ORIGINAL ARTICLE
Cardiovascular Disorders

JKMS

http://dx.doi.org/10.3346/jkms.2016.31.4.519 • J Korean Med Sci 2016; 31: 519-524

Electrocardiogram PR Interval Is a Surrogate Marker to Predict New Occurrence of Atrial Fibrillation in Patients with Frequent Premature Atrial Contractions

Kwang Jin Chun, Jin Kyung Hwang, So Ra Choi, Seung-Jung Park, Young Keun On, June Soo Kim, and Kyoung-Min Park

Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Received: 30 July 2015
Accepted: 14 January 2016

Address for Correspondence:
Kyoung-Min Park, MD
Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
E-mail: kyoungmin.park@samsung.com

The clinical significance of prolonged PR interval has not been evaluated in patients with frequent premature atrial contractions (PACs). We investigated whether prolonged PR interval could predict new occurrence of atrial fibrillation (AF) in patients with frequent PACs. We retrospectively analyzed 684 patients with frequent PACs (>100 PACs/day) who performed repeated 24-hour Holter monitoring. Prolonged PR interval was defined as longer than 200 msec. Among 684 patients, 626 patients had normal PR intervals (group A) and 58 patients had prolonged PR intervals (group B). After a mean follow-up of 59.3 months, 14 patients (24.1%) in group B developed AF compared to 50 patients (8.0%) in group A ($P < 0.001$). Cox regression analysis showed that prolonged PR interval (hazard ratio [HR], 1.950; 95% CI, 1.029-3.698; $P = 0.041$), age (HR, 1.033; 95% CI, 1.006-1.060; $P = 0.015$), and left atrial (LA) dimension (HR, 1.061; 95% CI, 1.012-1.112; $P = 0.015$) were associated with AF occurrence. Prolonged PR interval, advanced age, and enlarged LA dimension are independent risk factors of AF occurrence in patients with frequent PACs.

Keywords: Premature Atrial Contraction; PR Interval; Electrocardiography; Atrial Fibrillation

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia requiring medical therapy and is associated with an increased risk of ischemic stroke, embolic events, congestive heart failure, impaired quality of life, and death (1-5). However, AF is often asymptomatic and frequently diagnosed for the first time on admission for stroke management (6). Therefore, early diagnosis and proper management are important for prevention of cardiovascular complications of AF.

Premature atrial contraction (PAC) is frequently observed in clinical practice, and often considered a benign condition (7-9). However, frequent PACs have been reported to be associated with an increased risk of new occurrence of AF and adverse cardiovascular outcomes (10-12). Prolonged PR interval, which is a component of the Framingham risk score for AF, is also reported to be associated with increased risk of AF, pacemaker implantation, congestive heart failure, and all-cause mortality (13-15). A large prospective cohort study reported that neither mortality nor hospitalization rates due to coronary artery disease, heart failure, AF, or stroke was associated with prolonged PR interval (16). However, there has been no report addressing the association between prolonged PR interval and AF occurrence rate in patients with frequent PACs. In this study, we investigated whether prolonged PR interval could predict new occurrence of AF in patients with frequent PACs.

MATERIALS AND METHODS

Study population

In our study, we enrolled the patients with frequent PACs. Frequent PACs were defined as more than 100 PACs/day in 24-hour Holter monitoring at least two times in order to compensate the day-to-day variation. We retrospectively reviewed the medical records of 2,713 patients who performed 24-hour Holter monitoring at least two times at Samsung Medical Center from April 1999 and June 2008. Among these, a total of 967 patients had more than 100 PACs/day in all repeated Holter monitoring. Exclusion criteria were previously documented AF or atrial flutter, structural heart disease (atrial septal defect; ventricular septal defect; patent ductus arteriosus, and hypertrophic cardiomyopathy), history of congestive heart failure, high-grade atrioventricular block, presence of pacemaker or implantable cardioverter defibrillator (ICD), rheumatic heart disease, moderate-to-severe heart valve disease, and any mechanical or bioprosthetic heart valve. We also excluded patients who had taken any antiarrhythmic drug within five days and those who had taken amiodarone within two months. During enroll-

pISSN 1011-8934
eISSN 1598-6357

ment, 76 patients (11%) used beta blockers (BBs) and 104 patients (15%) used calcium channel blockers (CCBs). We did not exclude the patients with coronary artery disease without evidence of myocardial infarction.

Study design and end point

Demographic data, cardiovascular risk factors, medications, and indications for 24-hour Holter monitoring were analyzed by medical records review. Patients were divided into two groups according to baseline PR interval: group A (normal PR interval group) and group B (prolonged PR interval group). Prolonged PR interval was defined as baseline PR interval > 200 msec. The primary end point was new occurrence of AF as evaluated from the medical records of our hospital. New occurrence of AF was defined as AF documented by 12-lead electrocardiogram (ECG) or Holter monitoring during follow-up.

ECG, transthoracic echocardiography (TTE), and 24-hour Holter monitoring analysis

A baseline resting ECG performed within 30 days of Holter monitoring was analyzed to provide baseline rhythm and PR interval. The PR interval was automatically measured by the ECG system or manually measured using customized software (Cardio Calipers, version 3.3, Iconico, Inc., New York, NY, USA). TTE data, which was performed within three months, were also analyzed. The left ventricular (LV) end-diastolic dimension, LV end-systolic dimension, left atrial (LA) dimension, and left ventricular ejection fraction (LVEF) were estimated. All Holter monitoring data were analyzed by two independent cardiologists to provide the frequency of PACs and the presence of other arrhythmia. Patients with insufficient Holter monitoring data were excluded.

Statistics

Continuous variables are expressed as the mean ± standard deviation or median and interquartile range. Categorical variables are expressed as frequency and percentage. To evaluate difference according to PR interval, we used Student's unpaired t test for normally distributed data and Mann-Whitney test for skewed data. Categorical variables were analyzed with χ^2 test or Fisher's exact tests. A Kaplan-Meier and log-rank test was used to compare AF-free survival distributions between study groups. Cox regression analysis was used to calculate the hazard ratios (HR) and 95% confidence intervals (CI) of new-onset AF. Calculations were performed using SPSS software (SPSS for Windows, version 20.0, IBM Corp., Armonk, NY, USA). A P value of < 0.05 was considered to be significant.

Ethics statement

This study received institutional review board approval at Samsung Medical Center (IRB File No. 2015-04-042). Informed consent was waived due to retrospective study design.

RESULTS

Among 967 patients with more than 100 PACs/day, 133 had previously documented AF or atrial flutter, 74 had structural heart disease, 18 had permanent pacemakers, and 56 were lost to follow-up. A total of 684 patients (335 males, mean age 61.8 ± 15.0 years) were finally analyzed in this study (Fig. 1). The median number of PACs was 2,558 beats/day (inter-quartile range: 1,213-5,409 beats/day).

Baseline clinical characteristics of the study population

The median PR interval was 166 msec (interquartile range: 153-179 msec). Fifty-eight patients had a PR interval longer than 200 msec at baseline ECG. Clinical characteristics of the patients according to PR interval are summarized in Table 1. The mean age was significantly older ($P = 0.007$) and proportion of male was higher ($P = 0.004$) in group B. The prevalence of hypertension was also higher in group B ($P = 0.002$). The use of BBs and CCBs which could affect the heart rate did not differ between the groups A and B (11% vs. 12.1%, $P = 0.808$; 15.0% vs. 17.2%, $P = 0.652$, respectively). Mean heart rate was not also different ($P = 0.118$). The prevalence of diabetes, dyslipidemia, and coronary artery disease were not significantly different between the two groups. Mean LA dimension as determined by TTE was larger in group B ($P = 0.025$). The number of PACs and the LVEF were not significantly different between the two study groups.

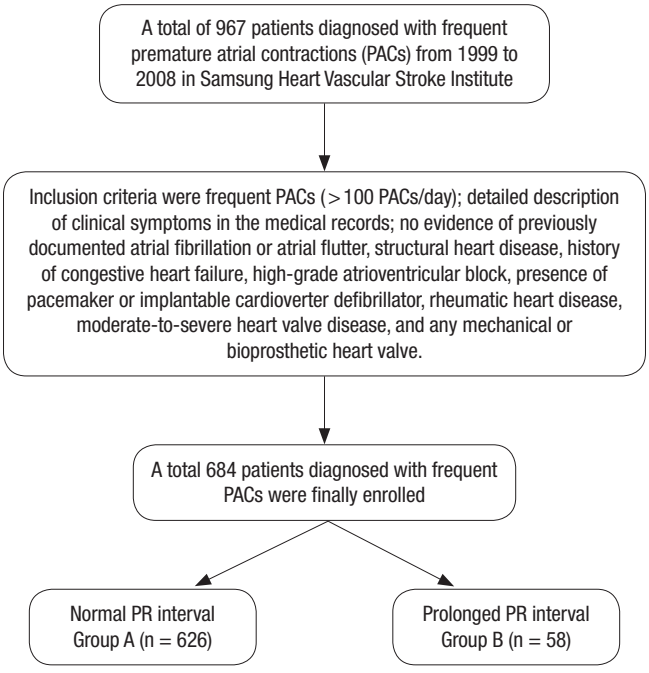

Fig. 1. Study flow chart.

http://dx.doi.org/10.3346/jkms.2016.31.4.519

Factors predicting new occurrence of AF

During a mean follow-up period of 59.3 ± 51.7 months, 50 patients (8.0%) in group A and 14 patients (24.1%) in group B developed new-onset AF ($P < 0.001$). Duration of follow-up was not significantly different between groups A and B ($P = 0.130$). Mean duration from initial Holter monitoring to new-onset AF was 52.9 ± 45.5 and 57.6 ± 41.5 months in groups A and B, respectively ($P = 0.601$). Table 2 shows the clinical characteristics according to new occurrence of AF. Univariate analysis revealed that age, hypertension, LA dimension, and prolonged PR inter-

Table 1. Baseline characteristics of the study groups

Variables	Normal PR interval (Group A, n = 626)	Prolonged PR interval (Group B, n = 58)	*P* value
Males, No. (%)	296 (47.3)	39 (67.2)	0.004
Age, yr	61.3 ± 15.1	67.0 ± 12.7	0.007
Weight, kg	61.9 ± 10.9	67.6 ± 11.2	< 0.001
BMI, kg/m^2	23.7 ± 3.8	25.3 ± 3.7	0.004
DM, No. (%)	111 (17.7)	13 (22.4)	0.376
Hypertension, No. (%)	296 (47.3)	40 (69.0)	0.002
Dyslipidemia, No. (%)	35 (5.6)	1 (3.1)	0.352
Coronary artery disease, No. (%)	69 (11.0)	8 (13.8)	0.523
Medication			
BB, No. (%)	69 (11.0)	7 (12.1)	0.808
CCB, No. (%)	94 (15.0)	10 (17.2)	0.652
ACE inhibitor, No. (%)	23 (3.7)	5 (8.6)	0.079
ARB, No. (%)	62 (9.9)	12 (20.7)	0.011
Diuretics, No. (%)	11 (1.8)	5 (8.6)	0.008
Aspirin, No. (%)	102 (16.3)	22 (37.9)	< 0.001
Clopidogrel, No. (%)	21 (3.4)	2 (5.2)	0.448
Antiarrhythmic drug, No. (%)	0 (0.0)	0 (0.0)	-
Echocardiographic parameter			
LVEF, %	63 (58-68)	65 (59-70)	0.381
LVEDD, mm	50 (47-54)	53 (49-56)	0.008
LVESD, mm	30 (27-34)	31 (28-34)	0.342
LA dimension, mm	39.3 ± 5.9	41.2 ± 6.2	0.025
PACs, beats/day	2,662 (1,219-5,575)	2,166 (1,094-4,739)	0.280
PR interval, msec	163 (152-176)	220 (209-236)	< 0.001
Heart rate, beats/min	70 ± 11	64 ± 16	0.118
Follow-up duration, month	58.6 ± 52.0	66.1 ± 47.7	0.130

BMI, body mass index; DM, diabetes mellitus; BB, beta blocker; CCB, calcium channel blocker; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; LVEDD, LV end-diastolic dimension; LVESD, LV end-systolic dimension; LA, left atrium; PAC, premature atrial contraction.

Table 2. Clinical characteristics of patients according to new occurrence of atrial fibrillation

Variables	AF occurrence		*P* value
	No (n = 620)	Yes (n = 64)	
Males, No. (%)	298 (48.1)	37 (57.8)	0.137
Age, yr	61.1 ± 15.3	68.4 ± 10.0	< 0.001
Weight, kg	62.3 ± 11.2	63.0 ± 10.1	0.472
BMI, kg/m^2	23.8 ± 3.8	24.0 ± 3.7	0.624
DM, No. (%)	111 (17.9)	13 (20.3)	0.634
Hypertension, No. (%)	291 (46.9)	45 (70.3)	< 0.001
Dyslipidemia, No. (%)	33 (5.3)	3 (4.7)	1.000
Coronary artery disease, No. (%)	67 (10.8)	10 (15.6)	0.246
Echocardiographic parameter			
LVEF, %	62.9 ± 7.8	61.7 ± 9.8	0.769
LVEDD, mm	50.2 ± 5.3	51.3 ± 5.7	0.142
LVESD, mm	30.9 ± 5.7	31.9 ± 6.6	0.483
LA dimension, mm	39.2 ± 5.9	41.4 ± 6.1	0.002
PACs, beats/day	2,662 (1,241-5,501)	2,081 (1,038-5,004)	0.118
PR interval, msec	165 (153-178)	172 (156-195)	0.032
Prolonged PR interval, No. (%)	44 (7.1)	14 (21.9)	< 0.001
Follow-up duration, month	56.1 ± 50.9	90.0 ± 49.9	< 0.001

AF, atrial fibrillation; BMI, body mass index; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; LVEDD, LV end-diastolic dimension; LVESD, LV end-systolic dimension; LA, left atrium; PAC, premature atrial contraction.

val were associated with new occurrence of AF. Kaplan-Meier estimates of new-onset AF-free survival according to PR interval are demonstrated in Fig. 2A (log rank $P < 0.001$). Cox regression analysis showed that age (HR, 1.033; 95% CI, 1.006-1.060; $P = 0.015$), prolonged PR interval (HR, 1.950; 95% CI, 1.029-3.698; $P = 0.041$), and LA dimension (HR, 1.061; 95% CI, 1.012-1.112; $P = 0.015$) were independent predictors of new occurrence of AF (Table 3). The receiver operating characteristic (ROC) curve analysis showed that PR interval longer than 200 msec predicted the development of AF with a sensitivity of 78% and a specificity of 93% (area under curve = 0.581).

Subgroup analysis of patients who received follow-up for more than one year

We conducted a subgroup analysis of 489 patients who received follow-up for more than one year (mean 82.0 ± 43.7 months).

Table 3. Multivariate analysis of the new occurrence of atrial fibrillation

Variables	HR (95% CI)	*P* value
Male	1.373 (0.811-2.324)	0.238
Age	1.033 (1.006-1.060)	0.015
Hypertension	1.404 (0.787-2.508)	0.251
Prolonged PR interval	1.950 (1.029-3.698)	0.041
LA dimension	1.061 (1.012-1.112)	0.015
PAC (Top quartile)	0.559 (0.275-1.137)	0.268

CI, confidence interval; LA, left atrium; PAC, premature atrial contraction.

Mean duration of follow-up was 82.4 ± 44.0 and 78.9 ± 42.1 months in groups A and B, respectively ($P = 0.717$). Kaplan-Meier estimates of new-onset AF-free survival according to PR interval are shown in Fig. 2B (log rank $P < 0.001$). In this subgroup, Cox regression analysis showed that age (HR, 1.041; 95% CI, 1.013-1.069; $P = 0.004$), prolonged PR interval (HR, 2.124; 95% CI, 1.115-4.046; $P = 0.022$), and LA dimension (HR, 1.051; 95% CI, 1.001-1.102; $P = 0.044$) were independent predictors of new occurrence of AF (Table 4).

DISCUSSION

We investigated whether prolonged PR could predict new occurrence of AF in patients who experienced more than 100 PACs/day. Two prospective studies previously reported that frequent PACs were an independent predictor of new occurrence of AF (11,17). In these two studies, frequent PACs were defined as more than 100 and 720 PACs/day, respectively. Additionally, two large prospective cohort studies recently reported that prolonged PR interval is associated with increased risk of new occurrence of AF (14,18), pacemaker implantation (14), and all-cause mortality (14). A meta-analysis also revealed the similar result (19), and another prospective cohort study reported that prolonged PR interval is associated with heart failure and death in patients with stable coronary artery disease (13). However, most of these previous studies evaluated the prognostic signifi-

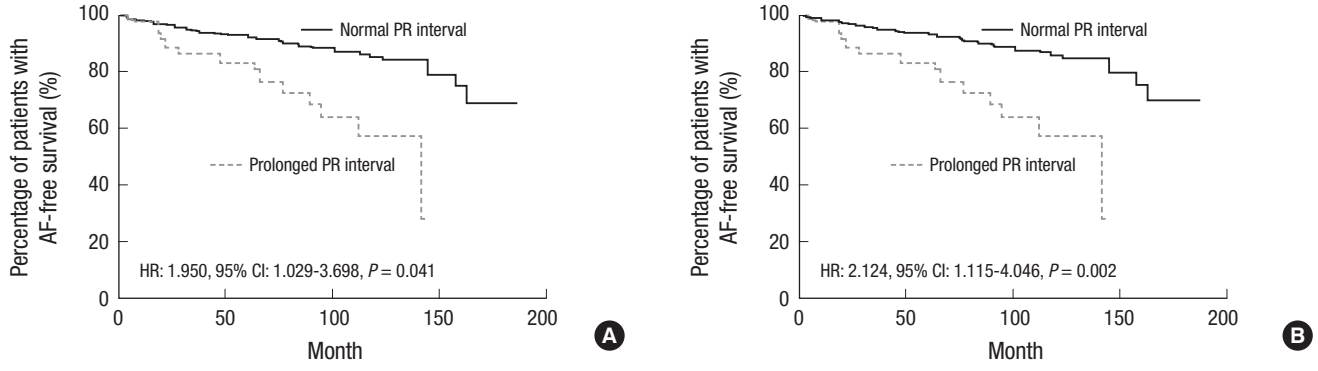

Fig. 2. Kaplan-Meier estimate of new-onset AF-free survival in patients with frequent PACs (**A**) and in patients with frequent PACs who received follow-up for more than one year (**B**). AF, atrial fibrillation; PAC, premature atrial contraction; HR, hazard ratio; CI, confidence interval.

Table 4. Multivariate analysis of new occurrence of atrial fibrillation in patients who received follow-up for more than one year

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Male	1.428 (0l858-2.376)	0.170	1.265 (0.739-2.166)	0.391
Age	1.054 (1.029-1.080)	< 0.001	1.041 (1.013-1.069)	0.004
Hypertension	2.264 (1.291-3.971)	0.003	1.401 (0.774-2.537)	0.265
Prolonged PR interval	3.528 (1.925-6.467)	< 0.001	2.124 (1.115-4.046)	0.002
LA dimension	1.074 (1.027-1.124)	0.002	1.051 (1.001-1.102)	0.044
PAC (Top quartile)	0.560 (0.271-1.157)	0.412	0.484 (0.226-1.035)	0.061

HR, hazard ratio; CI, confidence interval; LA, left atrium; PAC, premature atrial contraction.

http://dx.doi.org/10.3346/jkms.2016.31.4.519

cance of prolonged PR interval in the general population. None of previous studies addressed whether prolonged PR interval also could predict new occurrence of AF, especially in patients with frequent PACs.

Our main finding is that, in patients with frequent PACs, the prolonged PR interval is associated with new occurrence of AF and is an independent surrogate marker of AF development. Enlarged LA dimension and advanced age, known risk factors for AF, were also independent predictors in this study.

There are several potential mechanisms to explain the association between prolonged PR interval and new occurrence of AF. First, PR interval is influenced by the autonomic nervous system (20). Several studies have reported that both the sympathetic and parasympathetic nervous systems play a role in AF development (21,22). Prolonged PR interval might represent an abnormality of the cardiac autonomic nervous system. Second, PR prolongation can be explained by aging of the atrial myocardium and its conduction system, which is in line with AF genesis. It was previously reported that PR interval increased with age due entirely to prolongation of the interval between *P* wave onset and His bundle potential (23). Third, a meta-analysis of genome-wide association studies reported that chromosome loci from voltage-gated sodium channel genes and cardiac developmental genes were associated with PR interval, and five of the loci were also associated with AF (24). That study supports a possible shared genetic background between PR interval and AF.

Recently, 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 (25,26). Yamane et al. (27) reported that the number of PAC significantly decreases after successful PV isolation in patient with paroxysmal AF. Moreover, AF recurrences after PV isolation are associated with an increased the number of PAC in that same study (27). These findings indicate that PACs are a potent predictor of AF occurrence. In ischemic stroke patients without known AF, frequent PACs (PACs ≥ 70; forth quartile) are associated with a higher incidence of AF (28,29). A prospective study reported that frequent PACs are independent predictors for new AF in patients who complain of palpitation, dizziness, or syncope (11).

Until now, the factors that predict AF occurrence in patients with frequent PACs were unknown. Thus, we sought to investigate the factors that could predict AF in patients with frequent PACs. Our findings are not consistent with previous results regarding PACs. In our study, we did not find any association between the number of PACs and AF occurrence in patients with more than 100 PACs/day. The median values of PAC in all patients were 2,558 PACs/day, and median values in patients with or without AF development were not significantly different. We presumed that our patients might be more susceptible to the development of AF than average. Our cumulative incidence rate of AF was actually higher than previously reported (14,18), which supports the increased susceptibility of our study population to AF development. In other words, PAC burden itself was not associated with AF occurrence in patients with increased susceptibility for AF in this study population. The susceptibility of our study population to AF might confound the association between PAC and AF development compared to previous studies. Ultimately, we found that prolonged PR interval was an independent predictor of AF occurrence in patients with frequent PACs, which is also a potent risk factor for AF. In other words, a decrease in PACs burden is not the only solution to prevent the development of atrial fibrillation in the patients with frequent PACs with prolonged PR interval. The clinical implication of this study is that if a patient has frequent PACs (> 100 PACs/day) with prolonged PR interval on routine examination, we should observe this patient carefully at an outpatient clinic.

There are several limitations to our study. First, this study was a retrospective observational study and so we could not control for confounding factors. For example, although there was no statistical significant difference between study groups, we could not completely capture patient history of drugs that might affect PR interval, such as beta blockers and calcium channel blockers. Second, although we defined the number of frequent PACs base on previous studies, the definition is arbitrary. Third, a 24-hour Holter monitor was used to determine PAC burden. A longer duration of monitoring might be preferable because of day-to-day variability in PAC frequency, especially in the presence of frequent PAC burden of more than 100 beats/day. Whenever feasible, ambulatory monitoring for at least 48 hour is preferable.

In conclusion, our findings suggest that prolonged PR interval, advanced age, and enlarged LA dimension are associated with new occurrence of AF in patients with frequent PACs.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception and coordination of the study: Park KM, Chun KJ. Design of ethical issues: On YK, Kim JS. Acquisition of data: Hwang JK, Choi SR, On YK. Data review: Park KM, Chun KJ. Statistical analysis: Hwang JK, Park SJ, Kim JS, On YK. Manuscript preparation: Chun KJ, Park KM. Manuscript approval: all authors.

ORCID

Kwang Jin Chun http://orcid.org/0000-0001-7683-1343
Kyoung-Min Park http://orcid.org/0000-0002-8406-3142

Young Keun On http://orcid.org/0000-0003-1025-7283

REFERENCES

1. Tsang TS, Gersh BJ. Atrial fibrillation: an old disease, a new epidemic. *Am J Med* 2002; 113: 432-5.
2. Singh BN. Atrial fibrillation: epidemiologic considerations and rationale for conversion and maintenance of sinus rhythm. *J Cardiovasc Pharmacol Ther* 2003; 8 Suppl 1: S13-26.
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; 285: 2370-5.
4. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J* 2010; 31: 967-75.
5. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006; 8: 651-745.
6. Lin HJ, Wolf PA, Benjamin EJ, Belanger AJ, D'Agostino RB. Newly diagnosed atrial fibrillation and acute stroke. The Framingham Study. *Stroke* 1995; 26: 1527-30.
7. Fleg JL, Kennedy HL. Cardiac arrhythmias in a healthy elderly population: detection by 24-hour ambulatory electrocardiography. *Chest* 1982; 81: 302-7.
8. Folarin VA, Fitzsimmons PJ, Kruyer WB. Holter monitor findings in asymptomatic male military aviators without structural heart disease. *Aviat Space Environ Med* 2001; 72: 836-8.
9. Camm AJ, Evans KE, Ward DE, Martin A. The rhythm of the heart in active elderly subjects. *Am Heart J* 1980; 99: 598-603.
10. Dewland TA, Vittinghoff E, Mandyam MC, Heckbert SR, Siscovick DS, Stein PK, Psaty BM, Sotoodehnia N, Gottdiener JS, Marcus GM. Atrial ectopy as a predictor of incident atrial fibrillation: a cohort study. *Ann Intern Med* 2013; 159: 721-8.
11. Chong BH, Pong V, Lam KF, Liu S, Zuo ML, Lau YF, Lau CP, Tse HF, Siu CW. Frequent premature atrial complexes predict new occurrence of atrial fibrillation and adverse cardiovascular events. *Europace* 2012; 14: 942-7.
12. Todo K, Moriwaki H, Saito K, Naritomi H. Frequent premature atrial contractions in stroke of undetermined etiology. *Eur Neurol* 2009; 61: 285-8.
13. Crisel RK, Farzaneh-Far R, Na B, Whooley MA. First-degree atrioventricular block is associated with heart failure and death in persons with stable coronary artery disease: data from the Heart and Soul Study. *Eur Heart J* 2011; 32: 1875-80.
14. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, Benjamin EJ, Vasan RS, Wang TJ. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA* 2009; 301: 2571-7.
15. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009; 373: 739-45.
16. Aro AL, Anttonen O, Kerola T, Junttila MJ, Tikkanen JT, Rissanen HA, Reunanen A, Huikuri HV. Prognostic significance of prolonged PR interval in the general population. *Eur Heart J* 2014; 35: 123-9.
17. Binici Z, Intzilakis T, Nielsen OW, Køber L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. *Circulation* 2010; 121: 1904-11.
18. Nielsen JB, Pietersen A, Graff C, Lind B, Struijk JJ, Olesen MS, Haunsø S, Gerds TA, Ellinor PT, Køber L, et al. Risk of atrial fibrillation as a function of the electrocardiographic PR interval: results from the Copenhagen ECG Study. *Heart Rhythm* 2013; 10: 1249-56.
19. Cheng M, Lu X, Huang J, Zhang S, Gu D. Electrocardiographic PR prolongation and atrial fibrillation risk: a meta-analysis of prospective cohort studies. *J Cardiovasc Electrophysiol* 2015; 26: 36-41.
20. Spear JF, Moore EN. Influence of brief vagal and stellate nerve stimulation on pacemaker activity and conduction within the atrioventricular conduction system of the dog. *Circ Res* 1973; 32: 27-41.
21. Arora R. Recent insights into the role of the autonomic nervous system in the creation of substrate for atrial fibrillation: implications for therapies targeting the atrial autonomic nervous system. *Circ Arrhythm Electrophysiol* 2012; 5: 850-9.
22. Amar D, Zhang H, Miodownik S, Kadish AH. Competing autonomic mechanisms precede the onset of postoperative atrial fibrillation. *J Am Coll Cardiol* 2003; 42: 1262-8.
23. Fleg JL, Das DN, Wright J, Lakatta EG. Age-associated changes in the components of atrioventricular conduction in apparently healthy volunteers. *J Gerontol* 1990; 45: M95-100.
24. Pfeufer A, van Noord C, Marciante KD, Arking DE, Larson MG, Smith AV, Tarasov KV, Müller M, Sotoodehnia N, Sinner MF, et al. Genome-wide association study of PR interval. *Nat Genet* 2010; 42: 153-9.
25. Waktare JE, Hnatkova K, Sopher SM, Murgatroyd FD, Guo X, Camm AJ, Malik M. The role of atrial ectopics in initiating paroxysmal atrial fibrillation. *Eur Heart J* 2001; 22: 333-9.
26. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998; 339: 659-66.
27. Yamane T, Date T, Kanzaki Y, Inada K, Matsuo S, Shibayama K, Miyanaga S, Miyazaki H, Sugimoto K, Mochizuki S. Behavior of atrial ectopic beats before and after pulmonary vein isolation in patients with atrial fibrillation: a reduction in the number and arrhythmogenicity of ectopic firings. *Heart Rhythm* 2006; 3: 1421-7.
28. Wallmann D, Tüller D, Wustmann K, Meier P, Isenegger J, Arnold M, Mattle HP, Delacrétaz E. Frequent atrial premature beats predict paroxysmal atrial fibrillation in stroke patients: an opportunity for a new diagnostic strategy. *Stroke* 2007; 38: 2292-4.
29. Wallmann D, Tüller D, Kucher N, Fuhrer J, Arnold M, Delacretaz E. Frequent atrial premature contractions as a surrogate marker for paroxysmal atrial fibrillation in patients with acute ischaemic stroke. *Heart* 2003; 89: 1247-8.

 http://dx.doi.org/10.3346/jkms.2016.31.4.519