Int J Clin Exp Med 2014;7(11):4434-4440
www.ijcem.com /ISSN:1940-5901/IJCEM0002337

Original Article

A functional single-nucleotide polymorphism in interleukin-6 promoter is associated with p wave dispersion in hypertensive subjects with atrial fibrillation

Hai-Hua Geng[1], Rui Li[1], Ya-Min Su[2], Hai-Yan Pan[2], Min Pan[2], Xiao-Ping Ji[1]

[1]The Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education and Chinese Ministry of Health, Shandong University Qilu Hospital, Jinan 250012, China; [2]Department of Cardiology, Affiliated Hospital of Nantong University, Nantong 226001, China

Received September 5, 2014; Accepted November 8, 2014; Epub November 15, 2014; Published November 30, 2014

Abstract: Inflammation has been shown to be implicated in the pathophysiology of atrial fibrillation (AF). Interleukin-6 (IL-6) is a pleiotropic cytokine, functions as a mediator of inflammatory response and has both pro-inflammatory and anti-inflammatory properties. Little is known about genetic factors of inflammation in the accompanying atrial electrical remodeling expressed by P wave dispersion (P_{disp}). The aim of the present study is to evaluate the association of -634C/G polymorphism of IL-6 gene with P_{disp} in Han Chinese hypertensive patients with AF. A total of 100 patients with essential hypertension (EH) were eligible for this study. Patients with paroxysmal AF (n=50) were allocated to the AF group, and 50 subjects without AF to the control group. The PCR-based restriction fragment length polymorphism (PCR-RFLP) technique was used to assess the genotypes frequencies. The distribution of the IL-6 -634C/G genotypes (CC, CG, and GG) was 68.00%, 28.00%, and 4.00% in the controls, and 44.00%, 40.00%, and 16.00% in AF subjects, respectively (P=0.0269). The frequency of the G allele in the AF group was significantly higher than that in the control group (36.00% vs 18.00%, P=0.0041). Compared to the wild type CC, the G allele carriers (CG + GG genotypes) had a 2.7045-fold increased risk of AF (odds ratio =2.7045, 95% confidence interval =1.1966-6.1126, P=0.0156). AF patients with the CG + GG genotype had longer P_{disp} (P=0.0032) than did patients with the CC genotype. The longer P_{disp} in the subjects with the CG + GG genotype was also found in the control group (P=0.0016). These findings support that IL-6 -634C/G polymorphism is associated with P_{disp} and AF, suggesting an active implication of inflammation in the atrial electrophysiological remodeling predisposing to AF.

Keywords: Atrial fibrillation, interleukin-6, genetic polymorphism, P wave dispersion, essential hypertension, Chinese

Introduction

Atrial fibrillation (AF) represents the most common sustained cardiac arrhythmia seen in clinical practice, affecting 1-2% of the general population [1-6]. AF not only is an independent risk factor for death but also confers significant risk of morbidity from stroke associated with cardiogenic thromboembolism [7-10]. Essential hypertension (EH) is the most common cardiac condition associated with AF [5, 11]. The risk of AF in hypertensive compared with normotensive subjects was increased by 1.9 times in the Framingham Heart Study [12] and 1.4 times in the Manitoba Follow-up Study [13].

The role of hypertension as risk factor for AF is established but still incompletely known. The major pathophysiological change in AF is atrial fibrosis, which can be triggered in EH, at least partly, by the increased hemodynamic load and the accompanying activation of various humoral and inflammatory pathways [14, 15]. The change in atrial histology leads to atrial inhomogeneity of electrical properties and propensity to AF. The heterogeneous conduction in atria has been shown to be expressed in the surface electrocardiogram (ECG) as increased interlead variability of P wave duration. P wave dispersion (P_{disp}) is regarded as an electrocardiographic marker of inhomogeneous and discontinuous propagation of sinus impulses and contributes to the identification of subjects at risk for AF [2, 16, 17].

Recently, several lines of evidence support a strong association between low grade inflammation and the pathogenesis of AF, although it

is uncertain whether any inflammatory changes represent a cause or consequence of AF [2, 4, 8, 18]. Some studies have shown that concentrations of inflammatory mediators or markers, such as interleukin (IL)-6 and high-sensitivity C-reactive protein (hs-CRP), were increased in patients with AF and were associated with unsuccessful cardioversion [4, 5, 19]. The potential role of inflammation in the atrial electrophysiological remodeling predisposing to AF is currently under investigation. In a small pilot study, Tsioufis et al [2] first showed that elevated plasma hs-CRP concentration was an independent determinant of P_{disp} and AF among a cohort of 50 EH patients with paroxysmal AF.

IL-6 is a pleiotropic cytokine of 23.7 kDa secreted by many cells of the immune system, cardiovascular components, and adipose tissue, functions as a mediator of inflammatory response and has both pro-inflammatory and anti-inflammatory properties [20, 21]. Circulating levels of IL-6 differ greatly between individuals due to both genetic and environmental influences [5, 22]. Three single nucleotide polymorphisms (SNPs) in the IL-6 promoter region (-597G/A (rs1800797); -634C/G (rs1800796) and -174G/C (rs1800795)) have been reported to influence IL-6 transcription, and -174G/C was in tight linkage disequilibrium with -597G/A [23, 24]. The -174C allele is extremely rare and the -634C allele is common in eastern Asian populations, whereas in Caucasians the -174C allele is relatively frequent and the -634C allele is less frequent [25]. To date, the association of genetic factors of inflammation with atrial electrical remodeling has not been investigated before. We carried out a case-control study of the IL-6 -634C/G polymorphism to evaluate its putative association with P_{disp} in Han Chinese hypertensive patients with AF.

Subjects and methods

Study subject

A total of 100 EH patients with AF were eligible for this study. EH was defined according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) criteria [26] as diastolic blood pressure (DBP) equal to or over 90 mmHg and/or systolic blood pressure (SBP) equal to or over 140 mmHg (average of 2 measurements) or on treatment with anti-hypertension therapy. 50 patients with at least two documented episodes of paroxysmal AF during the last year were allocated to the AF group, and 50 subjects without AF to the control group. AF was defined according to the European Society of Cardiology (ESC) Guidelines for the management of AF [1]. Details of medical history, family history, and clinical symptoms were obtained from all participants using a standardized questionnaire, together with information of drug intake and cigarette smoking. Blood pressure, height, and weight were measured by trained physicians or nurses according to standardized protocols. Patients with acute coronary syndrome, diabetes mellitus, hypertrophic cardiomyopathy, significant valvular disease, left ventricular dysfunction (ejection fraction <50%), and neoplastic, renal, liver, thyroid diseases, or any noncardiac significant systemic disease were excluded. We also excluded subjects with atrioventricular block, bundle branch block, ventricular pre-excitation, or pacemaker implantation. All study participants were unrelated Han nationality residents. The study has been approved by the local medical ethics committee, and written informed consent was obtained from all participants.

Assessment of P_{disp}

After resting for at least 5 min at the supine position, the standard 12-lead surface ECG (25-mm/s, 1-mV/cm, and 100-Hz) was recorded. The P wave duration was measured manually by an experienced investigator blinded for the study, with the aid of a magnifying lens. The onset and offset of the P wave was defined as the junction between isoelectric line and the beginning of the P wave deflection, and the junction between the end of the P wave deflection and the isoelectric line, respectively. The average duration of the P wave in each lead, from a 20 s recording, was measured and afterwards the averaged maximum (P_{max}), and minimum (P_{min}) duration was recorded on each ECG. The P_{disp} was calculated by the difference between P_{max} and P_{min} [27]. Both the P wave measurements were corrected for heart rate (HR) by Bazett's formula, i.e. the corrected P wave parameters was equal to P wave parameters/$(HR)^{1/2}$ [28].

Echocardiography

Two-dimensional echocardiogram was recorded with each participants in the partial left

Table 1. Clinical characteristics of AF and control subjects

Characteristics	AF (n=50)	Controls (n=50)	*P* value
Age (years)	62.36 ± 9.25	61.86 ± 9.07	0.7855
Gender (% male)	64.00	70.00	0.5235
EH duration (years)	7.23 ± 5.28	7.56 ± 5.73	0.7652
BMI (Kg/m^2)	23.24 ± 3.21	23.37 ± 3.46	0.8460
Smoking (%)	18.00	14.00	0.5854
TC (mmol/L)	4.63 ± 0.46	4.49 ± 0.49	0.1440
LDL-C (mmol/L)	2.48 ± 0.43	2.41 ± 0.39	0.3959
HDL-C (mmol/L)	1.45 ± 0.24	1.40 ± 0.23	0.2901
TG (mmol/L)	1.62 ± 0.54	1.55 ± 0.49	0.4989
SBP (mmHg)	143.22 ± 24.63	141.51 ± 23.85	0.7251
DBP (mmHg)	81.99 ± 10.42	83.29 ± 11.54	0.5557
LVEF (%)	60.06 ± 6.32	61.14 ± 6.48	0.4009
Left atrial dimension (mm)	42.76 ± 6.95	37.22 ± 6.54	0.0001
Diuretics (%)	40.00	32.00	0.4047
Calcium antagonist (%)	48.00	52.00	0.6892
b-blocker (%)	34.00	28.00	0.5166
ACE inhibitor (%)	50.00	46.00	0.6889
ARB (%)	30.00	32.00	0.8288
P_{max} (ms)	114.39 ± 30.23	106.78 ± 28.46	0.1980
P_{min} (ms)	68.21±25.47	80.15 ± 27.39	0.0262
P_{disp} (ms)	46.28 ± 13.84	26.65 ± 9.89	0.0000

AF, atrial fibrillation; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, bodymass index; LVEF, left ventricular ejection fraction; TC, total cholesterol; LDL-C, low densitylipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, triglycerides; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

decubitus position after a resting period of at least 10 min. Left atrial (LA) diameter was obtained in the parasternal short-axis view. The left ventricular ejection fraction (LVEF) was determined by the Simpson's method [29].

Biochemical analysis

Venous blood samples were obtained after at least a 10-hour overnight fast and then centrifuged at 2500 rpm for 30 minutes at 4°C and immediately stored -80°C until analysis. Measurement of total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), and triglycerides (TG) was performed as described previously [30].

Genetic analysis

Genomic DNA was extracted from peripheral blood leukocytes by the salting-out method with minimal modifications. Determination of IL-6 -634C/G genotypes was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) as described previously [31].

Statistical analysis

All continuous variables are expressed as the mean and standard deviation (SD). Student's t-test was used to compare continuous variables from two groups. Genotypes and allele frequencies were obtained by direct count. Differences in the distribution of alleles and genotypes between the groups, and deviations from the Hardy-Weinberg equilibrium were assessed by χ^2 test. All significant tests were two-tailed and were considered statistically significant at $P<0.05$. SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

The clinical characteristics of all participants enrolled in the study are depicted in **Table 1**. No significant differences were seen between the two groups with regard to age, gender, EH duration, body mass index (BMI), smoking status, serum lipids levels, blood pressure, left ventricular ejection fraction (LVEF), and the use of antihypertensive drugs. However, compared to the controls, AF patients had larger left atrial dimension (P=0.0001). In terms of ECG-derived indexes regarding P wave variability, the AF group compared to the controls exhibited a shorter P_{min} (P=0.0262) and a greater P_{disp} (P=0.000). P_{max} despite a longer trend in the AF patients did not differ substantially in the two groups.

The distributions of IL-6 -634C/G genotypes and allele frequencies for two groups are given in **Table 2**. The genotype distribution among the subjects was in Hardy-Weinberg equilibrium in both the control group (χ^2=0.1326, P=0.7158) and the AF group (χ^2=0.8705, P=0.3508). The distribution of the IL-6 -634C/G genotypes (CC, CG, and GG) was 68.00%, 28.00%, and 4.00% in the controls, and 44.00%, 40.00%, and 16.00% in AF subjects,

Table 2. Distributions of *IL-6* -634C/G genotypes and alleles in AF and control subjects

Groups	n	Genotypes frequencies (n, %)			Alleles frequencies (n, %)	
		CC	CG	GG	C	G
controls	50	34 (68.00)	14 (28.00)	2 (4.00)	82 (82.00)	18 (18.00)
AF	50	22 (44.00)	20 (40.00)	8 (16.00)	64 (64.00)	36 (36.00)
P value			0.0269		0.0041	

Table 3. Comparision of *IL-6* -634C/G genotypes and alleles in AF and control subjects

	χ^2	Odds ratio (95% CI)	*P* value
CG + GG vs. CC	5.8442	2.7045 (1.1966-6.1126)	0.0156
CC + GG vs. CG	1.6043	0.5833 (0.2525-1.3477)	0.2053
CC + CG vs. GG	4.0000	0.2188 (0.0440-1.0877)	0.0455
GG vs. CC	5.6729	6.1818 (1.1995-31.8587)	0.0172
C vs. G	8.2192	0.3902 (0.2030-0.7501)	0.0041
G vs. C		2.5625 (1.3331-4.9256)	

respectively (P=0.0269). The frequency of the G allele in the AF group was significantly higher than that in the control group (36.00% vs 18.00%, P=0.0041).Compared to the wild type CC, the G allele carriers (CG + GG genotypes) had a 2.7045-fold increased risk of AF (odds ratio [OR]=2.7045, 95% confidence interval [CI]=1.1966-6.1126, P=0.0156). Seen **Table 3**.

Table 4 summarizes the effects of the different genotypes on clinical parameters. The carriers of the G allele (CG + GG) were pooled into one group, because the numbers of individuals with the GG genotype were small. No statistical differences were found in the age, gender, EH duration, BMI, smoking status, serum lipids levels, blood pressure, LVEF between the genotypes both in the AF and control groups. However, AF patients with the CG + GG genotype had greater left atrial dimensions (P=0.0319) and P_{disp} (P=0.0032) than did patients with the CC genotype. The longer P_{disp} in the subjects with the CG + GG genotype was also found in the control group (P=0.0016).

Discussion

To the best of our knowledge, this is the first study to provide evidence that polymorphism of inflammatory cytokine might influence the atrial electrical remodeling in EH patients. Both in the AF and control groups, subjects with the CG + GG genotype had greater P_{disp} than did patients with the CC genotype. Also, the G allele carriers had greater left atrial dimensions compared to the CC homozygotes in the AF group. There is a positive association between the IL-6 -634C/G polymorphim and risk of developing AF in hypertensive patients. Compared with the wild type CC, the G allele carriers (CG + GG genotypes) had a 2.7045-fold increased risk of AF. These findings support the hypothesis that inflammation plays a role in the underlying mechanisms of AF.

There has been growing interest in evaluate the role of IL-6 in AF in the past few years [32]. Published studies have shown that elevated circulating IL-6 level was correlated to new onset AF and chronic (persistent and permanent) as well as increased left atrial dimensions [33, 34]. In a cross-sectional study of 971 patients with coronary artery disease, among 6 inflammatory biomarkers, AF was associated with high IL-6 levels, and linked to IL-6 -174G/C polymorphism [35]. In addition, the development of postoperative AF in patients undergoing coronary artery bypass graft surgery was related with increased circulating IL-6 levels and promoter polymorphisms of the IL-6 gene [32]. Our previous study also reported that the IL-6 -634C/G polymorphism was associated with AF in elderly Han Chinese patients with EH [5].

There are data suggesting that low grade inflammation along with endothelial dysfunction and activation of renin-angiotensin system were implicated to the development of hypertensive target organ damage, including left ventricular and atrial myocardium [36]. Atrial fibrosis, loss of atrial myocardial mass and the associated structural heterogeneity of the atrial myocardium, lead to the inter- and intra-atrial conduction disturbances and shortening of the atrial refractory period. These alterations provided the electrophysiological substrate for AF [37]. Reflecting these abnormalities of conduction, P_{disp} has been regarded as an electrocardiographic marker of risk for the induction, and maintenance or recurrence of AF [2, 16]. Larger left atrial dimension was a precursor of AF in

Table 4. Clinical characteristics according to different genotypes in AF and control subjects

Characteristics	AF			Controls		
	CC (n=22)	CG + GG (n=28)	*P* value	CC (n=34)	CG + GG (n=16)	*P* value
Age (years)	62.79 ± 9.36	62.02 ± 9.17	0.7715	62.21 ± 9.15	61.12 ± 8.87	0.6934
Gender (% male)	63.64	64.29	0.9621	70.59	68.75	0.8947
EH duration (years)	7.31 ± 5.33	7.17 ± 5.21	0.9260	7.66 ± 5.85	7.35 ± 5.64	0.8604
BMI (Kg/m^2)	23.19 ± 3.20	23.28 ± 3.21	0.9219	23.28 ± 3.44	23.56 ± 3.48	0.7902
Smoking (%)	18.18	17.86	0.9763	14.71	12.50	0.8339
TC (mmol/L)	4.59 ± 0.45	4.66 ± 0.47	0.5968	4.54 ± 0.50	4.38 ± 0.47	0.2876
LDL-C (mmol/L)	2.42 ± 0.42	2.53 ± 0.43	0.3689	2.40 ± 0.38	2.43 ± 0.39	0.7973
HDL-C (mmol/L)	1.48 ± 0.25	1.43 ± 0.23	0.4663	1.44 ± 0.24	1.44 ± 0.22	1.0000
TG (mmol/L)	1.65 ± 0.55	1.60 ± 0.55	0.7510	1.57 ± 0.49	1.51 ± 0.48	0.6862
SBP (mmHg)	143.47 ± 24.69	143.02 ± 24.61	0.9492	141.45 ± 23.82	141.64 ± 23.85	0.9791
DBP (mmHg)	82.03 ± 10.45	81.96 ± 10.41	0.9812	83.24 ± 11.53	83.40 ± 11.54	0.9637
LVEF (%)	59.97 ± 6.30	60.13 ± 6.37	0.9298	61.06 ± 6.42	61.31 ± 6.49	0.8987
Left atrial dimension (mm)	40.38 ± 6.21	44.63 ± 7.14	0.0319	36.46 ± 6.50	38.84 ± 6.63	0.2360
P_{max} (ms)	113.54 ± 30.17	115.06 ± 30.32	0.8608	104.55 ± 27.89	111.52 ± 30.27	0.4263
P_{min} (ms)	74.14 ± 26.52	63.55 ± 25.03	0.1545	81.36 ± 28.44	77.58 ± 27.13	0.6585
P_{disp} (ms)	39.48 ± 13.22	51.65 ± 14.17	0.0032	23.22 ± 9.21	33.94 ± 13.03	0.0016

the Framingham Heart Study [38] and the Cardiovascular Health Study [39]. Electrophysiological features in tandem with left atrial dilation include dispersion of the atrial refractory period and prolongation of conduction time. Both these changes account for the development of multiple reentrant wave fronts starting and possibly perpetuating AF [14].

Our study has some potential limitations. Firstly, the cross-sectional study with no prospective data limits our ability to extract conclusions about the temporal relationships of inflammation and AF. The relatively limited cohort size restricts the generalizability of our results. Secondly, we could not exclude the presence of previous asymptomatic AF in the control group because the diagnosis was based solely on the medical history of the interviews with the participants. Thirdly, the absence of the assessment of serum IL-6 levels concordant with IL-6 -634C/G polymorphism may limit the outcomes. However, our previous report [31] along with the studies conducted in Japanese and Koreans [40, 41] indicate that IL-6 -634C/G is associated with circulating levels of IL-6 in eastern Asians. Finally, although all the study subjects were Han Chinese population and thus the possibility of ethnicity as a confounding factor could be excluded, the association of the IL-6 -634C/G polymorphism and AF in other populations remains unknown and needs further study.

In conclusion, our data support that IL-6 -634C/G polymorphism is associated with P_{disp} and AF, and the G allele has increased risk for AF in elderly Han Chinese patients with EH, suggesting an active implication of inflammation in the atrial electrophysiological and constructional remodeling predisposing to AF. The data in this study may be helpful for the future development of approaches to identify individuals that are at risk of AF and strategies to optimize treatment for this common and complex disease. However, given the inherent limitations of case-control studies and the complex nature of genetic susceptibility for chronic degenerative diseases, the prospective and interventional clinical studies with larger sample size are required to be conducted in individual ethnic groups to confirm our observations.

Acknowledgements

This work was supported by the Clinical Medicine Special Foundation of Nantong City (HS2013069), Special Coordination Funds for "226" Project of Nantong City, and "Summit of the Six Top Talents" Program of Jiangsu Province (2009046), China.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xiao-Ping Ji, The Key Laboratory of Cardiovascular Remodeling and

Function Research, Chinese Ministry of Education and Chinese Ministry of Health, Shandong University Qilu Hospital, 107 West Wenhua Road, Jinan 250012, China. E-mail: jixiaoping1964@hotmail.com

References

[1] Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le HJ, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010; 31: 2369-2429.

[2] Tsioufis C, Syrseloudis D, Hatziyianni A, Tzamou V, Andrikou I, Tolis P, Toutouzas K, Michaelidis A, Stefanadis C. Relationships of CRP and P wave dispersion with atrial fibrillation in hypertensive subjects. Am J Hypertens 2010; 23: 202-207.

[3] Jiang MH, Su YM, Tang JZ, Shen YB, Deng XT, Yuan DS, Wu J, Pan M, Huang ZW. Angiotensin-converting enzyme gene 2350 G/A polymorphism and susceptibility to atrial fibrillation in Han Chinese patients with essential hypertension. Clinics (Sao Paulo) 2013; 68: 1428-1432.

[4] Pan M, Zhu JH, Jiang WP, Liu ZH, Li HM, Yu XH, Yang XJ. Inflammation: a possible pathogenic link to atrial fibrillation. Med Hypotheses 2006; 67: 1305-1307.

[5] Li J, Song J, Jiang MH, Zheng JG, Gao SP, Zhu JH, Pan M. Interleukin-6 promoter polymorphisms and susceptibility to atrial fibrillation in elderly han chinese patients with essential hypertension. J Interferon Cytokine Res 2012; 32: 542-547.

[6] Han ZH, Ren XJ, Wang Y. Anticoagulation management of patients with long-term warfarin therapy after valve replacement during the perioperative period of pacemaker implantation. Int J Clin Exp Med 2013; 6: 594-598.

[7] Deng XT, Jiang MH, Zhu JH, Ge LJ, Guo J, Gao SP, Zheng JG, Luan H, Shi GL, Wang RX, Shi HF, Pan M. The Association of Interleukin 6-634C/G polymorphism with left atrial thrombus and severe spontaneous echocontrast in patients with atrial fibrillation. Clin Appl Thromb Hemost 2013; 19: 673-678.

[8] Gao SP, Deng XT, Ge LJ, Luan H, Zheng JG, Chen C, Jiang MH, Pan M. Is inflammation linked to thrombogenesis in atrial fibrillation. Int J Cardiol 2011; 149: 260-261.

[9] Su YM, Li J, Guo YF, Cai F, Xu B, Xu Y, Geng HH, Pan M. Correlation between Pre-miR-196a2 single nucleotide polymorphism and atrial fibrillation. Exp Clin Cardiol 2014; 20: 626-638.

[10] de Figueiredo MM, Rodrigues AC, Alves MB, Neto MC, Silva GS. Score for atrial fibrillation detection in acute stroke and transient ischemic attack patients in a Brazilian population: the acute stroke atrial fibrillation scoring system. Clinics (Sao Paulo) 2014; 69: 241-246.

[11] Verdecchia P, Reboldi G, Gattobigio R, Bentivoglio M, Borgioni C, Angeli F, Carluccio E, Sardone MG, Porcellati C. Atrial fibrillation in hypertension: predictors and outcome. Hypertension 2003; 41: 218-223.

[12] Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982; 306: 1018-1022.

[13] Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995; 98: 476-484.

[14] Aidietis A, Laucevicius A, Marinskis G. Hypertension and cardiac arrhythmias. Curr Pharm Des 2007; 13: 2545-2555.

[15] Magnani JW, Johnson VM, Sullivan LM, Gorodeski EZ, Schnabel RB, Lubitz SA, Levy D, Ellinor PT, Benjamin EJ. P wave duration and risk of longitudinal atrial fibrillation in persons >/= 60 years old (from the Framingham Heart Study). Am J Cardiol 2011; 107: 917-921.

[16] Celik T, Yuksel UC, Bugan B, Celik M, Fici F, Iyisoy A, Kilic S, Sonmez A, Yaman H, Isik E. P-wave dispersion and its relationship to aortic elasticity in young prehypertensive patients. Am J Hypertens 2009; 22: 1270-1275.

[17] Tong GM, Zhang HC, Guo JH, Han F. Detection of sleep apnea-hypopnea syndrome with ECG derived respiration in Chinese population. Int J Clin Exp Med 2014; 7: 1269-1275.

[18] Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. J Am Coll Cardiol 2007; 50: 2021-2028.

[19] Qiu XB, Xu YJ, Li RG, Xu L, Liu X, Fang WY, Yang YQ, Qu XK. PITX2C loss-of-function mutations responsible for idiopathic atrial fibrillation. Clinics (Sao Paulo) 2014; 69: 15-22.

[20] Helmersson-Karlqvist J, Bjorklund-Bodegard K, Larsson A, Basu S. 24-Hour ambulatory blood pressure associates inversely with prostaglandin F(2alpha), interleukin-6 and F(2)-isoprostane formation in a Swedish population of older men. Int J Clin Exp Med 2012; 5: 145-153.

[21] Liu W, Dong XS, Sun YQ, Liu Z. A novel fluid resuscitation protocol: provide more protection

on acute kidney injury during septic shock in rats. Int J Clin Exp Med 2014; 7: 919-926.
[22] Bennermo M, Nordin M, Lundman P, Boqvist S, Held C, Samnegard A, Ericsson CG, Silveira A, Hamsten A, Nastase MM, Tornvall P. Genetic and environmental influences on the plasma interleukin-6 concentration in patients with a recent myocardial infarction: a case-control study. J Interferon Cytokine Res 2011; 31: 259-264.
[23] Cardellini M, Perego L, D'Adamo M, Marini MA, Procopio C, Hribal ML, Andreozzi F, Frontoni S, Giacomelli M, Paganelli M, Pontiroli AE, Lauro R, Folli F, Sesti G. C-174G polymorphism in the promoter of the interleukin-6 gene is associated with insulin resistance. Diabetes Care 2005; 28: 2007-2012.
[24] Gallone S, Di SM, Fenoglio P, Rubino E, Criasia A, Pinessi L, Isaia G, Rainero I. Proinflammatory cytokine gene polymorphisms and susceptibility to Paget's disease of bone: an association study. Cytokine 2011; 56: 560-563.
[25] Gao SP, Pan M, Chen C, Ge LJ, Jiang MH, Luan H, Zheng JG, Deng XT, Pan HY, Zhu JH. The G to A polymorphism at -597 of the interleukin-6 gene is extremely rare in southern Han Chinese. Cytokine 2011; 55: 1-3.
[26] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289: 2560-2572.
[27] Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, Gialafos JE, Toutouzas PK. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J 1998; 135: 733-738.
[28] Bazett HC. The time relations of the blood-pressure changes after excision of the adrenal glands, with some observations on blood volume changes. J Physiol 1920; 53: 320-339.
[29] Pan M, Zhu JH, Liu ZH, Jiang WP, Cui ZC, Yu XH, Li HM, Yang XJ. Angiotensin-converting enzyme gene 2350 G/A polymorphism is associated with left ventricular hypertrophy but not essential hypertension. Hypertens Res 2007; 30: 31-37.
[30] Pan M, Jiang MH, Wei MF, Liu ZH, Jiang WP, Geng HH, Cui ZC, Zhang DL, Zhu JH. Association of angiotensin-converting enzyme gene 2350G>A polymorphism with myocardial infarction in a Chinese population. Clin Appl Thromb Hemost 2009; 15: 435-442.
[31] Pan M, Gao SP, Jiang MH, Guo J, Zheng JG, Zhu JH. Interleukin 6 promoter polymorphisms in normal Han Chinese population: frequencies and effects on inflammatory markers. J Investig Med 2011; 59: 272-276.
[32] Burzotta F, Iacoviello L, Di CA, Glieca F, Luciani N, Zamparelli R, Schiavello R, Donati MB, Maseri A, Possati G, Andreotti F. Relation of the -174 G/C polymorphism of interleukin-6 to interleukin-6 plasma levels and to length of hospitalization after surgical coronary revascularization. Am J Cardiol 2001; 88: 1125-1128.
[33] Psychari SN, Apostolou TS, Sinos L, Hamodraka E, Liakos G, Kremastinos DT. Relation of elevated C-reactive protein and interleukin-6 levels to left atrialsize and duration of episodes in patients with atrial fibrillation. Am J Cardiol 2005; 95: 764-767.
[34] Gedikli O, Dogan A, Altuntas I, Altinbas A, Ozaydin M, Akturk O, Acar G. Inflammatory markers according to types of atrial fibrillation. Int J Cardiol 2007; 120: 193-197.
[35] Marcus GM, Whooley MA, Glidden DV, Pawlikowska L, Zaroff JG, Olgin JE. Interleukin-6 and atrial fibrillation in patients with coronary artery disease:data from the Heart and Soul Study. Am Heart J 2008; 155: 303-309.
[36] Anand K, Mooss AN, Hee TT, Mohiuddin SM. Meta-analysis: inhibition of renin-angiotensin system prevents new-onset atrial fibrillation. Am Heart J 2006; 152: 217-222.
[37] Tai CT, Chen SA, Tzeng JW, Kuo BI, Ding YA, Chang MS, Shyu LY. Prolonged fractionation of paced right atrial electrograms in patients with atrial flutter and fibrillation. J Am Coll Cardiol 2001; 37: 1651-1657.
[38] Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82: 2N-9N.
[39] Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997; 96: 2455-2461.
[40] Paik JK, Kim OY, Koh SJ, Jang Y, Chae JS, Kim JY, Kim HJ, Hyun YJ, Cho JR, Lee JH. Additive effect of interleukin-6 and C-reactive protein (CRP) single nucleotide polymorphism on serum CRP concentration and other cardiovascular risk factors. Clin Chim Acta 2007; 380: 68-74.
[41] Saijo Y, Yoshioka E, Fukui T, Kawaharada M, Sata F, Sato H, Kishi R. Effects of the Interaction between Interleukin-6 -634C/G Polymorphism and Smoking on Serum C-Reactive Protein Concentrations. Hypertens Res 2007; 30: 593-599.