

Effects of telmisartan on paroxysmal atrial fibrillation in hypertensive patients

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Abstract: This study examined the effects and mechanisms of telmisartan in hypertensive patients with paroxysmal atrial fibrillation (PAF). Hypertensive patients with PAF (n=120) were randomized into test (telmisartan) and control (amlodipine besilate) groups. The pretreatment and post treatment left atrial dimension (LAD), high-sensitivity C-reactive protein (hs-CRP) levels, heart rate, blood pressure (BP), and recurrence times of atrial fibrillation (AF) were recorded. The pretreatment and post treatment heart rates and BPs did not differ in either group ($P>0.05$). The post treatment systolic BP (SBP) and diastolic BP (DBP) did not differ between the groups (SBP: test, 132±5mmHg; control, 133±6 mmHg; DBP: test, 82±4 mmHg; control, 83±4mmHg). The LAD (test, 36.7±5.1 mm; control, 31.3±4.1mm) and hs-CRP (test, 5.6±2.6mg/L; control, 3.1±1.9mg/L) levels declined significantly ($P>0.05$) after treatment in the telmisartan group but not in the control group. After treatment, the LAD (test, 31.3±4.1mm; control, 36.2±4.6mm), hs-CRP (test, 3.1±1.9 mg/L; control, 5.2±2.3mg/L) levels, and AF recurrence times were markedly lower in the test group (22) compared with the control group (44). Thus, telmisartan reduced the AF recurrence rates, LAD, and hs-CRP levels.

Keywords: Telmisartan, hypertension, paroxysmal atrial fibrillation.

INTRODUCTION

Along with lifestyle changes and increasing life stress, the incidence of cardiovascular disease, including hypertension that is complicated by atrial fibrillation (AF), is rising, which subsequently increases the medical burden and seriously affects the quality of life of the patients. AF (Liu *et al.*, 2011a), which is the most common arrhythmia, occurs in 1.3-1.5% of the elderly between 60 and 80 years of age (Fogari *et al.*, 2012; Zaman *et al.*, 2014; Guo *et al.*, 2015) and mainly results from hypertension in elderly people (Gorczyca-Michta *et al.*, 2013). Additionally, AF correlates with atrial remodeling and inflammatory responses (Sasaki *et al.*, 2014; Sonmez *et al.*, 2014), while atrial remodeling is related to the renin-angiotensin-aldosterone system (RAAS) and inflammatory responses (Mayyas *et al.*, 2013). Our study aimed to examine the effects and mechanisms of telmisartan treatment in hypertensive patients with paroxysmal atrial fibrillation (PAF) by comparing the left atrial dimension (LAD), high-sensitivity C-reactive protein (hs-CRP) levels and the recurrence rate of AF before and after treatment compared to those not treated.

MATERIALS AND METHODS

General data

A total of 120 hypertensive patients with PAF were

treated in our hospital between January 2010 and December 2013 and enrolled in the study. The symptoms of all of the subjects were consistent with the 2010 diagnostic criteria for hypertension and PAF. PAF is defined as at least two separate episodes of AF that terminate spontaneously in less than 7 days and usually within 48h (Bennett, 1984; Lousberg *et al.*, 2004). Hypertension refers to a blood pressure (BP) >140/90 mmHg or high systolic BP (SBP >140 mmHg) and/or diastolic BP (DBP >90 mmHg) in patients not taking antihypertensive drugs (Jelaković *et al.*, 2008). The exclusion criteria (Du *et al.*, 2013; Grundvold *et al.*, 2013) included hyperthyroidism, coronary arteriosclerosis, glycometabolic disorder, malignant tumor, valvular heart disease, persistent and permanent AF, evidence of other heart diseases on electrocardiogram (ECG) and heart Doppler ultrasound, or treatment with diuretics or β -receptor blockers. The subjects were evenly randomized to the test or control groups. The patients were administered enteric-coated aspirin tablets (CHADS2 score <2 or not taking warfarin tablets) or warfarin tablets (CHADS2 score > 2 or taking warfarin tablets) combined with either telmisartan (test group) or amlodipine besilate (control group) for 12 months. The test group included 38 males and 22 females with a mean \pm standard deviation age of 53±3 years. The control group included 35 males and 25 females with a mean \pm standard deviation age of 56±2 years. Gender, age and pretreatment LAD, hs-CRP level, heart rate (HR), and BP did not differ between the groups ($P>0.05$, table 1). All of the study

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subjects were patients with good treatment compliance who were willing to participate in the research. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Wuhan University of Science and Technology. Written informed consent was obtained from all participants.

Treatment methods

The patients underwent routine blood, urine, and biochemical tests. The patients in the test and control groups took telmisartan (40-80mg/day) or amlodipine besilate (5-10mg/day), respectively, according to their BP. The treatment duration was 12 months. During treatment, BP, HR and AF were recorded every 4 weeks.

Observation indexes

Before and after treatment, the following indexes were observed: hs-CRP [venous blood (5mL) was collected from the median cubital vein and determined with the enhanced immune nephelometry method], LAD (determined by ECG), BP, HR and AF recurrence times.

For the LAD detection by ECG, a Philips color Doppler ultrasonograph (Philips Healthcare, Best, The Netherlands) with a S5-1 probe (frequency, 1-5 mHz) was used. The M-type and 2D ECG (Simpson's method) were applied to measure the left atrial diameter through the parasternal long axis view of the left ventricle and the apical four-chamber cardiac view. For HR detection, the average HR in the long-term ECG was recorded. For the AF recurrence times, patients with sinus rhythms that spontaneously changed within 7d (the longest period) were considered to have a paroxysmal AF recurrence because AFs usually last less than 48 h. All of the study subjects underwent a dynamic and long-range ECG once every 4 weeks, and the patients with symptoms, such as palpitations, underwent ECG and long-term ECG to confirm the recurrence of AF.

STATISTICAL ANALYSIS

The data were statistically analyzed with SPSS13.0 (IBM Corporation, Armonk, NY, USA). The measurement data followed a normal distribution and is presented as mean \pm standard error. Paired Student's *t*-tests were used to compare the pretreatment and post treatment data. Comparisons between the groups were made with *t*-tests. χ^2 tests were used to compare the recurrence rate of AF between the groups. *P* values less than 0.05 were considered statistically significant. The correlation analyses consisted of a multiple linear regression analysis.

RESULTS

Comparisons of pretreatment and post treatment LAD, hs-CRP, HR and BP

After the 12-month treatment and follow-up (table 2), the

pretreatment HRs were comparable to the posttreatment HRs in the test and control groups ($P>0.05$), but the pretreatment BPs differed significantly from the posttreatment BP in both groups ($P<0.05$), which suggested that both drugs were effective for the treatment of hypertension. The LAD and hs-CRP levels in hypertensive patients with PAF were significantly decreased after telmisartan therapy ($P<0.05$) but not after amlodipine besilate therapy ($P>0.05$), which indicated that telmisartan reduced the LAD and hs-CRP levels.

Comparisons of posttreatment LAD, hs-CRP, HR and BP between the groups

Table 3 shows that the post treatment BPs decreased significantly in both groups, but they did not differ ($P>0.05$) between the groups, which suggested that both drugs were equally effective for the treatment of hypertension. Telmisartan was superior to amlodipine besilate for reducing the LAD and hs-CRP levels ($P<0.05$). The recurrence rate of AF during the follow-up was 36.7% in the test group, which was lower than the 73% in the control group and which indicated that telmisartan effectively decreased the recurrence rate of AF.

The relationships of the AF recurrence times with the LAD, hs-CRP, HR and BP

As shown in table 4, the AF recurrence times did not exhibit a linear correlation with HR, while they were weakly correlated with SBP and DBP. The AF indexes were strongly and positively associated with the LAD and hs-CRP levels, which indicated that the AF recurrence times were significantly correlated with the LAD sizes and the Hs-CRP levels. The bigger the LAD, the higher the hs-CRP, and the more AF recurrence times. Reducing the LAD and hs-CRP levels reduced the AF recurrence times. tables 2-4 comprehensively show that telmisartan significantly reduced the LAD and Hs-CRP levels and therefore effectively reduced the AF recurrence times.

DISCUSSION

AF, which is the most common arrhythmia, probably correlates with atrial ectopic foci, atrial reentrant wavelets, atrial anatomical abnormalities, anisotropic conductivity, and atrium size (Alasady *et al.*, 2013; Kottkamp, 2013; Andrade *et al.*, 2014; Aparina *et al.*, 2014). AF mechanisms may be related to myocardial cell degradation and the susceptibility of the extracellular matrix during interstitial fibrosis (Du *et al.*, 2013), which might also result from atrial remodeling that is induced by increased inflammatory responses. A RAAS (Giestas *et al.*, 2010; Spence, 2012) imbalance is one of the risk factors for hypertension, and RAAS activation is observed in hypertensive patients who are especially complicated by systolic or diastolic heart failure and in whom ventricular and atrial pressure changes, angiotensin-converting enzyme levels significantly increase, angiotensin II (AngII) receptor density markedly up

Table 1: Comparison of LAD, hs-CRP, HR, blood pressure before the treatment

Group	n	LAD (mm)	HsCRP (mg/l)	HR (times/min)	SBP (mmHg)	DBP (mmHg)
Control group	60	36.5±4.7	5.4±2.5	68±4	150±8	97±2
Test group	60	36.7±5.1	5.6±2.6	67±8	151±5	95±3
<i>t</i> value	-	0.23	0.43	0.87	0.82	0.84
<i>P</i> value	-	>0.05	>0.05	>0.05	>0.05	>0.05

Table 2: Changes in LAD, hs-CRP, HR, blood pressure before and after treatment in two groups

Group	n	LAD (mm)	hsCRP (mg/l)	HR (times/min)	SBP (mmHg)	DBP (mmHg)
Control group						
Before	60	36.5±4.7	5.4±2.5	68±4	150±8	97±2
After	60	36.2±4.6	5.2±2.3	71±5	133±6	83±4
<i>t</i> value	-	0.35	0.45	1.927	14.074	39.292
<i>P</i> value	-	>0.05	>0.05	>0.05	<0.0001	<0.0001
Test group						
Before	60	36.7±5.1	5.6±2.6	67±8	151±5	95±3
After	60	31.3±4.1	3.1±1.9	72±4	132±5	82±4
<i>t</i> value	-	7.71	3.05	1.974	16.719	40.493
<i>P</i> value	-	<0.05	<0.05	>0.05	<0.001	<0.0001

Table 3: Comparison of LAD, hs-CRP, HR, blood pressure between two groups after treatment

Group	n	LAD (mm)	hsCRP (mg/l)	HR(times/min)	SBP(mmHg)	DBP(mmHg)	Number of AF
Control group	60	36.2±4.6	5.2±2.3	71±5	133±6	83±4	44
Test group	60	31.3±4.1	3.1±1.9	72±4	132±5	82±4	22
<i>t</i> (χ^2) value	-	6.13	5.83	1.23	0.99	1.37	6.09
<i>P</i> value	-	<0.05	<0.05	>0.05	>0.05	>0.05	<0.05

Table 4: Relationships of AF recurrence times with LAD, HsCRP, heart rate and blood pressure correlation

		LAD	HsCRP	HR	SBP	DBP	AF times
LAD	Pearson correlation	1	.904**	-.263**	-.011	-.187*	.674**
	Significance (bilateral)		.000	.004	.907	.041	.000
	N	120	120	120	120	120	120
HsCRP	Pearson correlation	.904**	1	-.237**	-.036	-.160	.696**
	Significance (bilateral)	.000		.009	.693	.082	.000
	N	120	120	120	120	120	120
HR	Pearson correlation	-.263**	-.237**	1	-.052	.043	-.043
	Significance (bilateral)	.004	.009		.576	.637	.644
	N	120	120	120	120	120	120
SBP	Pearson correlation	-.011	-.036	-.052	1	.578**	-.251**
	Significance (bilateral)	.907	.693	.576		.000	.006
	N	120	120	120	120	120	120
DBP	Pearson correlation	-.187*	-.160	.043	.578**	1	-.278**
	Significance (bilateral)	.041	.082	.637	.000		.002
	N	120	120	120	120	120	120
AF times	Pearson correlation	.674**	.696**	-.043	-.251**	-.278**	1
	Significance (bilateral)	.000	.000	.644	.006	.002	
	N	120	120	120	120	120	120

** . Significantly correlated on the level 0.01(bilateral); * . Significantly correlated on the level 0.05(bilateral).

regulates and intracellular calcium overload increases in the myocardium through the Ang II type-1 (AT₁) receptor, which contributes to electrical remodeling in AF (Greiser and Schotten, 2011). Ang II also acts on the AT₁ receptor to promote atrial hypertrophy, protein accumulation in the extra cellular matrix and atrial fibrosis and to change the atrial effective refractory period and conduction and result in atrial remodeling, which, together with electrical remodeling, mainly results in persistent AF. hs-CRP is an inflammatory marker, and AF may be caused by the binding of hs-CRP to phosphatidylcholine to inhibit sodium-calcium exchange in myeloma vesicles and induce cellular energy failure and apoptosis, thus damaging the cell membrane and causing arrhythmia (Liu *et al.*, 2011b).

We discovered that both telmisartan and amlodipine besilate were effective for the treatment of hypertension, but that telmisartan was superior to amlodipine besilate for treating AF. In our study, the recurrence rate of AF was lower in the telmisartan group compared with that of the amlodipine besilate group, thus indicating that telmisartan effectively controlled BP and decreased the recurrence rate of AF. Telmisartan, which is a stronger AT₁ receptor blocker, maintains the RAAS balance, suppresses inflammatory mediators, and inhibits atrial remodeling and electrical remodeling, thus exhibiting good efficacy in treating AF. Additionally, telmisartan can decrease LAD. Tenekecioglu *et al.* (2014) demonstrated that hypertensive patients with PAF have larger LADs than patients with hypertension and left atrial enlargement, and an especially increased left atrial pressure increases atrial muscle tone, thus affecting myocardial cell function and inducing atrial remodeling. Telmisartan prevented AF and reduced the recurrence rate of AF.

RAAS is important in the initiation and development of hypertension. An AT₁ antagonist was effective for the treatment of hypertension, while telmisartan suppressed endogenous Ang II. Therefore, we used telmisartan to treat hypertensive patients with PAF. Our follow-up study showed that telmisartan effectively reduced BP, the recurrence rate of AF, LAD and hs-CRP levels, which suggested a new treatment for PAF. Moreover, telmisartan has been shown to be effective and safe.

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