The Comparative Effects of Telmisartan and Ramipril on P-Wave Dispersion in Hypertensive Patients: A Randomized Clinical Study

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Summary

Background: Prolongation of P-wave times and increase of P-wave dispersion (PWD) were shown to be independent predictors of atrial fibrillation (AF). Angiotensin II receptor blockers (AARBs) and angiotensin-converting enzyme inhibitors (ACEIs) have beneficial effects on atrial conduction times. However, there are not enough data about the comparative effects of those drugs on PWD.

Hypothesis: We aimed to compare the effects of telmisartan and ramipril on PWD after 6-month treatment in hypertensive patients.

Methods: In all, 100 newly diagnosed hypertensive patients were enrolled in the study and were randomly assigned to two groups. Group 1 and Group 2 each consisted of 50 patients, taking daily doses of 80 mg telmisartan and 10 mg ramipril, respectively. Twelve-lead surface electrocardiograms (ECG) were recorded from all patients before and after 6-month drug therapy. The P-wave duration (P_{dur}) measurements were calculated from the 12-lead surface ECG.

Results: When pretreatment PWD and $P_{maximum}$ values were compared with post-treatment values, a statistically significant decrease was found in both groups after 6 months (Group 1 and 2; $p < 0.001$ for PWD and $P_{maximum}$). P-wave dispersion and $P_{maximum}$ values after treatment in Group 1 were

statistically significantly lower than those in Group 2 after the 6-month treatment period ($p = 0.01$ for PWD; $p = 0.008$ for $P_{maximum}$).

Conclusions: Telmisartan has a much greater lowering effect on PWD and $P_{maximum}$ values than ramipril. This finding may be important in the prevention of AF in hypertensive patients.

Key words: P-wave dispersion, telmisartan, ramipril, hypertension

Introduction

P-wave dispersion (PWD) constitutes an important contribution to the field of noninvasive electrocardiology. Until now, the most extensive clinical evaluation of PWD has been made in the assessment of risk for atrial fibrillation (AF) in patients with hypertension, coronary artery disease, and in those undergoing bypass surgery.¹ Prolongation of PWD was shown to be an independent predictor for AF.²

Hypertension is currently among the leading causes of morbidity and mortality in the world.³ Atrial fibrillation is the most common arrhythmia, occurring in approximately 0.4 to 1.0% of the general population.⁴

Studies have shown that AF induced by rapid atrial pacing itself produces shortening of the atrial effective refractory period (AERP) and reverses the normal physiologic rate adaptation.⁵ Electrical remodeling increases the inducibility and stability of AF. Angiotensin II (Ang II) may be involved in the mechanism of atrial electrical remodeling.⁶

P-wave dispersion may indicate nonhomogeneous conduction in the left atrium.^{2,7} Pedersen *et al.*⁸ reported thattrandolapril reduces the risk of developing AF by 55%. Nakashima *et al.* demonstrated that Ang II contributes to electrical remodeling.⁶

We aimed to compare the effects of the angiotensin-converting enzyme inhibitor (ACEI), ramipril, with the Ang II receptor blocker (AARB), telmisartan, on PWD after a 6-month treatment period.

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Material and Methods

Patients

In all, 100 newly diagnosed hypertensive patients were enrolled in this controlled, randomized, prospective study. The diagnosis of essential hypertension was based on the criteria of the Seventh Report of the National Joint Committee for the Prevention, Detection, Evaluation, and Treatment of high blood pressure.⁹ Exclusion criteria are listed in Table I. All patients enrolled in the study gave a written informed consent; the study was planned in accordance with the Declaration of Helsinki and approved by the local ethics Committee of our Institute.

The patients were randomly assigned to one of two treatment arms. Treatment was allocated at a 1:1 ratio. Group 1 and Group 2 (50 patients each) received telmisartan and ramipril, respectively. After baseline assessment, each patient was randomly allocated to treatment arms taking a single 10 mg daily dose of ramipril or 80 mg telmisartan. The patients were followed for 6 months after treatment.

After a 10 min resting period, blood pressure was measured three times on the right arm in each patient with a standard mercury sphygmomanometer. Measurements were performed by the same investigator, in the same room, and at the same time of day. An average of three measurements was used for analyses.

All participants were offered National Cholesterol Education Program step I cholesterol-lowering and salt-restricted diet during the treatment period.¹⁰

Transthoracic echocardiography was performed using by Esaote 2.5 mHz probe (Esaote, Genova, Italy) for measurements of left ventricular ejection fraction (LVEF) and left atrial (LA) diameter.

Surface Electrocardiogram

Resting 12-lead surface ECG was recorded in all the patients before and after treatment (Hewlett Packard M1700A, Houston, Tex., USA). The ECG recordings were obtained at a paper speed of 50 mm/s and a signal size of 10 mm/mV at sinus rhythm.

P-Wave Duration Analyses

Dilaveris *et al.* showed that on-screen manual measurements were more reliable than the measurements of paper printouts in a well-designed study;¹¹ therefore, we performed on-screen manual measurements on the computer. P-wave duration (P_{dur}) measurements were calculated in 12-lead surface ECG simultaneously recorded before and after treatment. After scanning the ECG recordings of the patients with a high-resolution scanner (HP Scanjet 8200 digital flatbed scanner C9931A, 4800 × 4800 dpi, Hewlett Packard), they were transferred into the computer and opened with a high-performance graphic program (Adobe Photoshop 7.0, Adobe, Inc., San Jose, Calif., USA). Manual measurements of P_{dur} were performed with digital calipers on a high-resolution computer

TABLE I Exclusion criteria

Secondary or malignant hypertension
Chronic obstructive lung disease
Atrial fibrillation, flutter or any other atrial tachyarrhythmias requiring antiarrhythmic therapy
History of taking antiarrhythmic drugs, including digoxin, within 1 month
Hyperthyroidism
Severe valvular heart disease of hemodynamic significance
History of sensitivity to use of ACEIs or Ang II receptor blockers
Pregnancy or nursing
Myocardial infarction or cerebrovascular accident within 6 months
History of or proven coronary artery disease
Concurrent therapy with medications that could affect blood pressure
Severe renal or hepatic failure

Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors, Ang II = angiotensin II.

screen by two cardiologists blinded to the patients' clinical data. The P-wave onset was defined as the first atrial deflection from the isoelectric line and the offset was the return of the atrial signal to baseline. Mean P_{dur} was calculated as the mean value P_{dur} in each lead. The difference between maximum and minimum P_{dur} was defined as PWD ($PWD (ms) = P_{maximum} - P_{minimum}$). Two investigators blinded to the patients' clinical data calculated P_{dur} . Intra- and interobserver variability were obtained from random ECG recordings of 50 patients. While intra- and interobserver variability for $P_{maximum}$ were 3.4 and 3.9%, respectively, it was 2.7 and 3.5%, respectively, for PWD.

Statistics

Results are expressed as the mean $\pm$ standard deviation (SD) and percents. The differences between groups were tested for significance by chi-square and independent samples *t*-test. The two-tailed paired *t*-test was used to compare the means of ECG measurements of P_{dur} before and after treatment. Intra- and interobserver variability was calculated as a relative error. Differences were considered at $p < 0.05$. Statistical analyses were performed by using the 10.0 Statistical Package for Social Sciences Program for Windows (SPSS Inc., Chicago, Ill., USA).

Results

In all, 100 patients (mean age 51.8 ± 6.1 years, 56 men) were enrolled. No statistically significant difference was observed between the two treatment groups when basic clinical, demographic, and echocardiographic parameters of the patients were compared (Table II).

Blood pressure, heart rate, and echocardiographic parameters including LVEF and LA diameter were not statistically different between groups before and after treatment. Systolic and diastolic blood pressure measurements after treatment

were statistically significantly different from pretreatment measurements in both groups ($p < 0.001$ for systolic and diastolic blood pressure). Left atrial diameter, LVEF, and heart rate values after treatment were not different from pretreatment values in both treatment arms (Table III).

TABLE II Basic clinical characteristics of the patients

	Group 1 (n = 50)	Group 2 (n = 50)	p Value
Mean age (years)	51.04 ± 6.36	52.56 ± 5.78	0.21 ^a
Sex (M), n (%)	29 (58)	27 (54)	0.68 ^b
Hypercholesterolemia, n (%)	13 (26)	17 (34)	0.38 ^b
Diabetes mellitus, n (%)	10 (20)	7 (14)	0.42 ^b
FHPCAD, n (%)	8 (16)	11 (22)	0.44 ^b
Smoking, n (%)	15 (30)	9 (18)	0.16 ^b

Values are presented mean ± standard deviation or n (%).

^a Independent samples *t*-test.

^b Chi-square test.

Abbreviations: M = male, FHPCAD = family history of premature coronary artery disease.

TABLE III Comparison of the hemodynamic and echocardiographic parameters between two treatment arms before and after treatment

	Group 1 (n = 50)	Group 2 (n = 50)	p Value ^a
Systolic BP (mmHg)			
Before	155.90 ± 6.75	154.30 ± 5.44	0.19
After	133.50 ± 9.48	130.40 ± 13.39	0.18
p ^b	<0.001	<0.001	
Diastolic BP (mmHg)			
Before	96.40 ± 6.47	94.7 ± 5.83	0.17
After	81.40 ± 6.06	80.20 ± 7.75	0.39
p ^b	<0.001	<0.001	
Heart rate (beats/min)			
Before	73.80 ± 9.05	72.62 ± 9.77	0.53
After	72.98 ± 10.64	70.38 ± 11.43	0.24
p ^b	0.61	0.20	
LA diameter (mm)			
Before	43.30 ± 1.28	42.92 ± 1.39	0.13
After	43.30 ± 1.32	42.86 ± 1.39	0.11
p ^b	0.56	0.26	
LVEF (%)			
Before	61.58 ± 2.06	61.96 ± 1.87	0.33
After	61.70 ± 1.54	61.94 ± 1.40	0.41
p ^b	0.59	0.93	

Values are presented mean ± standard deviation.

^a Independent samples *t*-test.

^b Paired *t*-test.

Abbreviations: BP = blood pressure, LA = left atrium, LVEF = left ventricular ejection fraction.

When pretreatment PWD and P_{maximum} values were compared with post-treatment values, a statistically significant decrease was found in both groups after treatment (Table IV; Group 1 and 2; $p < 0.001$ for PWD and P_{maximum}).

P-wave dispersion and P_{maximum} values after treatment in patients taking telmisartan were statistically significantly lower than those in patients taking ramipril (Table IV, Fig. 1; $p = 0.01$ for PWD; $p = 0.008$ for P_{maximum}).

Atrial fibrillation developed in four patients in Group 2 and in two patients in Group 1 after the 6-month follow-up period; however, no statistically significant difference in AF frequency was observed between Groups 1 and 2 ($p = 0.68$).

TABLE IV Comparison of P-wave duration values between groups before and after treatment

	Group 1 (n = 50)	Group 2 (n = 50)	p Value ^a
PWD (ms)			
Before	40.60 ± 8.72	40.90 ± 9.01	0.86
After	31.00 ± 10.69	36.50 ± 10.31	0.01
p ^b	<0.001	<0.001	
P maximum (ms)			
Before	106.30 ± 9.78	105.70 ± 10.54	0.76
After	97.60 ± 7.43	101.80 ± 8.00	0.008
p ^b	<0.001	<0.001	
P minimum (ms)			
Before	65.70 ± 12.97	64.80 ± 13.77	0.73
After	66.00 ± 13.09	65.30 ± 13.18	0.79
p ^b	0.32	0.37	

Values are presented mean ± standard deviation.

^a Independent samples *t*-test.

^b Paired *t*-test.

Abbreviation: PWD = P-wave dispersion.

FIG. 1 Comparison of P-wave dispersion (PWD) values between Groups 1 and 2 after treatment. ■ = PWD before treatment (ms); □ = PWD after treatment (ms).

Discussion

This study showed that telmisartan in hypertensive patients significantly lowered PWD and P_{maximum} values compared with patients taking ramipril after 6-month treatment. Although AF frequency in the telmisartan group was lower than that in the ramipril group, no statistically significant difference was found between the two groups.

Angiotensin-converting enzyme inhibitors and AARBs have beneficial effects on ventricular function and arrhythmias;^{12, 13} however, little is known about their effects on atrial remodeling.

Pedersen *et al.*⁸ showed that trandolapril reduced the risk of developing AF by 55%. Angiotensin-converting enzyme inhibitors could be effective on the basis of their favorable effect on cardiovascular fibrosis and apoptosis.¹⁴ Lopez *et al.* showed the ability of losartan to regress fibrosis in hypertensive patients with myocardial fibrosis, independent of its antihypertensive efficacy.^{14, 15}

Nakashima *et al.*⁶ demonstrated that Ang II contributes to atrial electrical remodeling. In that study, the shortening of the atrial refractory period during rapid atrial pacing was prevented by treatment with candesartan or captopril.

Madrid *et al.* demonstrated that patients treated with amiodarone plus irbesartan had a lower rate of recurrence of AF than did patients treated with amiodarone alone.¹⁶

We found that PWD and P_{maximum} values in the telmisartan group were lower than those in the ramipril group. Because PWD indicates the nonhomogeneous conduction in the left atrium, this finding can be important for predicting the development of AF in hypertensive patients. Although AF frequency in the telmisartan arm was lower than that in the ramipril arm, no statistical significance was found between groups.

The question is why post-treatment PWD and P_{maximum} values were lower in the telmisartan group than in the ramipril group. Recent studies showed that non-ACE-dependent Ang II-forming activity caused by chymase was higher in the left atrium than in the other chambers, and fibroblast-mediated collagen synthesis might be stimulated even in the presence of ACEIs.⁶ As we know, AARBs are effective on both non-ACE- and ACE-dependent pathways. We considered that, compared with AARBs, ACEIs were not able to inhibit Ang II activity caused by chymase in the left atrium. Increased chymase activity may play an important role in nonhomogeneous conduction, which is simply represented by increased PWD in the left atrium. Therefore, AARBs may have a greater effect on atrial electrophysiologic properties than ACEIs and result in lower PWD values. They may also be more effective on fibroblast-mediated collagen synthesis than ACEIs.

The Heart Outcomes Prevention Evaluation (HOPE) trial showed that the ACEI ramipril is effective in preventing major cardiovascular events in high-risk patients without hypertension.¹⁷ The development of AF was not among the secondary or other outcomes of the HOPE study. At this point, we do not have enough data about the effects of ACEIs on AF development in hypertensives.

Mitchell *et al.* found that there is a circadian distribution of onsets for atrial tachyarrhythmias, with predominance at night.¹⁸ Ciaroni *et al.*¹⁹ showed that diurnal and nocturnal systolic blood pressure levels were important independent predictors for the onset of AF.

Telmisartan is distinguished from the other AARBs and most other antihypertensives by its long half-life and duration of action.²⁰ The long action time of telmisartan may prevent blood pressure surges, especially in the morning. Effective 24-h blood pressure control including morning surges may have an important effect on atrial conduction. It is possible that the improving effect of telmisartan on P_{dur} may be related to its effective 24-h blood pressure control.

Primary objectives of the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trials (ON-TARGET) are to determine whether the combination of telmisartan and ramipril is more effective than ramipril alone, and whether telmisartan is at least as effective as ramipril. It is important to note that AF is one of secondary outcomes of this study.²¹ In the long term, the inclusion of AF as secondary outcome will help in understanding the role of AARBs on atrial electrophysiologic properties in hypertensive patients.

Study Limitations

The small number of patients is the major limitation of this clinical study. We did not use 24-h ambulatory blood pressure monitoring to measure systolic and diastolic blood pressures; therefore we could not assess the circadian variation of blood pressure and those patients whose nocturnal vs. daytime blood pressure showed a decrease of < 10%.

Conclusion

We found that telmisartan had a much greater lowering effect on PWD and P_{maximum} values compared with that of ramipril in patients under treatment in this clinical study. This finding may be very important in the prevention of AF in patients with hypertension.

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