Paper

Perindopril decreases P wave dispersion in patients with stage 1 hypertension

Beste Ozben, Mutlu Sumerkan,* Azra Meryem Tanrikulu,* Nurdan Papila-Topal,* Ali Serdar Fak,* Ahmet Toprak†*

Key words: angiotensin-converting enzyme inhibitor, atrial fibrillation, electrocardiography, hypertension, perindopril, P wave dispersion

* Department of Cardiology, Marmara University Faculty of Medicine, Istanbul, Turkey.

† Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Turkey.

Correspondence to:
Dr Beste Ozben
Yildiz Caddesi Konak Apartmani No: 43/24, 34353 Besiktas/Istanbul, Turkey.
Tel: +90 535 347 6231
Fax: +90 212 258 9943
Email: bestes@doctor.com

Journal of the Renin-Angiotensin-Aldosterone System
(Including other Peptidergic systems)

June 2009
Volume 10
Number 2

Abstract

Introduction. Angiotensin-converting enzyme inhibitors prevent atrial fibrillation episodes by effective control of blood pressure and improving electrical and structural remodelling in the atria. Increased P wave dispersion (PWD) is a non-invasive electrocardiographic marker for paroxysmal atrial fibrillation. The aim of the study was to evaluate the effect of perindopril treatment on PWD in hypertensive patients.

Methods. Forty-eight hypertensive patients (mean age 57.4±11.8 years, 18 men) were included. Blood pressure values were determined and 12-lead electrocardiograms were recorded at the beginning and at the first week, first month, third month and sixth month of the perindopril treatment. The difference between maximum and minimum P wave durations was calculated as PWD.

Results. PWDs were significantly shortened at the first, third and sixth months (41.7±8.8 ms, 39.1±6.9 ms and 38.3±7.1 ms, respectively) compared with baseline and first-week measurements (54.3±9.2 ms and 49.0±9.1 ms, respectively, $p<0.001$). Baseline PWD was correlated with body mass index ($r=0.32$, $p=0.026$), while PWD at the sixth month of treatment was significantly correlated with left atrial volume index ($r=0.30$, $p=0.042$). Multiple linear regression analysis revealed that PWD at the sixth month was related to baseline PWD ($p=0.001$).

Conclusion. Perindopril treatment significantly reduced PWD in hypertensive patients.

Introduction

Atrial fibrillation (AF) is the most commonly observed arrhythmia in clinical practice and is associated with increased cardiovascular morbidity and mortality.[1-3] Epidemiological surveys have reported that age, male gender, ischaemic heart disease, hypertension, heart failure, valvular heart disease, diabetes and disorders of the thyroid, lung and pleura are the independent risk factors for the development of AF.[4,5] Hypertension is associated with left ventricular hypertrophy, impaired ventricular filling, left atrial enlargement and slowing of atrial conduction velocity. These changes in cardiac structure and physiology favour the development of AF.[6] Verdecchia *et al*.[7] reported that the risk of AF increased with age and left ventricular mass in hypertensive subjects with sinus rhythm and no other major predisposing conditions.

Conventional therapy of AF has focused on interventions to control heart rate and rhythm and the prevention of stroke through the use of anticoagulant medications. The most effective and safest option for the prevention of AF is primary prevention and the management of arterial hypertension.[8] In patients with AF, effective treatment of high blood pressure may reverse the structural abnormalities in the heart, reduce thromboembolic complications and prevent or retard the occurrence of AF.[6] In addition to blood pressure reduction, substances with an action of the autonomic nervous system and the renin-angiotensin-aldosterone system (RAAS) have a positive effect on the remodelling of the atrial myocytes, and thus on the occurrence of AF.[8]

P wave dispersion (PWD) is a non-invasive electrocardiographic marker for the development of paroxysmal AF.[9,10] The P wave, occurring by the spread of electrical excitation from the sinoatrial node over the atrial musculature, represents the depolarisation of the atria. PWD is defined as the difference between maximum and minimum P wave durations. Because of the re-entrant nature of AF, there should be areas in the atria with different conduction properties for initiation of AF, and prolongation of PWD should reflect both intra- and interatrial heterogeneity in the conduction of sinus nodal impulses. Thus, prolonged

PWD can be used as a predictor for the development of AF in various clinical settings.[11,12]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are able to prevent the occurrence of AF. However, there is a limited number of studies exploring the effect of these drugs on PWD.[13] The aim of the study was to explore the effect of perindopril treatment on PWD in patients with stage 1 essential hypertension.

Patients and methods

The clinical investigation conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee and all participants gave informed consent. Patients were selected among cases admitted to the Cardiology Outpatient Clinic of Marmara University Hospital between December 2006 and September 2007.

Forty-eight consecutive, newly diagnosed stage 1 essential hypertensive patients (systolic blood pressure ≥ 140 mmHg and < 160 mmHg and/or diastolic blood pressure ≥ 90 mmHg and < 100 mmHg) were included in the study. Subjects with valvular heart disease, coronary artery disease, pre-excitation syndrome, thyroid disorders, or lung disease were excluded. None of the patients had significant impulse generation or conduction defect, autonomic or metabolic abnormality, or any previous episode of AF. None of the patients received any antihypertensive drug other than perindopril, anti-arrhythmic drug or digitalis.

At baseline, all patients underwent echocardiographic examination and laboratory test including serum glucose, creatinine and lipid profiles. Standard 12-lead electrocardiograms were recorded. All patients were re-examined at the first week, first month, third month and sixth month of their treatment. Blood pressures were measured and standard 12-lead electrocardiograms were recorded at each visit.

All standard 12-lead electrocardiograms were recorded using 12-channel equipment (Nihon Kohden Cardiofax Q, Europe GmbH, Rosbach, Germany), at a paper speed of 25 mm/s and with 1 mV/cm standardisation, with the patient in a comfortable supine position. Electrocardiograms were scanned and magnified five times. P wave duration was measured digitally in three consecutive complexes of each lead (from the first electrical activity to the junction between the end of P wave deflection and the isoelectric line) by a single observer who was blinded to the patients. PWD was calculated as the difference between the maximum and minimum P wave durations. All patients were in sinus rhythm during the entire study period.

Statistical analysis

Statistical analyses were performed by a statistical software (SPSS 11.0 for Windows; Chicago, IL, USA). Continuous variables were expressed as mean±standard deviation and categorical variables as ratio. Friedman and Wilcoxon tests were used for the comparisons of P wave measurements, blood pressure and heart rate. Spearman's correlation test was performed to explore correlation between PWD and age, systolic and diastolic blood pressures, laboratory and echocardiographic parameters. Multivariate linear regression model included age, gender, blood pressure, left atrium diameter, left ventricular ejection fraction, serum creatinine and potassium levels for their association with PWD at the sixth month of treatment. A p value < 0.05 was considered as statistically significant.

Results

Forty-eight consecutive, newly diagnosed stage 1 essential hypertensive patients, who were prescribed perindopril, were included in the study. The mean age of the patients was 57.4±11.8 years (age ranged between 26 and 65 years). Thirty out of 48 (62.5%) were women. Five patients (10.4%) were diabetic and 31 patients (64.6%) had hyperlipidaemia. Twenty patients (41.7%) were smokers. Seventeen patients were prescribed perindopril 5 mg/day, while 31 patients were prescribed perindopril 10 mg/day. The clinical and laboratory characteristics of the patients are listed in table 1.

The echocardiographic measures are presented in table 2. All patients had normal left ventricular systolic function. None had significant valvular regurgitation or stenosis.

P wave durations (both maximum and minimum) and PWD at baseline and at each visit are presented in table 3. Maximum P wave durations were significantly shortened at the first, third and sixth months compared with baseline and first week (p=0.001). Minimum P wave duration was significantly prolonged at the first week of perindopril treatment compared with

SAGE Publications 2009 Los Angeles, London, New Delhi and Singapore

Table 1
The clinical characteristics and laboratory parameters of the patients.

Number of patients	48
Women/men (n/n)	30/18
Age (years)	57.4±11.8
Diabetes mellitus (%)	10.4
Hyperlipidaemia (%)	64.6
Smoking (%)	41.7
Perindopril dose (5/10 mg/day) (n/n)	17/31
Body mass index (kg/m^2)	29.1±4.6
Haemoglobin (g/dL)	11.2±1.7
Glucose (mg/dL)	99±19
Creatinine (mg/dL)	0.87±0.24
Potassium (mmol/L)	4.4±0.4
Total cholesterol (mg/dL)	210±51
Triglycerides (mg/dL)	137±74
HDL cholesterol (mg/dL)	53±14
LDL cholesterol (mg/dL)	129±45
ProBNP (ng/dL)	60.3±59.8
Microalbuminuria (mg/dL)	11.3±9.9

Key: HDL = high-density lipoprotein; LDL = low-density lipoprotein; proBNP = pro-B-type natriuretic peptide.

baseline, while minimum P wave durations were significantly prolonged at the first, third and sixth months of treatment compared with baseline and first week (p<0.001). PWD significantly shortened throughout the study compared with baseline (54.3±9.2 ms, 49.0±9.1 ms, 41.7±8.8 ms, 39.1±6.9 ms and 38.3±7.1 ms, respectively, p<0.001) (figure 1). Systolic and diastolic blood pressures significantly decreased compared with baseline (p<0.001 for both comparisons). However, systolic and diastolic blood pressures were similar between the third and the sixth months of treatment. Heart rates were unchanged during the study period (p=0.057). No arrhythmia was observed during the entire study period.

Baseline PWD correlated with body mass index (r=0.32, p=0.026), while there were no significant correlations between baseline PWD and age, blood pressures, heart rate, left atrium size or volume, left ventricular ejection fraction, left ventricular mass index, left ventricular myocardial performance index, serum creatinine, potassium, microalbuminuria or pro-B-type natriuretic peptide (proBNP) levels. On the other hand, PWD at the sixth month of perindopril treatment showed significant correlation with left atrial volume index (r=0.30, p=0.042).

We modelled a multivariate linear regression analysis to define the independent association between PWD at the sixth month of treatment and age, gender, body mass index, blood pressure, left atrium size, left ventricular ejection fraction, mitral E velocity/lateral annulus E' velocity ratio, baseline PWD, daily perindopril dose, proBNP and serum potassium levels. The adjusted R square of the model was 0.694 with p value of 0.014. Linear regression model revealed that PWD at the sixth month of treatment was significantly associated with baseline PWD (standardised beta=0.528, p=0.001).

Discussion

AF is the most common arrhythmia affecting the general population.[14] In patients with arterial hypertension, the risk of AF is increased to as much as 42%, and the emergence of AF in hypertension contributes to increased cardiovascular morbidity and mortality.[5] AF is responsible for atrial electrical and structural remodelling that both contribute to the maintenance and recurrence of this arrhythmia.[15,16] Inhibition of the RAAS with ACE inhibitors or angiotensin receptor blockers not only provides blood pressure reduction,

Table 2
Baseline echocardiographic measures of the patients.

Left atrial diameter (cm)	3.58±0.42 (range 2.96-4.53)
Left atrium volume (ml)	25.33±7.36 (range 13.82-43.81)
Left ventricular end diastolic diameter (cm)	4.42±0.42 (range 3.65-5.65)
Left ventricular end systolic diameter (cm)	2.72±0.45 (range 2.09-4.40)
Interventricular septum thickness (cm)	1.10±0.13 (range 0.77-1.31)
Posterior wall thickness (cm)	1.00±0.11 (range 0.71-1.20)
Left ventricular mass index (g/m^2)	122.78±28.47 (range 72.37-260.18)
Left ventricular ejection fraction (%)	68.0±7.3 (range 60-83)
Mitral E wave velocity (m/s)	0.70±0.16 (range 0.41-1.03)
Mitral A wave velocity (m/s)	0.77±0.15 (range 0.46-1.13)
Deceleration time (ms)	196.68±54.11 (range 140.98-286.60)
Isovolumetric relaxation time (ms)	88.16±15.81 (range 63.49-128.50)
Mitral lateral annulus E' velocity (cm/s)	9.50±2.72 (range 4.62-15.98)
Mitral lateral annulus A' velocity (cm/s)	11.29±2.81 (range 3.59-16.55)
Mitral E velocity/lateral annulus E' velocity	7.76±2.02 (range 4.10-12.20)
Myocardial performance index	0.28±0.10 (range 0.22-0.42)

Table 3
P wave measures and blood pressures at baseline and at each visit.

	Baseline	First week	First month	Third month	Sixth month	p
Pmax (ms) (range)	109±12 (80-144)	108±11 (84-132)	104±13[b,e] (80-144)	104±11[b,e] (84-140)	104±11[b,e] (84-136)	0.001
Pmin (ms) (range)	55±10 (36-84)	59±9[c] (40-80)	63±11[a,e] (40-96)	65±11[a,d] (44-92)	66±12[a,d] (44-96)	< 0.001
PWD (ms) (range)	54.3±9.2 (32-80)	49.0±9.1[a] (32-80)	41.7±8.8[a,d] (24-80)	39.1±6.9[a,d,g] (24-56)	38.3±7.1[a,d,g] (24-56)	< 0.001
Systolic BP (mmHg) (range)	146.8±12.5 (135-155)	134.9±14.5[a] (125-155)	126.8±11.0[a,d] (120-150)	122.1±6.5[a,d,g] (120-140)	120.7±6.1[a,d,f] (110-135)	< 0.001
Diastolic BP (mmHg) (range)	87.7±7.9 (70-95)	83.9±9.3[b] (70-95)	80.1±8.2[a,e] (60-95)	79.1±4.8[a,d] (60-90)	76.7±3.9[a,d,f] (40-90)	< 0.001
HR (/min) (range)	76±11 (51-100)	75±10 (52-96)	74±11 (50-100)	74±10 (50-100)	74±10 (50-94)	0.057

Key: Post-hoc comparisons: [a] p<0.001 *vs.* baseline; [b] p<0.01 *vs.* baseline; [c] p<0.05 *vs.* baseline; [d] p<0.001 *vs.* first week; [e] p<0.05 *vs.* first week; [f] p<0.001 *vs.* first month; [g] p<0.01 *vs.* first month. BP = blood pressure; HR = heart rate; Pmax = maximum P wave duration; Pmin = minimum P wave duration; PWD = P wave dispersion.

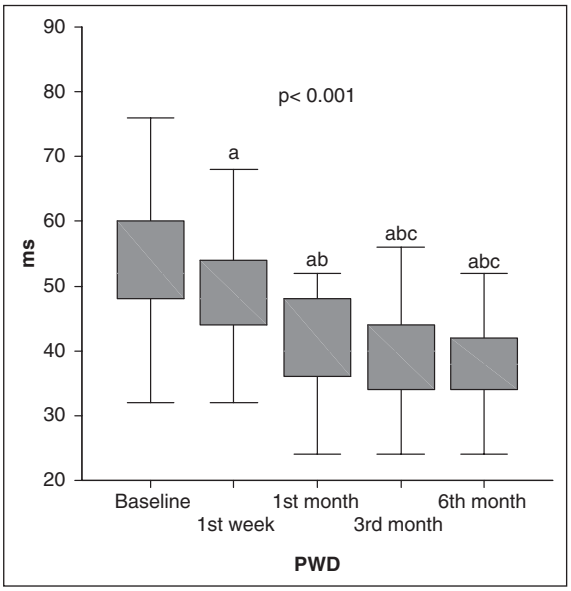

Figure 1
P wave dispersion (PWD) distribution during the entire study period. Post-hoc analysis: **a:** p<0.001 *vs.* baseline; **b:** p<0.001 *vs.* 1st week; **c**: p<0.01 *vs.* 1st month.

but also decreases the incidence of AF by improving electrical and structural stability within the atria (reducing collagen deposits in atria, reducing delay in atrial activation and heterogeneity).[17-24]

AF is characterised by multiple circulating re-entrant wavelets due to disorganised atrial depolarisation and inhomogeneous and discontinuous propagation of sinus impulses.[25] Prolongation of intra- and interatrial conduction times (marked by maximum P wave duration) and the inhomogeneous propagation of sinus impulses (marked by PWD) are electrophysiological characteristics of the atrium that is prone to AF.[26] Thus, antihypertensive drugs which also reduce PWD are expected to decrease the incidence of AF. Angiotensin receptor blockers and ACE inhibitors have beneficial effects on atrial conduction times. In this study, we have found that perindopril therapy significantly shortened maximum P wave duration and PWD in hypertensive patients. This is the first study that shows significant decrease in PWD with perindopril therapy. This finding is important in the prevention of AF by perindopril therapy and is in agreement with some previous studies.[27-29]

Celik *et al.*[13] and Fogari *et al.*[30] have shown that non-anti-arrhythmic drugs interfering with the RAAS reduce PWD. Celik *et al.*[13] compared the effects of daily doses of 80 mg telmisartan and 10 mg ramipril on PWD after 6-month treatments in hypertensive patients and found that both telmisartan and ramipril significantly decreased P maximum values and PWD, while telmisartan had a much greater effect on PWD and P maximum values compared with ramipril. Fogari *et al.*[30] found that ramipril and valsartan significantly shortened PWD and maximum P wave durations.

In our study, a significant decrease in PWD was observed even in the first week of treatment with significant reduction of blood pressure. We believe that lowering of blood pressure could be an important mechanism for these drugs in prevention of AF. However, Fogari *et al.*[30] stated that ACE inhibitors or angiotensin receptor blockers exerted anti-arrhythmic action beyond their blood

pressure-lowering effects. They found that, although amlodipine, ramipril and valsartan significantly reduced blood pressure, PWD values were significantly shortened with ramipril and valsartan only, not with amlodipine. Similarly, we did not find any correlation between blood pressure and PWD in our study. Therefore, there could be other mechanisms for ACE inhibitors and angiotensin receptor blockers to reduce PWD in addition to their effective blood pressure control. Inhibition of angiotensin II-induced fibrosis, reduced atrial stretch, interference with ion-channel function and modulation of refractoriness, improved left ventricular haemodynamics and modulation of sympathetic nerve activity may be important mechanisms to explain the anti-arrhythmic actions of RAAS inhibitors.[17,31-35]

In our study, there was a significant association between PWD and body mass index. Obesity is now accepted as a risk factor for AF. Obesity increases the risk of developing AF by 49% in the general population, and the risk escalates in parallel with increased body mass index.[36] Kosar *et al*.[37] reported that obesity affected PWD and changes in PWD were closely related to body mass index. Left atrium size was correlated with PWD, as expected. We did not find any significant association between PWD and other well-known risk factors of AF, including age. Although amino-terminal proBNP levels have been suggested to predict newly detected AF in subjects in the general population,[38] there was no significant association between proBNP level and PWD in our study. Perindopril dose did not influence PWD in our study. Our study revealed that only baseline PWD was related to PWD at the sixth month of treatment.

Conclusion

Prolongation of maximum P wave duration and increase of PWD were shown to be independent predictors of AF. RAAS inhibition by ACE inhibitors reduces PWD and prevents or delays AF episodes. Perindopril therapy significantly shortened maximum P wave duration and PWD in addition to blood pressure control. This finding suggests that perindopril therapy might also help in prevention of AF episodes while maintaining blood pressure control.

References

1. Go AS, Hylek EM, Phillips KA *et al*. 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.
2. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002; **113**:359-64.
3. Vidaillet H, Granada JF, Chyou PH *et al*. A population-based study of mortality among patients with atrial fibrillation or flutter. *Am J Med* 2002; **113**:365-70.
4. 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**:476-84.
5. 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.
6. Healey JS, Connolly SJ. Atrial fibrillation: hypertension as a causative agent, risk factor for complications, and potential therapeutic target. *Am J Cardiol* 2003;**91**:9G-14G.
7. Verdecchia P, Reboldi G, Gattobigio R *et al*. Atrial fibrillation in hypertension: predictors and outcome. *Hypertension* 2003;**41**:218-23.
8. Geller JC. Atrial fibrillation as end point of hypertension. Can antihypertensive therapy prevent it? *MMW Fortschr Med* 2003;**145**:38-41.
9. Dilaveris PE, Gialafos EJ, Sideris SK *et al*. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. *Am Heart J* 1998;**135**:733-8.
10. Dilaveris PE, Gialafos EJ, Andrikopoulos GK *et al*. Clinical and electrocardiographic predictors of recurrent atrial fibrillation. *Pacing Clin Electrophysiol* 2000;**23**:352-8.
11. Babaev AA, Vloka ME, Sadurski R, Steinberg JS. Influence of age on atrial activation as measured by the P-wave signal-averaged electrocardiogram. *Am J Cardiol* 2000;**86**:692-5.
12. Michelucci A, Bagliani G, Colella A *et al*. P wave assessment: state of the art update. *Card Electrophysiol Rev* 2002; **6**:215-20.
13. Celik T, Iyisoy A, Kursaklioglu H *et al*. The comparative effects of telmisartan and ramipril on P-wave dispersion in hypertensive patients: a randomized clinical study. *Clin Cardiol* 2005;**28**:298-302.
14. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;**271**:840-4.
15. Allessie MA. Atrial electrophysiologic remodeling: another vicious circle? *J Cardiovasc Electrophysiol* 1998;**9**:1378-93.
16. Nattel S, Shiroshita-Takeshita A, Cardin S, Pelletier P. Mechanisms of atrial remodeling and clinical relevance. *Curr Opin Cardiol* 2005;**20**:21-5.
17. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. *Circulation* 2000;**101**:2612-17.
18. Li D, Shinagawa K, Pang L *et al*. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. *Circulation* 2001;**104**:2608-14.
19. Klein HU, Goette A. Blockade of atrial angiotensin II type 1 receptors: a novel antiarrhythmic strategy to prevent atrial fibrillation? *J Am Coll Cardiol* 2003; **41**:2205-06.
20. Ueng KC, Tsai TP, Yu WC *et al*. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation. Results of a prospective and controlled study. *Eur Heart J* 2003;**24**:2090-8.
21. Pedersen OD, Bagger H, Kober L, Torp-Pedersen C. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. *Circulation* 1999;**100**:376-80.
22. Vermes E, Tardif JC, Bourassa MG *et al*. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the Studies Of Left

Ventricular Dysfunction (SOLVD) trials. *Circulation* 2003; **107**:2926-31.
23. Olsson LG, Swedberg K, Ducharme A *et al.* CHARM Investigators. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**:1997-2004.
24. Maggioni AP, Latini R, Carson PE *et al.* Val-HeFT Investigators. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). *Am Heart J* 2005;**149**:548-57.
25. Moe GK, Allessie MA, Lammers WJEP, Bonke FIM, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP and Jalife J (eds.). *Cardiac Arrhythmias*. San Diego: Grune & Stratton, 1985;265-76.
26. Dilaveris PE, Gialafos EJ, Chrissos D *et al.* Detection of hypertensive patients at risk for paroxysmal atrial fibrillation during sinus rhythm by computer-assisted P wave analysis. *J Hypertens* 1999;**17**:1463-70.
27. Yin YH, Liu ZC, Wu JJ *et al.* Long-term clinical efficacy of losartan or perindopril combination therapy with low-dose amiodarone in patients with paroxysmal atrial fibrillation. *Zhonghua Xin Xue Guan Bing Za Zhi* 2006;**34**:299-302.
28. Yin Y, Dalal D, Liu Z *et al.* Prospective randomized study comparing amiodarone vs. amiodarone plus losartan vs. amiodarone plus perindopril for the prevention of atrial fibrillation recurrence in patients with lone paroxysmal atrial fibrillation. *Eur Heart J* 2006;**27**:1841-6.
29. Abuladze GV, Dzhindzholiia NR, Narsiia EV, Dzhincharadze BZ, Kadzhaia TZ. The therapeutic efficiency of complex-ACE inhibitor (perindopril) and traditional antiarrhythmic-treatment for prevention atrial fibrillation paroxysms after successful electric cardio version. *Georgian Med News* 2008;**155**:17-19.
30. Fogari R, Derosa G, Ferrari I *et al.* Effect of valsartan and ramipril on atrial fibrillation recurrence and P-wave dispersion in hypertensive patients with recurrent symptomatic lone atrial fibrillation. *Am J Hypertens* 2008;**21**:1034-9.
31. Shinagawa K, Mitamura H, Ogawa S, Nattel S. Effects of inhibiting Na(+)/H(+)-exchange or angiotensin converting enzyme on atrial tachycardia-induced remodeling. *Cardiovasc Res* 2002;**54**:438-46.
32. Caballero R, Delpón E, Valenzuela C, Longobardo M, Tamargo J. Losartan and its metabolite E3174 modify cardiac delayed rectifier K(+) currents. *Circulation* 2000;**101**:1199-205.
33. Li Y, Li WM, Xue JY, Han W, Yang SS, Gu HY. Effects of losartan on acute atrial electrical remodeling. *Chin Med J (Engl)* 2004;**117**:643-6.
34. Ciulla MM, Paliotti R, Esposito A *et al.* Different effects of antihypertensive therapies based on losartan or atenolol on ultrasound and biochemical markers of myocardial fibrosis: results of a randomized trial. *Circulation* 2004;**110**:552-7.
35. Ehrlich JR, Hohnloser SH, Nattel S. Role of angiotensin system and effects of its inhibition in atrial fibrillation: clinical and experimental evidence. *Eur Heart J* 2006;**27**:512-18.
36. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity – results of a meta-analysis. *Am Heart J* 2008;**155**:310-15.
37. Kosar F, Aksoy Y, Ari F, Keskin L, Sahin I. P-wave duration and dispersion in obese subjects. *Ann Noninvasive Electrocardiol* 2008;**13**:3-7.
38. Asselbergs FW, van den Berg MP, Bakker SJ *et al.* N-terminal pro B-type natriuretic peptide levels predict newly detected atrial fibrillation in a population-based cohort. *Neth Heart J* 2008;**16**:73-8.