The Comparison of The Efficacy and The Confidence of The Vasodilator Therapy With Felodipine And Lisinopril in Chronic, Moderate to Severe Aortic Regurgitation

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SUMMARY

Purpose: Afterload reduction decreases volume overload on the left ventricle in chronic asymptomatic aortic regurgitation (AR). In this prospective, randomized trial, we aimed to compare the effects of a 6-months long treatment with lisinopril versus felodipine on left ventricular function and hemodynamic parameters.

Methods: 41 asymptomatic patients with moderate to severe chronic, isolated AR were randomly assigned to treatment with either lisinopril (20 mg) or felodipin (10 mg). Echocardiographic ([ESV], [EDV], [EF], [FSV], [LVSV], [RV], [RF], [FCO], [LVCO], [SW], [CW], [LVWS]) and hemodynamic parameters [SBP], [DBP], [SVR]) at baseline and at 6 months were compared.

Results: At 6 months, with lisinopril, SBP 8,9 %, DBP 5,9 %, SVR 16,7 %, RV 8,4 %, RF 11 %, SW 6 %, CW 7.2 % decreased and FSV 11,2 %, LVSV 3 % increased ($p<0.05$). With felodipine, SBP 11,3 %, DKB 9,4 %, SVR 17,3 %, RF 9,7 %, SW 10,8 %, CW 8,9 % decreased and FSV 5,6 % increased ($p < 0.05$). At the end of 6 months, the increase in FSV was significantly greater in the lisinopril group ($p < 0.05$) and the increase in heart rate was significantly greater in the felodipin group ($p < 0.05$).

Conclusion: In chronic asymptomatic AR, a 6-months long treatment with either lisinopril or felodipin is associated with similar effects as assessed by echocardiography. The only difference in between the two drugs is a more profound increase in FSV with lisinopril and a more profound increase in HR with felodipin. Whether this difference makes any clinical sense needs confirmation with a larger population and a longer follow-up.

Key words: Chronic aortic regurgitationi, felodipine, lisinopril, echocardiography

Kronik, Orta-Ciddi Aort Yetmezliginde Felodipin Ve Lisinopril Vazodilatör Tedavisinin Etkinliginin Ve Güvenilirliginin Karsilastirilmasi

ÖZET

Amaç: Aort Yetmezligi varliginda ciddi hacim yüküne karsi çalismak zorunda olan sol ventrikül (LV) kompansatuar mekanizmalar ile pompa fonksiyonunu uzun süre normal düzeylerde tutabilir. Fakat ileri dönemlerde ventrikül fonksiyonlarindaki bozulma beklenen sonuçtur. Ciddi AY'nde vazodilatör tedavinin uygulanma nedeni de LV dilatasyonu ve operasyon gerekliligini mümkün oldugunca geciktirebilmektir. Bu çalisma ciddi, izole, asemptomatik, kronik AY olan olgularda farkli iki ajan ile saglanan vazodilatör tedavinin etkinligini karsilastirmak üzere yapilmistir.

Gereç ve Yöntem: Kronik, asemptomatik ve transtorasik ekokardiyografi ile en az 2. AY olan yas ort. 48,4±17 olan 21 erkek (%51) , 20 kadin (%49) toplam 41 olgu çalismaya alindi.Transtorasik ekokardiyografi ile EDV (Diastol sonu volüm), ESV(Sistol sonu volüm), EF, FSV (Ileriye dogru atim volümü), LVSV (Sol ventrikülün toplam atim volümü), RV (Geriye kaçan volüm), RF (Geriye kaçan volüm fraksiyonu), FCO (Ileriye dogru kardiyak output), LVCO (Sol ventrikül toplam kardiyak outputu), SW (Sistolik is yükü) , CW (Kardiyak yük), LVWS(Sol ventrikül duvar stresi) parametreleri ve noninvaziv olarak SKB (sistolik kan basinci), DKB (diastolik kan basinci), SVR (Sistemik vasküler rezistans)ölçümleri yapilarak hastalar felodipin veya lisinopril tedavi grubuna alindi. Maksimum 10 mg felodipin veya 20 mg lisinopril olacak sekilde toplam 6 ay uygulanan vazodilatör tedavi sonrasi ekokardiyografi tekrarlandi. 6 aylik tedavi periyodu boyunca ortaya çikan major klinik olaylar (ölüm, AVR gereksinimi, semptom gelisimi) ve ilaç yan etkileri kaydedildi.

Bulgular: Toplam 36 olgu çalismayi tamamladi. Felodipin grubunda 2 olgu ilaç yan etkisi nedeniyle, 2 olgu yeni baslayan atrial fibrilasyon sebebiyle çalisma disi birakildi. Her iki ilaç grubunda da major klinik olay gözlenmedi. Çalismanin sonunda lisinopril grubunda SKB'da %8.9 , DKB'da %5.9 , SVR'da %16.7 azalma, FSV'de %11.2, LVSV'de % 3 artma, RV'de %8.4 , RF'da %11, SW'de %6 ve CW'de %7.2 azalma saptandi ($p < 0.05$).Felodipin grubunda SKB'da %11.3, DKB'da %9.4 , SVR'da %17.3 azalma, FSV'de %5.6 artma, RF'da %9.7, SW'de %10.8 ve CW'de %8.9 azalma saptandi ($p<0.05$). Iki ilaç grubu olusturduklari degisimlerin büyüklügü açisindan karsilastirildiginda ise lisinopril grubunda FSV artisi, felodipin grubunda ise kalp hizi artisi anlamli olarak fazla bulunmakla beraber kalbin is yükü her iki grupta da degisim göstermedigi için , bahsedilen bulgular klinik olarak anlamli kabul edilmedi.

Sonuç: Kronik asemptomatik AY de hem felodipin hem de lisinopril faydali etkilere sebep oldu. Birbirlerine istatistiksel anlamda klinik olarak üstünlükleri saptanmadi.

Anahtar Sözcükler: kronik aort yetmezligi, felodipin, lisinopril, ekokardiyografi

INTRODUCTION

Chronic AR leads to left ventricular volume overload and eccentric hypertrophy (1-2). Slowing down the left ventricle decompensation process by decreasing the volume overload in the left ventricle is aimed with vasodilator treatment by decreasing the afterload and the diastolic regurgitant flow from the aorta to the left ventricle. In heart failure, vasodilators delay left ventricular decompansation by decreasing the afterload and increasing the stroke volume (2-3). In mitral and aortic regurgitation, forward cardiac output is increased when the regurgitant volume is decreased by afterload reduction with vasodilator treatment (4-5). Such an effect has been reported with drugs such as captopril, felodipine, nifedipine, hydralazine, and enalapril. (6-11).

The Renin–angiotensin–aldosterone system (RAAS) plays a major role in the physiopathology of heart failure, particularly in late phases when left ventricular dilatation occurs as a result of the remodelling process. For this reason it is considered that blockade of this system by angiotensin-converting enzyme inhibitors (ACE-I) and thus retardation of left ventricular dilatation can be particularly beneficial in patients with severe AR. Calcium channel blockers have already been shown to provide beneficial hemodynamic effects and delay left ventricular dilatation in chronic AR.

In this study we aimed to compare the effects of a six-month long vasodilator treatment with two different agents (a calcium channel blocker felodipine and an ACE-I lisinopril) on left ventricular morphology and functions in patients with asymptomatic, chronic, moderate-severe AR.

METHODS

The study included 41 cases with moderate-severe chronic AR on a color Doppler echocardiogram. Symptom presence, atrial fibrillation, acute (within the preceeding 6 months) or rapidly progressive AR**,** history of coronary artery disease, concomittant valve disease (moderate-severe mitral stenosis and mitral insufficiency, aortic stenosis with a mean systolic gradient over 25 mmHg), congenital heart disease, history of positive inotropic drug use, insufficient echocardiographic image quality, ejection fraction < 50 %, comorbidities (serious anemia, serum creatinine > 2.5 mg / dL, chronic liver disease) were the exclusion criteria.

Initial evaluation included history, physical examination, 12 lead electrocardiography (ECG), chest radiography and transthoracic echocardiography. Eligible patients then were randomly assigned to either felodipine or lisinopril treatment. Both drugs were started at low doses (2,5 mg / day for both) and titrated to target doses (10 mg /day for felodipine, 20 mg / day for lisinopril) at 3 days intervals when tolerated. Patients were kept on the maximum tolerated dose of the initially assigned treatment for 6 months and blood pressure levels, side effects of the drugs and major clinical events (death, AVR requirement, and symptom occurrence) were checked monthly. The echocardiographic examination was repeated at the end of the 6th month.

Echocardiographic evaluation:

The echocardiographic examination was carried out with Vingmed System Five (GE Vingmed Sound; Horten, Norway) echocardiography device and 1,5 – 3,6 MHz ultrasound probe with the patient on left lateral decubitus position after at least a 10-minute long rest. Blood pressure and heart rate were recorded. Parasternal long and short axis, apical 4- and 5-chamber views were obtained. The peak of the R wave on a simultaneously recorded surface ECG was used to mark end-diastole. On the parasternal long axis view, AR severity was quantified by the proportion of the width of the diastolic regurgitant jet to the left ventricular outflow diameter. The AR was classified as mild, moderate and severe with diastolic regurgitant jet width to left ventricular outflow tract diameter ratios of less than 25 %, 26-64 % and 65 % or above, respectively (guideline). The left ventricular outflow diameter was measured on the parasternal long axis and the mitral annulus diameter on the apical 4-chamber views. Transaortic and transmitral flow were recorded on the apical 4- and 5-chamber views by Doppler echocardiography and systolic and diastolic velocity time integrals were measured using the software supplied by the echocardiography

equipment and the following parameters were calculated (12):

Left ventricular End Diastolic Volume (EDV) : Left ventricular End Systolic Volume (ESV): Ejection Fraction (EF) : (enddiastolic volume – endsystolic volume) / enddiastolic volume

Forward Stroke Volume (FSV): (mitral flow volume): (mitral diastolic velocity integral x 3.14 x (mitral annulus diameter)^2 / 4

Total Stroke Volume (LVSV): (aortic flow volume) (aortic systolic velocity integral x 3.14 x (left ventricular outflow diameter)^2 / 4

Aortic Regurgitant Volume (RV): Total stroke volume – forward stroke volume

Regurgitant Fraction (RF): Aortic regurgitant volume / Total stroke volume

Forward Cardiac Output (FCO): Forward stroke volume x heart rate (stroke / minute)

Total Cardiac Output (LVCO): Total stroke volume x heart rate

Systemic Vascular Resistance (SVR): (Mean arterial pressure / forward cardiac output) x 80

Stroke Work (SW): Systolic arterial pressure x Total stroke volume x 0.0136

Cardiac Work (CW): Systolic Stroke Work x Heart rate

Left Ventricular Median Wall Stress (LVMWS): 0.334 x Systolic arterial pressure x (end systole left ventricle diameter/systolic posterior wall thickness) / (1 + systolic posterior wall thickness/end systole left ventricle diameter)

Statistical analysis:

A commercially available software (SPSS 11.0 for Windows) was used for the statistical analysis. Variables were figured as mean ± standard deviation. For each drug group paired-samples T test was used as a variable dependent sampling for the initial and final values, and independent samples T test was used to compare the two groups. The parameters which could not be categorized were studied with the Mann-Whitney U test. A p value of less than 0.05 was considered statistically significant.

RESULTS

Of the 41 patients, 20 (48.7 %) were randomized to felodipine and 21 (51.3 %) to lisinopril. The 6-month follow-up was completed in all cases except one in the felodipine group. In the felodipine group, where the target dose of 10 mg/day was attained in 2 patients (13.3%), the average daily dose was 5.7 ± 1.8 mg and in the lisinopril group where the target dose of 20 mg/day was attained in 9 patients (42%), the average daily dose was 14.3 ± 5.1 mg.

The demographical characteristics of the patients in the 2 groups were similar (Table 1). Fourteen patients (38.8%) had systemic hypertension and the frequency of hypertension was not different between the two groups. Rheumatic disease, degenerative disease and aortic root dilatation was present in 18 (50 %), 10 (27.7 %) and 8 (21.3 %) patients, respectively and there was no significant difference between the two groups with regard to the distribution of the etiology of AR. The AR was graded echocardiographically as mild-moderate in 23 (60.5%), moderate-severe in 13 (39.5%).

There was no significant difference between the two groups with respect to the presence of cardiomegaly on chest X-Ray and the severity of AR, aortic root diameter and left ventricular hypertrophy on echo. Likewise, the baseline hemodynamic and echocardiographic measurements were similar (Table 2).

None of the 40 patients developed symptoms or died or required AVR during follow-up. Felodipine had to be discontinued due to side effects in 4 patients. On the other hand, in the lisinopril group no side effects were observed, and all patients randomized to lisinopril completed the 6 months treatment. Therefore, echocardiographic examination at the 6-month was available in 15 patients from the felodipine group and 21 from the lisinopril group. The hemodynamic variables before and after treatment are given in Table 3-4. Although not statistically significant, the heart rate tended to increase with felodipine and decrease with lisinopril treatment. The heart rate attained at 6 months with felodipine was significantly greater than that in the lisinopril group (72.5 ± 6.4 vs 77.20 ± 3.90).

Table 1. Clinical Characteristics of the Patients

	Felodipin	**Lisinopril**	**p**

	(n: 20)	(n: 21)	
Age (year)	52.5 ± 17.1	44.7 ± 16.4	NS
Duration of AR (year)	2.8 ± 2.5	2.8 ± 2.5	NS
Male / Female	10 / 10 (50%) / (50%)	10 / 11 (48%) / (52%)	NS
LVH	13 (65%)	11 (52.4%)	NS
Cardiomegaly	11 (55%)	8 (38,1%)	NS
HT	8 (40%)	8 (38,1%)	NS
DM	0	0	NS
Smoking	8 (40%)	6 (28,6%)	NS
Etiology of AR			
1.Rheumatismal	8 (40%)	11 (52.4%)	NS
2.Degenerative	9 (45%)	5 (23.8%)	NS
3.Aortic root dilatation	3 (15%)	5 (23.8%)	NS

(NS: not significant, p> 0.05)

Table 2. Baseline Hemodynamic and Echocardiographic Parameters of the Patients

	Felodipin (n: 20)	Lisinopril (n: 21)	p
Aortic diameter	3.3±0.5	3.4±0.5	NS
Grade of AR			
2.	11(%55)	15(%71.4)	NS
3.	9(%45)	5(%23.8)	NS
4.	0	1(%4.8)	NS
EDV (ml)	137.9±26.2	141.9±26.4	NS
ESV (ml)	49.1±16.2	49.1±13.5	NS
EF	64.7±6.4	65.3±4.4	NS
HR	75.8±5.8	73.3±6.4	NS
SBP (mmHg)	136±19.1	140.9±16.4	NS
SVR	1408±216.5	1528±321.8	NS
FSV (ml)	81.2±8.9	79.8±10.6	NS
LVSV (ml)	138.3±17.6	136.6±12.3	NS
RF	40.5±5.8	40.6±8.3	NS
RV (ml)	57±12.8	56.5±13.8	NS
FCO	50.1±24	55.9±14.5	NS
LVCO	93.9±32.6	96.2±23	NS
SW	258.6±60.9	261.6±39.9	NS
CW	19712±5138	19224±3553	NS
LVWS	67.6±20.1	74.2±15.9	NS

(Endsystolic volume [ESV], enddiastolic volume [EDV], ejection fraction [EF], forward stroke volume [FSV], left ventricular stroke volume [LVSV], regurgitant volume [RV], regurgitant fraction [RF], forward cardiac output [FCO], left ventricular cardiac output [LVCO], stroke work [SW], cardiac work [CW], left ventricular wall stress, [LVWS]) and hemodynamic parameters (systolic blood pressure [SBP], diastolic blood pressure [DBP] and systemic vascular resistance [SVR])

When the magnitude of change of heart rate at the end of 6 months was compared, a significant difference was detected between the 2 groups ($p < 0.05$) (Table V). In the felodipine group a 11.3 % decrease in the systolic and a 9.4 % decrease in the diastolic blood pressure were found at 6-month follow-up ($p < 0.05$). The corresponding numbers for the lisinopril group were 8.9 % and 5.9 % ($p < 0.05$). Systemic vascular resistance was decreased by 17.3 % in the felodipine group and 16.7 % in the lisinopril group ($p < 0.05$ for both). The initial and final echocardiographic variables are given in Tables 3 and 4.

Table 3. The Comparison of the echocardiographic parameters of the patients in Lisinopril group

	Initial	6. Month	p
EDV	141.9 ± 26.4	142.4 ± 33.5	NS
ESV	49.1 ± 13.5	48.6 ± 19.2	NS
EF	65.3 ± 4.4	66.3 ± 5.8	NS
HR	73.3 ± 6.4	72.5 ± 6.4	NS
SBP	140.9 ± 16.4	128.3 ± 12.5	<0.05
SVR	1528 ± 321.8	1271.8 ± 204.7	<0.05
FSV	79.8 ± 10.6	88.7 ± 8.6	<0.05
LVSV	136.6 ± 12.3	140.9 ± 12.3	<0.05
RV	56.5 ± 13.8	51.7 ± 13	<0.05
RF	40.6 ± 8.3	36 ± 6.9	<0.05
FCO	55.8 ± 14.5	58.8 ± 19.4	NS
LVCO	96.2 ± 23	93.6 ± 30.3	NS
SW	261.6 ± 40	245.8 ± 34	<0.05
CW	19224 ± 3553	17829.4 ± 2936.7	<0.05
LVWS	74.2 ± 15.9	73.9 ± 15.6	NS

Table 4. The Comparison of the echocardiographic parameters of the patients in Felodipine group

	Initial	6. month	p
EDV	137.80 ± 28.99	143.47 ± 30.10	NS
ESV	47.93 ± 17.62	49.87 ± 18.99	NS
EF	65.67 ± 6.92	65.27 ± 7.64	NS
HR	75.27 ± 6.55	77.20 ± 3.90	NS
SBP	132.67 ± 19.54	117.67 ± 16.35	<0.05
SVR	1370.1 ± 223.87	1132.60 ± 138.26	<0.05
FSV	81.93 ± 9.62	86.53 ± 9.01	<0.05
LVSV	139.33 ± 18.92	140.27 ± 20.40	NS
RV	57.40 ± 12.61	53.73 ± 16.05	NS
RF	40.67 ± 5.52	36.87 ± 6.64	<0.05
FCO	54.20 ± 21.55	59.53 ± 23.23	NS
LVCO	98.00 ± 30.32	85.66 ± 40.83	NS
SW	254.73 ± 66.49	227.20 ± 61.02	<0.05
CW	19262 ± 5566	17532.93 ± 4725.7	<0.05
LVWS	66.47 ± 22.38	59.47 ± 19.57	NS

The EDV, ESV and EF did not show any statistically significant differences in either group at the end of the 6-month follow-up. The FSV was increased by 5.6 % in the felodipine group ($p < 0.05$) and 11.2 % in the lisinopril group ($p < 0.05$ for both). The LVSV was not changed in the felodipine group but increased by 3 % in the lisinopril group ($p < 0.05$). The RV was not changed in the felodipine group but decreased by 8.4 % in the lisinopril group ($p < 0.05$). The RF decreased by 9.3 % in the felodipine group and 11 % in the lisinopril group ($p < 0.05$ for both). The FCO and LVCO were not changed significantly at 6 months in either group. The SW decreased by 10.8 % in the felodipine group and 6 % in the lisinopril group ($p < 0.05$ for both comparisons). The CW decreased by 8.9 % in the felodipine group and 7.2 % in the lisinopril group ($p < 0.05$ for both groups). The LVWS did not change significantly in either group. When the magnitude of changes brought out by the two drugs were compared, felodipine was found to increase the heart rate more than lisinopril ($p < 0.05$) and lisinopril was found to increase the FSV more than did lisinopril ($p < 0.05$) at the end of a 6-month long treatment (Table 5). The

2 drugs had similar effects on the rest of the parameters studied.

Table 5. The Comparison of the Change of the Echocardiographic Parameters between the groups

	Felodipin	Lisinopril	p
EDV	-5.6 ± 12.1	-0.4 ± 17.5	NS
ESV	-1.9 ± 8	0.5 ± 10.9	NS
EF	-0.4 ± 6.4	-0.9 ± 3.2	NS
HR	-1.9 ± 4.9	0.8 ± 3.2	<0.05
SBP	15 ± 9.6	12.6 ± 7.5	NS
SVR	237.5 ± 186.5	256.2 ± 214	NS
FSV	-4.6 ± 5.3	-8.9 ± 6.6	<0.05
LVSV	-0.9 ± 9.2	-4.3 ± 5	NS
RV	3.7 ± 11.4	4.8 ± 7.5	NS
RF	3.8 ± 6.1	4.5 ± 5	NS
FCO	-5.3 ± 32.3	-2.9 ± 22.9	NS
LVCO	12.3 ± 55.8	2.6 ± 33	NS
SW	27.5 ± 27.5	15.8 ± 17	NS
CW	1729.7 ± 2334	1394.8 ± 1649	NS
LVWS	7. ± 12.8	0.3 ± 11.6	NS

DISCUSSION

In patients with asymptomatic moderate-severe AR and normal left ventricular functions, AVR can be postponed by decreasing the afterload. Various vasodilators have been tried in chronic asymptomatic AR and although some detected differences, the overall hemodynamic effects have been positive (6-11).

This study was designed to compare the effects of vasodilator treatment with felodipine and lisinopril in patients with chronic, moderate-severe and asymptomatic AR. Felodipine is a calcium channel blocker with pronounced arteriolar dilatation effects. The negative inotropic effect of felodipine is less important but in comparison to nifedipine it is more evident. It has negligible effects on heart rate. Like other calcium channel blockers, felodipine decreases the left ventricular afterload by peripheral vasodilatation and increased calcium intake of the hypertrophied myocardium (10).

Lisinopril inhibits the synthesis of angiotensin II which is a potent vasoconstrictor agent. Angiotensin II triggers protein synthesis and cell growth and causes myocardial hypertrophy. Moreover it creates endothelial dysfunction and enhances cytokine production. The RAAS has been shown to be activated in patients with AR (13). Therefore the blockade of this system on top of vasodilatation might have additive favorable effects in patients with AR (14,15).

In previous studies with vasodilator agents in chronic AR, the left ventricular parameters were obtained by using various techniques such as cardiac catheterization, radionuclide ventriculography, Doppler echocardiography and MRI (9,10,14,15,16). We preferred echocardiography as the method for evaluating left ventricular functions owing to its practicality, non-invasive nature and accuracy.

Hemodynamic Parameters:

In our study, felodipine led to a slight increase in the heart rate, a finding that is supported by previous studies (10). On the other hand, in the lisinopril group a slight slowing down of the heart rate was observed. When the differences were compared at the end of 6 months treatment, a statistically significant difference was noticed between the two groups. Although no statistically significant change was observed in the study with captopril, the reflex tachycardia common in other vasodilators was not observed and it was attributed to RAAS blockage by the ACE-Is (14). Since AR is a condition which develops during diastole, anything that shortens the period of diastole may be expected to be useful. Increased heart rate enables this activity since it shortens the diastole. On the other hand, when the heart rate

is slowed down, just an opposite condition may develop and AR may increase. However, these conditions develop under either extreme bradycardia or tachycardia. In our study, since the heart rate values remained within the normal physiological limits and neither tachycardia nor bradycardia occurred, we believe that the difference in between the two drugs with regard to their effects on the heart rate has minimal, if any, effects on the course of AR. It has been shown that the vasodilator treatment does not deliver its effects via heart rate (17).

At the end of 6 months treatment SVR decreased by approximately 17 % in both groups. Sondergaard and colleagues (10) observed a 24 % decrease in SVR with felodipine 10 mg/day and found that the benefit as the decrease of RV and RF was most pronounced in patients with the highest SVR at the beginning of therapy. Similarly in their study with enalapril in chronic AR, Globitis et al. (15) observed that patients who had the highest initial SVR had the most profound RV decrease after therapy. In our study no difference was observed between lisinopril and felodipine with respect to their effect on SVR. This may be due to the drug doses that could be attained. In the felodipine group, the proportion of patients who were able to tolerate the maximum dose was less than that in the lisinopril group. The difference between the initial SVR values might be another reason. Although not statistically significant, the initial SVR values in the lisinopril group were higher in comparison to the felodipine group. Thus, the effect of felodipine might have been less than expected, because the effects of vasodilators are more pronounced in patients with higher initial SVR (10,15).

In our study, the SBP decreased significantly in both the felodipine and the lisinopril groups and the magnitude of SBP change in both groups were similar. In previous studies with felodipine, SBP decreases of up to 24 % were observed (10), higher than the 11 % decrease that we observed in our group. However felodipine dose was kept constantly at 10 mg/day in those studies. The inability of our patient group to tolerate the 10 mg/day target dose may explain the relatively low SBP decrease that we observed. In studies with ACE-Is, SBP was not changed in a study with captopril (14) and a statistically insignificant slight decrease in SBP was observed in another study with enalapril (15). In our study SBP decreased to a similar extent with lisinopril and felodipine. The fact that more patients in the lisinopril group tolerated the maximum medication dose as compared to the felodipine group may explain this finding. Although statistically nonsignificant, higher initial vascular resistance values in the lisinopril group as compared to the felodipine group might be an other explanatory factor. Enhanced activity of the vasodilator treatment in the presence of high systemic vascular resistance was proven before (11).

Echocardiographic parameters:

At 6 months, no significant EDV, ESV and EF changes were found in both drug groups. Reske et al. (24) proved that the decrease in RF with captopril is independent of EF. A similar condition was also observed in studies with nitroprussid and hydralazine (5-9). Lin and colleagues (11) compared hydralazine and enalapril and demonstrated an evident regression in LVEDV and LVESV with enalapril, but not with hydralazine. Similar to the study by Reske et al. (14), no EF change was observed with either drug. Sondergaard et al. (10) found that LVEDV, LVESV, and EF did not change with felodipine. The results of our study are parallel to other studies with felodipine in that LVEDV, LVESV, and EF parameters were not changed. However, in the lisinopril group, as opposed to other studies (11) these parameters remained unchanged in our study. There must be a relatively long interval for the ACE-I therapy to exert effects on left ventricular volumes. The 6-months duration of therapy that we utilized in our study may have thus precluded any possible benefit of lisinopril on left ventricular volumes.

At the end of the study significant FSV and LVSV increases were detected in the lisinopril group. RV and RF were remarkably regressed but LVCO was not changed. Slightly decreased heart rate by lisinopril might be the reason why cardiac output was not raised. These results match the previous studies with ACE-Is. While RV and RF regressed significantly, EF was not changed in the study with captopril (14). Globits et al. (15)

demonstrated a remarkable regression of RV at the end of 3 months treatment with enalapril. In our study, the left ventricular volumes only tended to regress with lisinopril therapy. Consequently the observed RV and RF decreases without any significant volume changes in our study can be attributed to the SVR decrease delivered by lisinopril rather than left ventricular remodelling.

In the felodipine group, LVSV was not changed, FSV increased and RF decreased significantly at the end of 6 months of treatment. A trend towards a decrease in RV was observed. Sondergaard et al. (10) observed a decrease in RV and RF with felodipine.

When the magnitude of change brought out by the two drugs at the end of 6 months were compared, lisinopril delivered a more significant increase in FSV as compared to felodipine. We consider this finding clinically insignificant in itself.

Most recent data regarding vasodilator therapy in chronic AR come from Evangelista et al. (20), where they followed 95 patients with asymptomatic chronic AR for 7 years under nifedipine, enalapril or as controls. Vasodilator therapy was found not to delay AVR and left ventricular volumes, functions and aortic regurgitant volume remained unchanged. With these results and the findings in our study, one has to really question the benefits, if any, of vasodilator therapy in patients with asymptomatic chronic AR.

Conclusion

We were unable to detect any major difference between lisinopril and felodipine and in case a decision is made to proceed with vasodilator therapy in asymptomatic chronic AR, either may be used with modest effects on left ventricular geometry and systolic performance.

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