioned studies clearly demonstrated that APCs, whether detected on the 12 lead ECG or 24-hour ECG monitoring, are associated with an increased risk of AF [14]. In our study, ROC curve analysis were performed to define

Table 3
Univariate and multivariate Cox analyses for new-onset AF in patients with asymptomatic atrial premature complex at 8-year follow-up.

Variable N (%)	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
HTN	1.530 (1.012–2.312)	0.044		
CRF	2.312 (1.016–5.261)	0.046		
APC burden (%)	1.025 (1.009–1.042)	0.002	1.025 (1.002–1.049)	0.047
APC running HR (fastest)	1.010 (1.003–1.016)	0.005	1.021 (1.002–1.040)	0.034
Minimal HR	0.980 (0.961–1.000)	0.052	0.961 (0.928–0.995)	0.025
LVEF	0.978 (0.964–0.993)	0.004		
LAVI	1.021 (1.007–1.035)	0.002	1.521 (1.507–1.535)	0.037
E velocity	2.856 (1.443–5.654)	0.003		
TR grade	1.932 (1.206–3.096)	0.006		

OR, odds ratio; CI, confidence interval; CHF, congestive heart failure; HTN, hypertension; CRF, chronic renal failure; APC, atrial premature complex; HR, heart rate; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; E, peak mitral flow velocity of the early rapid filling wave; TR, tricuspid regurgitation.

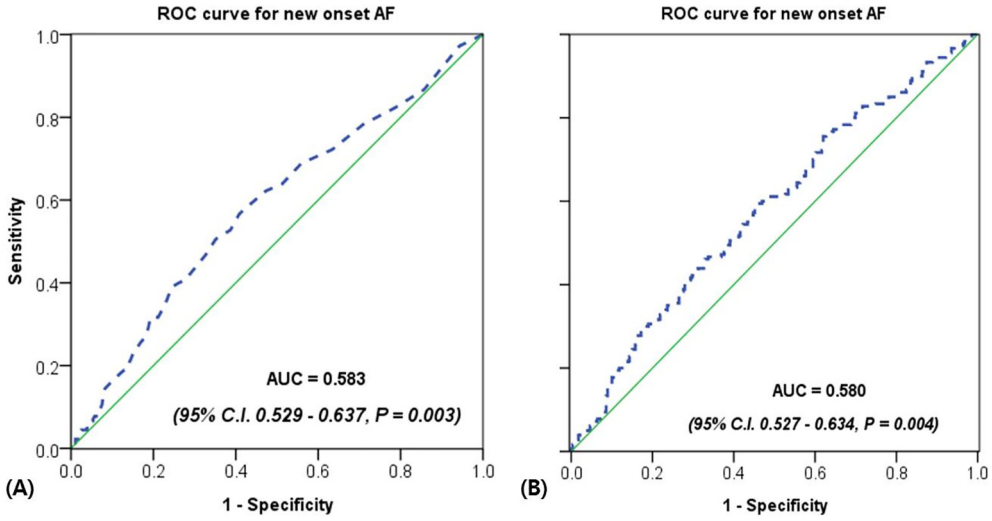

Fig. 1. Receiver operating characteristic (ROC) curve analysis performed to define cut-off point for new onset AF in patients with asymptomatic APCs. (A) APC burden (%) = 10.5%/24 h Holter monitoring [sensitivity = 0.972; specificity = 0.943], (B) APC burden (n) = 128 beats/24 h Holter monitoring [sensitivity = 0.994; specificity = 0.986].

cut-off point for new onset AF in patients with asymptomatic APCs. (A) APC burden (%) = 10.5%/24 hours Holter monitoring [sensitivity = 0.972; specificity = 0.943], (B) APC burden (n) = 128 beats/24 hours Holter monitoring [sensitivity = 0.994; specificity = 0.986] in Fig. 1 which is consistent with previous study. However, there is no universal agreement regarding the cut-off number for APC to be considered frequent. Healthy population may require greater atrial ectopic burden to unmask AF.

Previous study reported that frequent atrial couplets, atrial bigeminy, frequent runs, and long runs of APCs to be associated with increased risk of AF. However, because of small numbers in individual subgroups, only isolated APCs remained significantly associated with AF on multivariate analysis [15]. And, in particular, there was limited data about the clinical and ECG characteristics for prediction of new-onset AF in asymptomatic patients with APCs in the long-term follow up. In our study, Higher APCs burden, higher fastest APCs running HR and lower minimal HR were associated with new-onset AF in asymptomatic patients with APCs.

APCs and VPCs increased per 5-rear increase in age [16]. And in the EMBRACE trial, factors predictive of AF detection were also older age and a higher number of APCs on 24-hour Holter monitoring (628.8 versus 44.5, $P < 0.001$) [17]. However, in our study, there was no difference of age between non-AF group and new onset AF group in patients with asymptomatic APCs.

There are no prior reports of any positive longitudinal relationship between ECG characteristics and new onset AF in patients with asymptomatic APCs. This is the first study to evaluate the clinical and ECG characteristics for prediction of new-onset AF in asymptomatic patients with APCs.

It is of interest that as lower as minimal HR decreased, the incidence of new onset AF was increased in patients with asymptomatic APCs in the long-term follow up (Table 3), which is consistent with previous study that frequent APCs correlated closely with pacemaker implantation caused by sick sinus syndrome, high degree atrioventricular block and AF. And in terms of sick sinus syndrome as an indication of for pacemaker, the etiology of sick sinus syndrome included long pause, tachycardia-bradycardia syndrome, and sinus bradycardia [18].

We hypothesized that asymptomatic atrial ectopic beats may also be a risk factor for new onset AF on the basis of the following facts. First of all, it has been demonstrated that frequent APCs have a direct role in AF pathophysiology. APCs and AF are closely related. Most of APCs originate from pulmonary veins. AF has been shown to originate from the same focal trigger points [7]. And frequent atrial ectopic activity could be marker of longstanding hypertension, asymptomatic atherosclerosis, or cardiac structural abnormality, which predispose to thrombus formation and embolism [19].

Although the mechanism for the association between APCs and cardiac conduction system dysfunction was unclear, frequent atrial stimulation might cause atrial substrate remodeling near the sinus nodal area, causing dysfunction of the sinus node. AF could cause profound electrophysiological and structural remodeling of the atrioventricular node [20]. These findings suggest that frequent APCs might mimic, at least in part, the pathophysiology of AF in the human heart and contribute to sinus and, possibly, atrioventricular node dysfunction.

Previous study reported that frequent atrial ectopic activity might be a surrogate marker for the first AF episode or silent AF and a risk factor for recurrence in patients with cryptogenic stroke or TIA [21]. During the arterial blood pressure monitoring, we can see the transient lowering blood pressure when atrial ectopic beats occurs, which was consistent with previous study [22]. However, further prospective studies are needed to determine if a true causal mechanism exists between frequent APCs and cryptogenic stroke or TIA, as well as to access whether the mechanisms is dependent on a specific subtype of APCs.

4.3. Study limitations

First, this study was a single-center, retrospective study derived from a real world practice with inherent limitations. Hence the results of our study should be considered as hypothesis generating, and future prospective studies are warranted to confirm our results. Second, asymptomatic episodes of AF may not have been recognized because AF recurrence was based on clinical symptoms and ambulatory monitoring for a short period. Third, patients with potentially reversible causes were excluded from the study. Therefore, the results of this study cannot be transferred to other patient populations with first detected PAF. Fourth, the patients with APCs could not be monitored continuously. Therefore, there was limitation to generate the direct correlation of APCs burden with clinical outcomes. However, to minimize the selection bias of under/overestimation of APCs burden in patients with asymptomatic APC, 2.8 times per patients of 24 hours Holter monitoring were done during the long-term follow-up. And if the patient had APCs-related symptom, 24 hours Holter monitoring was done in those patients. And this study has presents a new vision for APCs focusing on the neurologic effects beyond arrhythmia.

5. 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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Conflicts of interest

No other conflicts of interest.

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