Comparative effects of losartan and nifedipine therapy on exercise capacity, Doppler echocardiographic parameters and endothelin levels in patients with secondary pulmonary hypertension

Sekonder pulmoner hipertansiyonu bulunan hastalarda losartan ve nifedipin tedavisinin egzersiz kapasitesi, Doppler ekokardiyografi parametreleri ve endotelin düzeylerine etki açısından karşılaştırılması

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Abstract

Objective: Pulmonary hypertension (PHT) is associated with high mortality and morbidity. Interest has increased in the use of drugs that, because of their neurohumoral inhibitory effects, inhibit the renin angiotensin system. In this study, we sought to examine whether losartan therapy is non-inferior to nifedipine in the treatment of secondary PHT.

Methods: This prospective randomized study consisted of 63 patients (mean age, 63.7±9.1 years) with PHT who underwent Doppler echocardiographic examination. A baseline 6-minute walk test (6MWT) and cardiopulmonary exercise test (CPET) were performed, and the endothelin-1 level of each patient was measured. Patients were assigned to two groups receiving treatment with nifedipine (n=30) and losartan (n=33). After 2 months of treatment, those measurements were repeated. The groups were compared with regard to effectiveness for the studied parameters using 2*2 factorial ANOVA design for repeated measurements.

Results: When posttreatment values were compared with baseline values in both groups, the following statistically significant changes were noted: the mean values of both mean and systolic pulmonary artery pressures (PAPs) were reduced ($p<0.05$) on Doppler echocardiography; exercise duration, work rate, and end-tidal carbon dioxide pressure ($PETCO_2$) were higher ($p<0.05$ for all); and the minute ventilation (VE) and ventilatory equivalents for carbon dioxide (VE/VCO_2) were lower ($p<0.05$ for both) according to the results of a CPET. No statistically significant change was noted in the mean levels of serum endothelin-1. With regard to the results cited above, no statistically significant difference was detected between the losartan and nifedipine groups ($p > 0.05$).

Conclusion: The findings of this study indicate that losartan is non-inferior to nifedipine for reducing PAP and improving exercise capacity. However, the short-term use of losartan or nifedipine had no statistically significant effect on endothelin-1 levels in patients with secondary PHT.

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Key words: Pulmonary hypertension, cardiopulmonary exercise test, losartan, nifedipine

Özet

Amaç: Pulmoner hipertansiyon (PHT) artmış mortalite ve morbidite ile ilişkilidir. Nörohumoral inhibitor etkileri nedeniyle renin-anjiyotensin sistemini bloke eden ilaçlara ilgide bir artış dikkati çekmektedir. Bu çalışmada losartan tedavisinin nifedipinden daha az etkili bir ajan olup olmadığının araştırılması amaçlanmıştır.

Yöntemler: Bu çalışmaya Doppler ekokardiyografi ile PHT saptanan 63 hasta (ortalama yaş 63.7±9.1) dahil edildi. Bazal durumda 6 dk yürüme testi ve kardiyopulmoner egzersiz testi (KPET) yapıldı, endotelin-1 düzeyleri çalışıldı. Tüm hastalar aldıkları tedaviye göre 2 gruba ayrıldı: nifedipin (n=30) ve losartan (n=33). İki aylık tedaviden sonra bu ölçümler tekrarlandı. Gruplar, tekrarlayan çalışılmış parametrelere olan etkinlik açısından 2*2 faktöryel dizayn ANOVA testi ile karşılaştırıldı.

Bulgular: Tedavi öncesi ile karşılaştırıldığında her iki grupta sistolik ve ortalama pulmoner arter basıncı anlamlı şekilde daha düşük ($p<0.05$); KPET ile saptanan egzersiz süresi, iş gücü, end-tidal karbon dioksid basıncı ($PETCO_2$) daha yüksek ($p<0.05$) ve dakika ventilasyon ve karbondi-

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oksid ventilatuvar eşdeğerı (VE/VCO_2) ise daha düşük ($p<0.05$) idi. Serum endotelin düzeylerinde anlamlı bir fark saptanmadı. Saptanan bu bulgular açısından losartan ve nifedipin tedavileri arasında anlamlı bir fark saptanmadı ($p > 0.05$).
Sonuç: Bulgularımız losartan tedavisinin pulmoner arter basıncını düşürmede ve egzersiz kapasitesini iyileştirmede nifedipinden daha az etkin olmadığını göstermektedir. Ancak her iki ilacın kısa süreli kullanımının PHT'u olan hastalarda endotelin düzeyine anlamlı bir etkisi olmamıştır.
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Anahtar kelimeler: Pulmoner hipertansiyon, kardiyopulmoner egzersiz testi, losartan, nifedipin

Introduction

Despite the major advances in medicine and available therapeutic options, pulmonary hypertension (PHT) is still associated with high mortality and morbidity rates (1). Vasodilating, antiproliferative, and anticoagulating agents are used to treat PHT because pulmonary vasoconstriction, endothelial dysfunction, vascular smooth muscle cell proliferation, and thrombosis have a role in the etiopathogenesis of that disorder.

Since smooth muscle cell proliferation, vasoconstriction play role in the pathogenesis, calcium channel blockers are among the therapeutic options used in the treatment of PHT. Of these agents nifedipine and diltiazem are the most commonly used agents in the studies (2, 3). Depending on the patients' heart rate nifedipine or diltiazem is chosen.

In addition to being effective vasodilators, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) exert neurohumoral inhibitory actions, such as the inhibition of vascular remodeling and smooth muscle cell proliferation and amelioration of endothelial dysfunction. These beneficial effects, which have long led to the use of ACEIs or ARBs in the treatment of heart failure and hypertension, render those agents as appropriate for use in the treatment of PHT. However, data regarding the use of ACEIs or ARBs in the treatment of PHT are limited.

Morrell et al. (4) in a pilot study evaluated the effect of losartan in PHT secondary to chronic obstructive pulmonary disease (COPD). Although no significant change in PAP and exercise capacity was noted, a trend through benefit was observed in patients with high transtricuspid pressure gradient. Based on these findings the authors stressed the importance of further studies on this subject.

Considering these literature data we hypothesized that losartan may favorably affect pulmonary vascular remodeling and might be non-inferior to nifedipine in the treatment of secondary PHT, and therefore in this study, we compared the effects of the ARB losartan with those of the calcium channel blocker nifedipine as measured in the results of an echocardiographic study, a 6-minute walk test (6MWT), a cardiopulmonary exercise test (CPET), and endothelin-1 levels in patients with PHT due to lung disease and/or hypoxia and left heart disease.

Methods

We enrolled in this randomized prospective study 63 patients who, on the basis of Doppler echocardiographic results (a mean pulmonary artery pressure (PAP) of >26mmHg), were diagnosed as having PHT. Exclusion criteria were as follows: acute infectious or inflammatory disease, exacerbation of chronic obstructive pulmonary disease (COPD), malignancy, acute coronary syndrome in the last 4 weeks, uncontrolled arrhythmia and hypertension, decompensated heart failure, acute pulmonary emboli, thrombus in a lower extremity, oxygen saturation below 85% at rest, or failure to cooperate with CPET.

All patients were informed about the study, which had been approved by the Local Ethics Committee, and each subject provided informed consent.

The New York Heart Association (NYHA) functional class was determined for each patient. Detailed history was obtained and physical examination was done in all the patients. Laboratory findings, pulmonary function testing, pulse oxymetry, arterial blood gases analysis, Doppler echocardiography and electrocardiography were used to define patient characteristics. At baseline Doppler echocardiographic study, 6MWT, and CPET were performed, and venous blood samples were drawn for endothelin-1 level measurement.

Doppler echocardiographic examination

Doppler echocardiographic examinations were performed with a HP Sonos 7500 machine (Philips Medical Systems, Andover, MA) by 2 cardiologists who were blinded to the study protocol. The mean PAP was measured with the following formula: mean PAP=80-0.45*PAT (pulmonary acceleration time) (5).

Pulmonary hypertension was classified according to mean PAP: mild (26-35 mm Hg), moderate (36-45 mm Hg), or severe (>45 mm Hg). The right ventricular ejection fraction (EF), diastolic and systolic volumes were measured in an apical 4-chamber view via Simpson's method (6). Patients having PHT due to left heart disease (systolic or diastolic dysfunction, moderate-severe valvular heart disease) and hypoxemic lung disease (COPD, asthma, interstitial lung disease) were enrolled in the study. Left sided valvular heart disease (moderate or severe mitral or aortic valve disease) was considered as the etiology of PHT in the absence of other PHT causes. Left ventricular systolic dysfunction was defined as global or regional wall-motion abnormality on echocardiography or ventriculography, ejection fraction (EF) less than 50%, or fractional shortening less than 25%. Diastolic dysfunction was defined as mitral E/A ratio less than 1 and isovolumetric relaxation time ≥110 msec or mitral E-wave deceleration time ≥240 msec on Doppler echocardiography. Blood samples obtained to determine the endothelin-1 level were centrifuged within 1 hour at 1600 rpm for 15 minutes at 4°C and were stored at -20°C. Endothelin-1 levels were studied via enzyme-linked immunosorbent assay (Biomedica, catalog number BI-20052, Biomedica Gruppe, Vienna, Austria).

Cardiopulmonary exercise test

Cardiopulmonary exercise test was performed via a bicycle ergometer (Ergoline Ergometrics 900 machine, SensorMedics, Yorba Linda, CA, USA) and a Hans Rudolph mouth-breathing face mask (7900 series). The exercise test had a symptom-limited maximum incremental protocol on an upright cycle ergometer. After 3 minutes of rest on the ergometer, each patient began to exercise at an initial work load of zero W at 60 rpm for 3 minutes, which was followed by an incremental increase in the work load of 15 W every minute. The patients were encouraged to exercise until they felt unable to continue. All patients followed the same protocol under standard conditions (room temperature, 20-25°C; humidity, <50%). The maximum heart rates of each patient obtained during peak exercise and oxygen pulse values (the amount of oxygen consumed per heart beat during exercise) were recorded. The anaerobic threshold (AT) was determined by means of the V-slope method (7). Minute ventilation (VE, BTPS), oxygen uptake (VO_2, STPD), carbon dioxide output (VCO_2, STPD), and other exercise variables were computer-calculated breath by breath, interpolated second by second, and averaged over 10-second intervals. Ventilatory efficiency during exercise was expressed as the ratio of ventilation to carbon dioxide output at AT (VE/VCO_2 @AT). The end-tidal carbon dioxide pressure at AT ($PETCO_2$@AT) and VE/VCO_2@AT values were averaged as the AT was reached. The maximum work rate (WR) was accepted as the patients' endurance during exercise for at least 20 to 30 seconds when they were exercising at their peak work load.

Study protocol

The patients were randomized into 2 groups in a 1 to 1 fashion. After randomization 3 patients in the nifedipine group refused to participate in the protocol. Those in group 1 (n=30) began treatment with nifedipine (Adalat Crono, Bayer AG, Leverkusen, Germany) at a daily dose of 30 mg/d, and the patients in group 2 (n=33) received losartan (Cozaar, Merck Sharp & Dohme, Wilmington, DE, USA) 50 mg/d. Then, after checking the blood pressure value of each patient, the dosages of those drugs were increased to their tolerated doses. After an average 8-weeks treatment period, the same procedures were performed, and blood samples were drawn to determine the endothelin-1 level.

Statistical analysis

Statistical analysis was performed with SPSS software (Statistical Package for the Social Sciences, version 10.0, SSPS Inc, Chicago, IL, USA). Continuous variables were expressed as the mean±the standard deviation. In the nifedipine and losartan groups, the unpaired *t* test for independent samples was used to compare continuous variables, and the Chi-square test was used to compare qualitative variables. The paired *t* test was used to compare pretreatment and posttreatment parameters. The groups were compared with regard to effectiveness for the studied parameters using 2*2 factorial ANOVA design for repeated measurements. A p value of <0.05 was considered statistically significant.

Results

The NYHA classification of the patients is presented in Table 1. PHT was mild in 41.9%, moderate in 54.8% and severe in 3.3% of the patients. Patients in both groups were comparable with regard to age, clinical, echocardiographic and laboratory findings (Table 2). Thirty-four (51%) of the patients smoked. The etiology of PHT was identified as lung disease and/or hypoxemia in 23 patients (36.5%) (COPD in 18 and asthma in 5 cases); and left heart disease in the remaining 40 patients (63.5%) [in the form of left ventricular systolic and/or diastolic dysfunction (n=22) (systolic dysfunction in 1 and diastolic dysfunction in 21 cases) and left sided valvular heart disease (n=18) (mitral regurgitation in all)]. The groups were similar with regard to etiology of PHT. In the losartan and nifedipine groups PHT was due to left heart disease in 69.7% and 56.7% of patients and lung disease and/or hypoxia in 30.3% and 43.3%, respectively (p=0.3). The losartan and nifedipine groups were quite similar to each other concerning the other medications that the patients were on in addition to study drugs: inhaler steroid (12.1% vs 30%, p=0.08), inhaler anticholinergic (12.1% vs 26.7%, p=0.1), inhaler beta-agonist (18.2% vs 30%, p=0.2), theophylline (9.1% vs 10.0%, p=0.9), diuretic use (15.2%vs 20%, p=0.6), aspirin (51.5% vs 46.7%, p=0.8), beta-blocker (21.2% vs 33.3%, p=0.3) and statin (24.2% vs 26.7%, p=0.8).

With regard to echocardiographic findings, the prevalence's of left ventricular hypertrophy and diastolic dysfunction did not differ between the nifedipine and losartan groups. Left ventricular systolic dysfunction (ejection fraction <50%) was detected in only 1 patient in the losartan group. The prevalence of mitral valve disease, all of which in the form of mitral regurgitation (grade ≥1/4) was quite similar between both groups (Table 2). No significant aortic valve disease was present in any of the patients in either group. With regard to etiology of the PHT the average difference in mean PAP achieved with treatment were comparable between the nifedipine and losartan groups (p >0.05).

As expected, dyspnea was the most common symptom which was diagnosed in 46 (73%) of the study subjects followed by palpitation, chest pain, fatigue and weakness.

The mean values of the pulmonary function test results and the diffusion capacities were within the normal range in both groups. Neither adverse events nor ischemic electrocardiographic changes occurred during CPET. The performance-limiting symptoms were leg pain in 47.6% of the patients, shortness of breath in 36.5%, fatigue in 14.3%, and palpitation in 1.6%. The mean duration of treatment was 63.5±14.2 days. After that period, the NYHA functional class had improved in 27 (42.9%) of the patients. The improvement in functional class was grade 1 in 25, and grade 2 in 2 patients. When compared with baseline values, the average values of the mean PAP (37.1±4.1 vs 33.2±4.0 mm Hg; p=0.01) had decreased with statistical significance at the end of the treatment period.

Nifedipine was administered in a mean daily dose of 41.0±20.6 (range: 30-120) mg. The Doppler echocardiographic findings, the

results of 6MWT and CPET, and the levels of endothelin-1 in patients who received nifedipine therapy are presented in Table 3. The posttreatment results showed that with respect to echocardiographic findings, the average value of mean PAP and the right atrial diameter had decreased with statistical significance ($p<0.05$ for both). The 6MWT had significantly improved ($p<0.05$). Among the CPET parameters, WR, test duration, and $PETCO_2$@AT had increased, and the VE and VE/VCO_2@AT had decreased with statistical significance as a result of nifedipine treatment ($p<0.05$) (Fig. 1). Serum levels of endothelin-1 had decreased at the end of the treatment period, but that difference did not reach to statistical significance.

Like nifedipine treatment, therapy with losartan at a mean dose of 63.6±22.6 (range: 50-100) mg/d decreased the average value of the mean PAP with statistical significance, according to the results of Doppler echocardiography (Table 3). The increase in the right ventricular ejection fraction after losartan therapy was more pronounced than that resulting from nifedipine

Table 1. Patients' functional classification according to the New York Heart Association classification

NYHA Classification	Study Subjects, n (%)
Class I	20 (31.7)
Class II	27 (42.9)
Class III	14 (22.2)
Class IV	2 (3.2)

NYHA - New York Heart Association

Table 2. Baseline clinical, demographic, and laboratory findings of groups treated with nifedipine or losartan

Patient Characteristics	Nifedipine Group (n=30)	Losartan Group (n=33)	p*
Age, years	64.7±8.5	63.3±9.4	NS
Sex, n	15 F, 15 M	22 F, 11 M	NS
Smoking, %	53.3	54.4	NS
COPD, %	36.6	21.2	NS
Asthma, %	7.9	1.6	NS
Hypertension, %	53.3	60.6	NS
Diabetes mellitus, %	6.6	9.0	NS
Dyslipidemia, %	46.6	51.5	NS
Atrial fibrillation, %	6.7	12.1	NS
LVH, %	66.7	48.5	NS
Diastolic dysfunction, %	36.7	24.2	NS
LVWM abnormality, %	0	3.0	NS
LV ejection fraction, %	55.4±2.0	56.6±3.3	NS
Fractional shortening, %	32.4±2.1	33.1±1.9	NS
Mitral regurgitation, %	53.3	57.6	NS
Fasting blood sugar, mg/dL	96.9±20.1	102.7±19.8	NS
Creatinine, mg/dL	0.9±0.1	0.8±1.7	NS
Phosphorus, mg/dL	3.2±0.5	3.4±0.6	NS
ALT, U/L	17.1±4.7	20.8±10.2	NS
ESR, mm	20.8±13.4	15.9±12.1	NS
CRP, mg/L	4.8±3.8	3.7±3.3	NS
Hemoglobin, g/dL	14.0±1.4	13.4±1.2	NS
Leucocyte, K/mm^3	6.6±2.0	6.5±1.2	NS
Thrombocyte, K/mm^3	249±64	247±51	NS
Total cholesterol, mg/dL	215±44.7	212±44	NS
Triglycerides, mg/dL	134±55	126±72	NS

Data are presented as mean±SD and group percentages
*Unpaired t test for independent samples, Chi-square test
ALT - alanine aminotransferase, COPD - chronic obstructive pulmonary disease, CRP - C-reactive protein, ESR - erythrocyte sedimentation rate, F - female, LV - left ventricle, LVH - left ventricular hypertrophy, LVWM - left ventricular wall motion, M - male, NS - nonsignificant

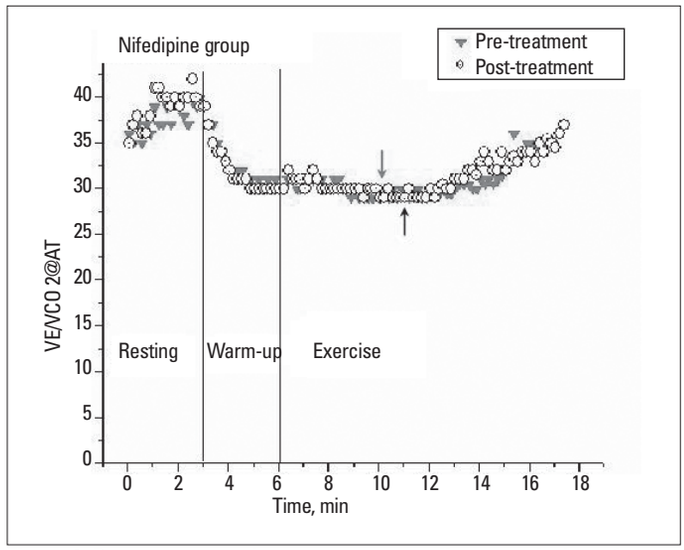

Figure 1. Pre-treatment and post-treatment ventilatory equivalents for carbon dioxide at the anaerobic threshold of cardiopulmonary exercise test parameters in groups treated with nifedipine (pre-treatment grey arrow, post-treatment black arrow)

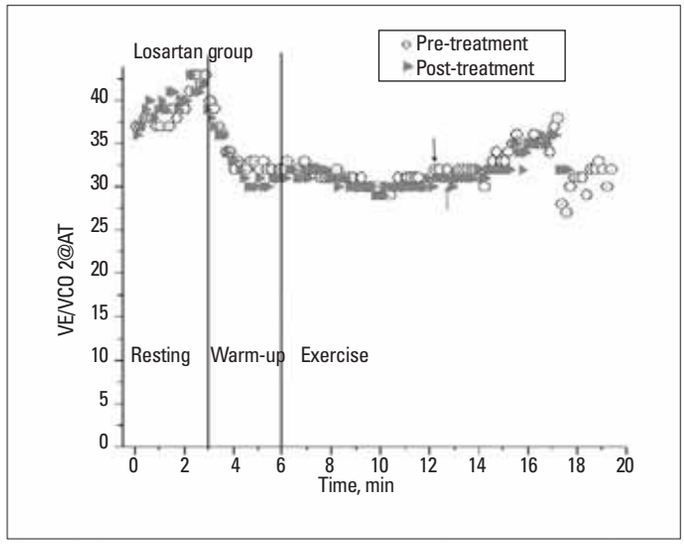

Figure 2. Pre-treatment and post-treatment ventilatory equivalents for carbon dioxide at the anaerobic threshold of cardiopulmonary exercise test parameters in groups treated with losartan (pre-treatment black arrow, post-treatment grey arrow)

Table 3. Comparison of effectiveness of nifedipine and losartan in patients with pulmonary hypertension

Variables	Nifedipine			Losartan			F	p[c]
	Pretreatment Value	Posttreatment Value	p[a]	Pretreatment Value	Posttreatment Value	p[b]		
Doppler echocardiography								
RV diameter, cm	3.4±0.3	3.2±0.3	NS	3.2±0.4	3.3±0.3	NS	0.158	0.693
RA diameter, cm	4.0±0.3	3.7±0.4	0.04	3.9±0.3	3.7±0.3	NS	1.456	0.234
PAP, mean, mm Hg	37.1±3.9	32.2±4.1	0.001	37.1±4.3	34.3±3.7	0.01	1.5	0.2
RV EF, %	53.6±5.5	56.7±7.2	NS	53.9±6.8	57.2±6.1	0.051	0.071	0.791
RV end-diastolic volume, mL	50.4±16.0	44.5±16.5	NS	49.5±19.1	43.3±12.1	NS	0.083	0.774
RV end-systolic volume, mL	23.4±8.7	19.8±6.9	NS	22.4±9.7	19.0±6.4	NS	0.220	0.641
RV stroke volume, mL	27.7±9.0	27.0±8.4	NS	26.9±8.7	26.8±8.1	NS	0.486	0.489
RV wall thickness, cm	0.63±0.14	0.64±0.20	NS	0.63±0.16	0.64±0.18	NS	2.018	0.162
6MWT								
Distance on 6MWT, m	419.2±88.5	435.7±64.3	<0.05	416.0±57.9	445.8±71.0	<0.05	4.788	0.053
CPET								
VO_2, L/min	1.5±0.3	1.5±0.4	NS	1.7±0.4	1.7±0.3	NS	3.298	0.075
VE, L/min	31.3±6.9	28.1±6.4	<0.05	31.9±6.0	28.5±5.1	<0.05	7.300	0.09
VE/VCO_2@AT	31.6±3.5	30.2±3.7	<0.05	31.5±3.8	30.4±4.2	<0.05	0.009	0.926
$PETCO_2$@AT, kPa	5.0±0.5	5.1±0.4	<0.05	4.9±0.4	5.0±0.5	<0.05	0.086	0.819
Heart rate, bpm	138.1±19.2	128.1±21.0	0.009	140.2±21.0	138.0±27.9	NS	0.698	0.407
Oxygen pulse, mL/beat	11.1±2.6	11.7±2.9	NS	12.4±3.5	15.5±17.1	NS	1.944	0.170
WR, W	70.6±30.5	79.2±28.1	0.01	91.2±25.5	98.8±24.8	0.03	9.025	0.054
VO_2/WR, mL/min/W	14.1±10.1	10.6±2.2	NS	13.0±11.6	10.9±2.1	NS	0.045	0.832
$ATVO_2$, L/min	1.2±0.3	1.1±0.3	NS	1.3±0.3	1.2±0.4	NS	1.060	0.308
AT VO_2 , mL/kg/min	20.1±21.6	15.0±3.9	NS	17.3±3.7	16.0±5.0	NS	1.522	0.223
Test duration, min	4.3±2.0	5.0±1.7	0.006	5.8±1.6	6.2±1.5	0.03	7.752	0.058
Endothelin-1, fmol/mL								
Serum endothelin-1, fmol/mL	1.06±2.46	0.87±2.3	NS	0.82±1.61	0.65±1.34	NS	0.162	0.689

Data are presented as mean±SD.
The factorial 2*2 design ANOVA test was used to elucidate intragroup and intergroup differences:
[a]-p value for nifedipine therapy for pre and posttreatment difference
[b]-p value for losartan therapy for pre and posttreatment difference
[c]-p value for intergoup difference between nifedipine and losartan therapies
AT - anaerobic threshold, CPET - cardiopulmonary exercise test, EF - ejection fraction, NS - nonsignificant, PAP - pulmonary artery pressure, $PETCO_2$ - end-tidal carbon dioxide pressure, RA - right atrium, RV - right ventricle, VE - minute ventilation, VE/VCO_2 - ventilatory equivalents for carbon dioxide, VO_2 - oxygen uptake, WR - work rate, 6MWT - 6-minute walk test

treatment, but the difference did not reach statistical significance (p=0.7). The 6MWT results had significantly improved (p<0.05). Of the CPET parameters, the test duration, WR, and $PETCO_2$@AT had increased and the VE and the VE/VCO_2@AT had decreased with statistical significance (p<0.05 for all) (Fig. 2). The posttreatment levels of endothelin-1 were lower than pretreatment values, but as in nifedipine group, that change was not statistically significant.

When the nifedipine and losartan groups were compared, no difference in treatment efficacy was noted. A reduction in PAP and an improvement in right ventricular ejection fraction were shown by Doppler and 2-D echocardiography, respectively. The improvement in the 6-minute walk distance; the increase in WR, the duration of exercise, the $PETCO_2$@AT, and the oxygen pulse on CPET; and the decrease in VE, VE/VCO_2@AT, and serum levels of endothelin-1 were similar in both groups (p >0.05).

Discussion

Our study demonstrates that in patients with mild-to-moderate PHT, the ARB losartan is non-inferior to nifedipine in reducing the PAP and improving exercise capacity. We also demonstrated that the decrease in PAP measured by Doppler echocardiography is clinically relevant, because patients' exercise capacity during CPET had improved at the end of the treatment period. To our knowledge, this is the first study that has compared the effects on PAP

reduction of an ARB with those of a calcium channel blocker for use in patients with PHT. Our goal was to determine the response of pulmonary functional, vascular endothelial, and neurohumoral parameters to losartan or nifedipine therapy.

Because most patients with PHT present to our clinics with a complaint of dyspnea, the early diagnosis of this condition should be a primary consideration, and appropriate therapy must be initiated without delay. Currently available medications are not effective in inhibiting the progression of PHT, and the mortality in patients with that disorder is still very high. For that reason, endothelin antagonists, phosphodiesterase enzyme inhibitors, and drugs that inhibit the renin-angiotensin system are used to treat PHT (8).

When one considers the effects of increased angiotensin-converting enzyme concentration in lung tissue, it becomes obvious that angiotensin II has a vital role in the development of PHT in the presence of chronic hypoxia (9). The results of pathologic examination have revealed medial hypertrophy, neointimal proliferation, and adventitial thickening in addition to vasoconstriction in the pulmonary tree of patients with PHT; these important findings demonstrate the neurohumoral and vascular remodeling processes in the clinical course of that disease (10). By developing treatment strategies that inhibit those processes, it would be possible to stop or even reverse the progression of PHT, which is an attractive therapeutic goal. We measured the serum levels of endothelin-1 in our patients, but if we had obtained pathologic specimens from their pulmonary vasculature, we could have identified changes related to vascular remodeling.

Nong and colleagues (11) demonstrated that quinapril increased the tolerance to hypoxia in patients with PHT. In that study, the reduction of PAP and the neurohumoral inhibitory effects of quinapril had an important role in this effect. Zakheim et al. (12) reported that in rats, long-term ACEI treatment prevented right ventricular hypertrophy, PHT development, and vascular remodeling. In a study, the effects of amlodipine alone and amlodipine plus perindopril in combination were compared in hypoxia-induced PHT in rats (13). Medial thickening, which decreased after treatment with amlodipine, was completely prevented by combination therapy. Pulmonary vascular resistance decreased in both treatment arms, but right ventricular hypertrophy was prevented only in the group that received the combination therapy. That study shows that in addition to vasodilation, the neurohumoral inhibition provided by treatment with an ACEI has therapeutic benefits (13).

Morrell et al. (4) compared losartan with placebo in a pilot study in patients with PHT secondary to COPD. Although there was no clear improvement in exercise capacity a clinically significant reduction in transtricuspid gradient was observed in more patients in the losartan group (50%) than in the placebo group (22%). Further analysis showed that reduction in these effects were more marked in patients with higher baseline transtricuspid gradient. This finding implies that losartan might be more effective in reducing PAP in patients with significant PHT.

Our results support those reported in the literature; i.e., that approximately 2 months of losartan or nifedipine therapy decreases Doppler echocardiographically measured PAP and improves exercise capacity determined by 6MWT and CPET.

The CPET is a noninvasive and objective test used to evaluate the response to treatment and to determine course of that disease. Of all the CPET findings, an increase in VE/VCO_2 is one of the most useful parameters that indicates ventilation-perfusion mismatch. The slope of VE/VCO_2 or the VE/VCO_2 ratio measured at the anaerobic threshold is elevated in patients with PAH and reflects impaired pulmonary circulation (increased dead space ventilation resulting from decreased pulmonary capillary blood flow caused by elevated PAP) that is the hallmark of PAH (14, 15). Raeside et al. (16) showed that among the CPET parameters, PAP measurements were correlated with VE/VO_2 and VE/VCO_2. We believe that by determining VE and VE/VCO_2@AT in patients with PHT, we can noninvasively evaluate the response to treatment. In our study, the mean values of VE and VE/VCO_2@AT had decreased and $PETCO_2$@AT had increased at the end of the treatment period in both groups. We found that after a period of losartan and nifedipine therapy, ventilation-perfusion mismatch could be corrected, a result that can be detected by a decrease in VE and VE/VCO_2@AT, an increase in $PETCO_2$@AT and WR, and prolongation of the duration of exercise. Other parameters of CPET (eg, levels of VO_2 or oxygen pulse) did not change with statistical significance, perhaps primarily because of the brief duration of therapy. If we had prolonged the treatment period, we might have detected statistically significant changes. The improvement in the WR and the duration of exercise in our study subjects was thought to have resulted from the correction of ventilation-perfusion mismatch, an effect independent of the right ventricular ejection fraction. Although we detected an improvement in the parameters of the ventilation-perfusion mismatch, we did not note an improvement in VO_2, perhaps because our patients exhibited comorbid conditions such as COPD and diabetes mellitus (17, 18).

Endothelin-1 is a potent vasoconstrictor and a stimulant for smooth muscle cell proliferation. It has been shown that this peptide has an important role in the development of PHT and that levels of endothelin-1 correlate well with severity of PHT and the prognosis of patients with that disorder (19, 20). In our study, we found that after treatment with either nifedipine or losartan, the serum levels of endothelin-1 were lower than pretreatment serum levels, although that difference was not statistically significant. We believe that, our patients' endothelin-1 levels would decrease if we could have "prolonged" the duration of treatment.

Study limitations

We used Doppler echocardiography to measure PAP, but right-sided heart pressure could have been determined more accurately by an invasive method. The duration of treatment in was relatively brief, if we could have prolonged the treatment duration, performed cardiac catheterization, and obtained

additional measurements such as a calculation of the cardiac output or the degree of pulmonary and systemic vascular resistance, data on the efficacy of the treatments in both groups would be more valuable, and we could have obtained more detailed results about the above-mentioned neurohumoral inhibitory effects of losartan. The decrease in PAP with losartan use in patients with left heart disease might have also been resulted partly of it's beneficial hemodynamic effects on left heart disease in these patients. Another major limitation of our study was the lack of a control group, the presence of which could have been used to exclude the placebo effect.

Conclusion

The findings of this study indicate that losartan therapy is non-inferior to nifedipine at reducing Doppler echocardiographically measured PAP and improving exercise capacity in patients with secondary PHT. Both of these agents seemed to have no effect on endothelin levels. Further trials with increased patient numbers are needed to better clarify this issue.

Clinical Implications

New approaches and new pharmacotherapeutic options are needed for the treatment of patients with PHT. In the early stages of that disorder the results of CPET and 6MWT can provide useful information to clinicians that can also be used to evaluate the response to therapy. Drugs that inhibit unwanted neurohumoral processes such as medial hypertrophy, neointimal proliferation, and adventitial thickening might be included in the treatment regimen of those patients.

Conflict of interest: None declared

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