

A COMPARATIVE STUDY THE EFFECTS OF RAMIPRIL AND EPROSARTAN ON BLOOD PRESSURE AND DIASTOLIC FUNCTION IN PATIENTS WITH ESSENTIAL HYPERTENSION

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Atriyovenriküler (AV) blok akut inferior miyokard enfarktüsünün (ME) sık komplikasyonlarında biridir ve bu nispeten sık görülen komplikasyon yüksek mortaliteye neden olması dolayısıyla klinik olarak büyük önem taşır. Bu çalışmada akut inferior ME seyrinde görülebilen atriyovenriküler tam blok gelişimi ile ilişkili olabilecek klinik faktörler ve elektrokardiyografik parametreler araştırılmıştır.

AV tam blok gelişen 79 hasta ile AV blok izlenmeyen randomize 119 akut inferior ME'li hasta karşılaştırılmıştır. AV tam blok gelişen hastalarda başvuru ortalaması kan basıncı, trombolitik tedavi oranları ve ejeksiyon oranları düşük, hipertansiyon, senkop, zirve kreatin kinaz (CK-MB) düzeyleri, 3 damar hastalığı, ventriküler aritmi ve hastane içi mortalite oranları daha yüksek olarak bulunmuştur. Akut inferior ME'li 65 ve üzerindeki hastalarda AV tam blok gelişimi 2.2 kat daha yük-

sektir. Ayrıca, RV4'de 1 mm'nin üzerinde ST yükselmesi AV tam blok gelişimi 3.7 kat, DIII'de 2.75 mm'nin üzerinde ST yükselmesi 12.3 kat, DIII'deki ST yüksekliğinin DII'dekine oranının 1.5'den fazla olması 3.7 kat artırırken trombolitik tedavi AV tam blok gelişimi 3.2 kat azaltmaktadır.

Sonuç olarak, başvurudaki basit elektrokardiyografik ölçümler AV tam blok gelişimi için tarama testi olarak ve yüksek riskli hastaların belirlenmesinde kullanılabilir. Bu hastalar daha kararsız klinik durumlar açısından dikkatle izlenmeli veya profilaktik kalp pili yerleştirilmesi açısından değerlendirilmelidir.

Anahtar kelimeler: Atriyovenriküler tam blok, Akut inferior miyokard enfarktüsü, Hastane içi mortalite

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INTRODUCTION

Cardiovascular diseases (CVD) are the leading causes of death among adults in the industrialized world (29,2% of total global deaths) and in developing countries, and will probably remain so in the near future (WHO 2003). Hypertension is one of the major risk factors for cardiovascular diseases, such as left ventricular hypertrophy, myocardial infarction, stroke, and renal diseases. However, if blood pressure (BP) is effectively controlled, target-organ damage can be prevented and, in the long term, the likelihood of these complications can be reduced^{1,2}. Unfortunately, reports from several countries around the world have shown that hypertensive patients with well-controlled blood pressure (BP) represent only a small percentage of the hypertensive population (less than 30%). Because

hypertension places patients at increased risk of target organ damage, it is widely accepted that to reduce cardiovascular morbidity and mortality, blood pressure must be controlled, and therefore antihypertensive agents should be administered.

One of the most frequent complications of arterial hypertension is left ventricular hypertrophy (LVH). Left ventricular hypertrophy is present in 50% of patients with arterial hypertension. Hypertension associated LVH is an independent risk factor for cardiovascular morbidity and mortality, including myocardial infarction, congestive heart failure, and sudden cardiac death³. Echocardiography is the best method to diagnose hypertensive heart disease. Ambulatory 24-hour measurements are better correlate, in contrast, causal blood pressure measurements. Patients with echocardiographically determined LVH had a fivefold higher cardiovascular event rate compared with those without LVH, despite similar blood pressure values. Severe LVH decreases the diastolic distensibility with impaired

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relaxation, then induces diastolic dysfunction. Diastolic dysfunction is an important pathophysiology between hypertension and heart failure, affecting around half of hypertension patients. Diastolic heart failure is often diagnosed when symptoms and signs of heart failure occur in the presence of a preserved left ventricular ejection fraction (normal ejection fraction) at rest. Patients with diastolic dysfunction have an increased risk of developing heart failure, but there is no targeted therapy for this condition. Many studies have shown that treating hypertension can regress left ventricular hypertrophy, the effect on diastolic dysfunction is not known. Much less information is available on the comparative effects of angiotensin-converting enzyme inhibitors (ACEIs) with angiotensin receptor antagonist on the diastolic abnormalities frequently occurring in hypertensive patients, often but not always concomitant with ventricular hypertrophy, which is also an important cause of heart failure.

The renin-angiotensin system (RAS), which is a complex system of enzymes, peptides, and proteins, plays a central role in the maintenance of blood pressure, extracellular fluid volume, and electrolyte balance. Medication for this complex system, such as ACEIs, has been reported to reduce the incidence of recurrent myocardial infarction, unstable angina or sudden death in patients with previous myocardial infarction, left ventricular dysfunction, significant regression in left ventricular hypertrophy and fibrosis⁴.

Angiotensin II receptor antagonists, a novel class of antihypertensive agents, offers a new opportunity to manipulate the RAS for blood pressure control. The efficacy of these agents for blood pressure control is similar to that of ACEIs, and their potential antihypertrophic activities are considerable. Clinical observation also revealed that angiotensin-II receptor blockade could blunt the development of ventricular hypertrophy in the absence of a hypotensive effect. So inhibition of the renin-angiotensin system, either with or angiotensin II receptor antagonists, could have antihypertensive effects and retard the ventricular hypertrophy process/diastolic dysfunction state⁵.

However, the effects of angiotensin II receptor antagonists on diastolic dysfunction are unclear. The results of the Valsartan In Diastolic Dysfunction (VALIDD) trial⁶ announced at the American College of Cardiology meeting, did not show any benefit for an ARB-based regimen over aggressive blood pressure lowering with a regimen of non-renin-angiotensin system-inhibiting drugs in prehyperten-

sive adults with diastolic dysfunction, as measured by tissue Doppler imaging.

Diastolic dysfunction is difficult to study. A long-term study is needed if it is going to be events-driven, rather than just depending on studies of function. There was an intriguing finding in the CHARM-Preserved study of a borderline benefit in preventing hospitalizations for heart failure compared with placebo on top of all other treatments, although there was no mortality benefit⁷. The currently finalized Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE)⁸ trial, a true large-scale, robust, well-designed comparison of irbesartan with all other drugs that are not renin-angiotensin system blockers in patients with diastolic dysfunction. The follow-up was mean 49,5 months. The results did not show any benefit for an ARB-based regimen over primary composite outcome of death from any cause or hospitalization for cardiovascular reasons occurred in 742 patients (36%) in the irbesartan group and in 763 patients (37%) in the placebo group. There were 100,4 events per 1000 patients-years in the irbesartan group and 105,4 events per 1000 patients-years in the placebo group (95% CI 0,86-1,05; $p=0,35$). No significant differences were found between the two groups for any of the prespecified secondary outcomes, including rates of death and protocol-specified hospitalization.

However, the fact that diastolic dysfunction has not responded particularly well to ACE inhibitors or to ARBs up to this point leads it be to suspect that the etiology of the dysfunction, which is obviously related to the abnormal tissue properties of the left ventricle, is not being driven primarily by the renin-angiotensin system.

The aim of our research was to perform a double-blind randomized study to evaluate diastolic function could be influenced by inhibition of the renin-angiotensin-aldosterone (RAA) system with an ACE inhibitor (ramipril) and an angiotensin II antagonist (eprosartan), as well as blood pressure reduction and changes in the index of diastolic function with drug therapy.

METHODS

Patient population: This double blind study originally included 100 outpatients (48% males and 52% females) who had moderate to severe essential hypertension stage II-III (average sitting DBP > 95 mmHg and SBP > 160-180 mmHg) moderate hypertension - 40 pts. (40%) and severe - 60 pts. (60%), mean age, 51.6 ± 9.8 years, with heart failure NYHA class I - 35 pts. (35%) and class II - 65 pts. (65%),

Table 1: Ambulatory blood pressure monitoring (Ramipril vs Eprosartan)

Parameters of ABPM	I group (Ramipril)		%	II group (Eprosartan)		%
	Baseline	6 months		Baseline	6 months	
	M±m	M±m		M±m	M±m	
SBP(mmHg)mean/24 hour	153,2±2,5	138,2±2,4***	10	155,6±2,2	126,4±2,2***	18,8
DBP(mmHg)mean/24 hour	93,6±1,5	83,9±1,2***	10,3	93,5±1,3	79,9±1,4***	14,4
SBP(mmHg)mean/day	155,7±2,5	140,0±2,5***	10	156,9±2,0	128,0±2,2***	18,4
DBP(mmHg)mean/day	95,4±1,6	84,6±1,3***	11,2	94,8±1,38	82,1±1,5***	12,7
SBP(mmHg)mean/night	145,7±2,2	131,2±2,1***	9,5	148,2±2,7	119,1±2,2***	19,6
DBP(mmHg)mean/night	85,1±1,4	77,6±1,0***	8,8	88,8±1,4	74,0±1,4***	16,6

ABPM=ambulatory blood pressure monitoring; SBP=systolic blood pressure; DBP=diastolic blood pressure;***p<0,0001.

with diastolic dysfunction determined by Doppler echocardiography. Both groups had been treated with Indapamid 2,5 mg daily. Baseline characteristics of the previously treated patients were not significantly different. The history of hypertension - 5,1±2,7 years.

The exclusion criteria included: Pregnancy or lactation, secondary hypertension, bilateral renal artery stenosis, angina pectoris, chronic obstructive pulmonary disease (COPD), heart failure or history of heart failure NYHA class III-IV, second or third degree atrioventricular (AV) block, clinically relevant arrhythmia or valvular heart disease, uncontrolled diabetes mellitus, neoplasm, and eprosartan or ACE inhibitor intolerance or withdrawal during a washout period. Patients with evidence of chronic liver disease (alanine transaminase [ALT] > 80 IU/L, aspartate transaminase [AST] > 90 IU/L and total bilirubin > 3.2 mg/dL), creatinine > 2.5 mg/dL, or obesity (body mass index > 28) were also excluded from the study.

Treatment: After a 2 weeks washout period (considered long enough to remove the effects of previous medications) for those who were already on antihypertensive agents. Patients were arbitrary randomly for treatment separated into two equally sized groups: I group included - 50 pts. to the Ramipril (average doses 14,7 mg once daily) and Indapamid 2,5 mg once daily; II - 50 pts. to the Eprosartan (average doses 740 mg once daily) and Indapamid 2,5 mg once daily. The total treatment period was 6 months. This was a randomized, double-blind, active control and parallel group study. The same drug was used throughout the study, and the study followed the guidelines of the institutional review board at Institute of Cardiology. The research ethics committee approved this study, and all subjects gave written informed consent at the time of enrollment.

RESULTS

A total of 132 patients were evaluated for eligibility. One hundred patients fulfilled the inclusion criteria,

and 48 males and 52 females, mean age, 51.6±9.8 years with a mean blood pressure of 191.6±12.6 mmHg and 108.0±9.0 mmHg, respectively were studied. Fifty patients were treated with ramipril and 50 with eprosartan. Withdrawal from the study was due to loss of follow-up (twenty in the ramipril group and twelve in the eprosartan group), lack of efficacy (four in the ramipril group and nobody in the eprosartan group), and other causes (sixteen in the ramipril group and twelve in the eprosartan). There were statistically significant clinical differences between these two groups. After 6 months of antihypertensive therapy, mean values of the systolic and diastolic BP was significantly reduced (SBP/24 hour 155.6±2.2 to 126.4±2.9 mmHg, DBP/24 hour 93.5±1.3 to 79.9±1.4 mmHg, P < 0.0001) in patients receiving treatment with eprosartan (Table I); however, in those receiving ramipril treatment, only systolic BP was reduced significantly from 153.2±2.5 to 138.2±2.4 mmHg (P < 0.0001) (Table I). There were more patients in the eprosartan group (64,0%) than in the ramipril group (36,4%) that achieved a sitting DBP/24 hours of less than 80 mmHg at visit month 6, and the difference was statistically significant (P = 0.01, Fisher's exact test). Mean SBP/day was reduced significantly with 10% versus 18,4% (P < 0.0001) in the ramipril and eprosartan groups, respectively; mean DBP/day - 11,2% vs 12,7% (P < 0.0001) in the ramipril and eprosartan groups, respectively. There were more patients in the eprosartan group (68,0%) than in the ramipril group (45,4%) that achieved a sitting SBP/day of less than 135 mmHg at visit month 6, and the difference was statistically significant (P = 0.01), similar, were more patients in the eprosartan group (56,3%) than in the ramipril group (35,7%) that achieved a DBP/day of less than 85 mmHg, (P = 0.01). There were statistically significant changes in means SBP and DBP/night among the ramipril and eprosartan groups reduced with 9,5% vs 19,6%, P < 0.0001 and 8,8% vs 16,6%, P < 0.0001, respectively (Table I). The tar-

Table 2: Diastolic function (Ramipril vs Eprosartan)

Parameters of diastolic function	I group (Ramipril)		%	II group (Eprosartan)		%
	Baseline M±m	6 months M±m		Baseline M±m	6 months M±m	
E/A	0,79±0,04	1,25±0,04***	56	0,70±0,02	1,27±0,05***	68,5
IVRT	127,1±3,3	102,5±2,8***	20,5	131,0±2,0	100,6±2,2***	24,5
DT	200,5±6,0	183,2±4,2*	10	218,1±6,4	189,0±6,0***	13,2

E/A=E/A ratio; IVRT=isovolumic relaxation time; DT=deceleration time; *p<0,01; ***p<0,0001.

get values of means SBP and DBP/night achieved of less than 120 mmHg and less than 70 mmHg, respectively, were more patients in the eprosartan group (55,6%) than in the ramipril group (25,1%), (P = 0.01). Both of treatments regimens were conditioned reduction of all parameters of ABPM, but the best results were obtained in those patients, which had receiving eprosartan treatment. Therefore, the patients will be really protected from morning hypercatecholaminemia and consecutive hypertensive morning peak, which associates with high incidence of stroke and acute myocardial infarction. Eprosartan therapy produces low fluctuations on blood pressure during day period, which may be affected target-organs damage.

Despite the preserved systolic function (EF 60,5±0,7%), was determined on patients with moderate-severe hypertension the functional classe NYHA 1,6±0,08.

The diastolic function in patients with moderate to severe hypertension was affected predominantly by the "relaxation abnormality" type in 89,0%, sometimes - "restrictive physiology" - 9,0% and insignificant - "pseudonormalization" type in 2%. There were no statistically significant patterns types differences between these two groups. Additionally, values of diastolic function as: E/A ratio, isovolumic relaxation time, and deceleration time assessed by Doppler echocardiography were no differences in the baseline characteristics between these patients. Thus, mean E/A ratio 0,75±0,02, deceleration time 200,5±6,0 msec and isovolumic relaxation time 127,1±3,3 msec were registered in boths groups (P>0,05). Evaluating the values of diastolic function, there was significant difference observed after 6 months of eprosartan treatment: 1) significantly improvement E/A ratio from baseline to follow-up 68,5% (P<0,0001) vs 56% (P<0,0001) in ramipril treatment; 2) there were no significant difference observed in the change of values of isovolumic relaxation time between ramipril and eprosartan reduced with 20,5% vs 24,5% at an almost identical change of

values of deceleration time reduced with 10,0% vs 13,2%, respectively (Table II).

The combination of double antihypertensive agents (Indapamide + Ramipril or Eprosartan) during 6 months demonstrated a significant improvement of the diastolic parameters such as: E/A ratio, isovolumic relaxation time and deceleration time. Although no statistically significant between these two groups, eprosartan tended to have a greater reduction in isovolumic relaxation time and deceleration time and more important increased E/A ratio was registered in to eprosartan group. Thus, during a 6 months treatment, there were established the rate pattern of ventricular filling by "relaxation abnormality" type in 34,2% Ramipril vs 10% Eprosartan.

No serious clinical or laboratory adverse event was observed among the study populations. The number of adverse events reported in each treatment group did not differ substantially. There were more reported cases of cough in the ramipril group than in the eprosartan group (1,4% versus 0%). Additionally, we compared the percent based on the level of blood pressure reduction, including nonresponders, < 140% SBP reduction, and < 90% DBP reduction. There was significant difference observed in the change of values of level of blood pressure reduction between ramipril and eprosartan: lack of efficacy (5,7% in the ramipril group and nobody in the eprosartan group).

DISCUSSION

Antagonists of the renin-angiotensin system, such as angiotensin type 1 (AT1) receptor inhibitors and angiotensin-converting enzyme inhibitors, are becoming increasingly popular agents in treating patients with systemic hypertension and minimizing organ damage.

In the present study, we compared the effects of ramipril, an ACEIs, with eprosartan, an AT1 receptor inhibitor in a group of newly diagnosed hypertensive patients with multiple risk factors such as diastolic dysfunction. This randomized, double-blind study in

patients with moderate to severe essential hypertension demonstrated that eprosartan (an angiotensin II receptor blocker) 600-800 mg once daily is well-tolerated and effective at reducing seated systolic blood pressure (SBP) and diastolic blood pressure (DBP). A similar magnitude of SBP reduction was also found in patients taking ramipril 10-20 mg. The subjects were monitored and tested at 0 and 6 months to determine their individual effects on levels of systolic and diastolic blood pressure and parameters of diastolic function. After 6 months of antihypertensive therapy, in present study, mean values of the SBP/day, night and DBP/day, night was significantly reduced in patients receiving treatment with eprosartan: mean SBP/day with 18% ($P<0.0001$) eprosartan vs 10% ramipril; mean DBP/day - with 12,7% ($P<0.0001$) eprosartan vs 11,2% ($P<0,005$) ramipril; mean SBP/night - 19,6% ($P<0.0001$) eprosartan vs 9,5% ($P<0,005$) ramipril; mean DBP/night - 16,6% ($P<0.0001$) eprosartan vs 8,8% ($P<0,005$) ramipril. There were more patients in the eprosartan group than in the ramipril group that achieved a sitting SBP and DBP (day, night and 24 hour from ABPM) at visit month 6, and the difference was statistically significant ($P = 0.01$, Fisher's exact test).

Angiotensin II (All) receptor blockers offer an alternative means of blocking the renin-angiotensin-aldosterone system (RAAS) to angiotensin converting enzyme (ACE) inhibitors. Being highly selective for the All receptor subtype AT1, All receptor blockers may avoid side effects associated with ACE inhibitor treatment, such as cough. Eprosartan is a non-biphenyl, non-tetrazole competitive blocker that is chemically distinct from other All receptor blockers, which may account for differences in its pharmacological properties. It induces dual blockade of AT1 receptors both presynaptically and postsynaptically, reducing sympathetic nerve activity to a significantly greater degree than other AT1 receptor blockers. At the recommended dose of 600 mg once daily, eprosartan effectively lowers blood pressure (BP) in hypertensive patients to a similar degree as seen with other All receptor blockers and ACE inhibitors. However, a greater proportion of patients achieved adequate BP control compared with enalapril. When eprosartan is given in combination with hydrochlorothiazide (HCTZ), it provides a significantly greater BP reduction compared with eprosartan alone. Eprosartan has a side-effect profile that is similar to placebo and to other All receptor blockers, but is better than that of enalapril because it lacks the propensity to cause dry cough. Eprosartan is not

metabolized by the cytochrome P450 enzyme system, and so has no interaction with drugs that affect this system. Eprosartan completely reverses renal vasoconstriction induced by All and may, therefore, have further applications in situations where stimulation of the RAAS is a problem. In summary, eprosartan, alone or in combination with HCTZ, provides an effective and well-tolerated approach to lowering BP in patients with all grades of hypertension. Further development of eprosartan may offer therapeutic opportunities that go far beyond the current recommendations. The clinical efficacy of eprosartan for blood pressure control has been shown in other placebo-controlled trials and comparative studies^{9,10}. In a relative small, double blind randomized trial, which to compare the effects of eprosartan and enalapril on BP, platelets, and endothelium function in patients with essential hypertension. Eprosartan was effective and well-tolerated in the treatment of mild-to-moderate hypertension, and the DBP response reduction to eprosartan was better than that to enalapril. In this study, eprosartan was as effective as ACE inhibitors in lowering blood pressure and was even better in terms of the responder rate¹¹. Similar to other clinical trials comparing ACE inhibitors with AT-1-receptor antagonists, patients with ACE inhibitors had more side effects, mainly coughing, which is related to bradykinin activation¹².

Withdrawal from the our study was due to loss of follow-up (15,2% in the ramipril group and 9% in the eprosartan group), lack of efficacy (5,7% in the ramipril group and nobody in the eprosartan group), and other causes (22,8% in the ramipril group and 19,3% in the eprosartan), rate of cough was among them (1,4% in the ramipril group and nobody in the eprosartan group), rates of hypotension and renal dysfunction were not registered.

Only five trials (LIFE, SCOPE, MOSES, JIKEY HEART, VALUE) have compared angiotensin receptor antagonists with other antihypertensive agents. The different comparators used make meta-analysis of these studies difficult. In the MOSES trial on about 1500 hypertensive patients with a previous cerebrovascular event comparison was made of treatment by either eprosartan or the nitrendipin. During a mean follow-up of 2,5 years, and for similar blood pressure decrease, cardiovascular events were significantly less in eprosartan-treated patients. Direct comparisons between the overall and cause-specific beneficial effects of angiotensin receptor antagonists and ACE inhibitors (the classes specifically opposing the cardiovascular influences of

the renin-angiotensin system) in hypertension are available, this makes the results of an large trial on high risk hypertensive and normotensive patients randomized to ramipril or telmisartan (ONTARGET). Primary composite outcome of death from cardiovascular causes, myocardial infarction, stroke or hospitalisation for heart failure occurred in 1423 patients (16.7%) in the telmisartan group, 1412 patients (16.5%) in the ramipril group and 1386 patients (16.3%) in the combination group. Compared to the ramipril group, the telmisartan group had a lower rate of cough (1.1% vs 4.2%; $p < 0.001$) and a higher rate of hypotension (2.6% vs 1.7%; $p < 0.001$). Compared to the ramipril group, the combination group had higher rates of hypotension (4.8% vs 1.7%; $p < 0.001$) and renal dysfunction (13.5% vs 10.2%; $p < 0.001$)¹³.

Heart dysfunction in hypertension may be primarily diastolic. In several studies hypertensive patients hospitalized for congestive heart failure commonly (40%) had systolic function that was preserved or normal. In untreated hypertensive patients, pulmonary capillary wedge pressure increases dramatically with low levels of workload, despite preserved systolic function. This response can be favorably influenced by treatment.

Much less information is available on the comparative effects of ACEIs with angiotensin receptor antagonist on the diastolic abnormalities frequently occurring in hypertensive patients.

Ramipril, is an angiotensin-converting enzyme inhibitor. This prodrug itself is a poor inhibitor of ACE but is rapidly hydrolysed after absorption to the active metabolite ramiprilat, which has a higher affinity for ACE than enalaprilat or captopril. In several clinical studies involving patients with essential hypertension, ramipril therapy induced positive changes in cardiac structure and function¹⁴⁻¹⁶, reduces arterial stiffness in the carotid artery¹⁴, prevented LVH in patients with mild hypertension during 3-year study, significant reduction in blood pressure¹⁵, no significant change from baseline in height-indexed left ventricular mass, diastolic diameter of the left ventricle, interventricular septum thickness or thickness of the posterior wall in contrast with felodipine, which significant increases from base-line in these indices; ramipril reduced heart rate and cardiac workload in patients under stress¹⁶.

All patients in present study had diastolic dysfunction due to an impaired left ventricular relaxation, as IVRT > 100 msec, DT > 220 msec and E/A < 1. Traditional medical therapy, for management of systolic dysfunction, can not be administered in the treat-

ment of diastolic dysfunction. Management of diastolic dysfunction involves two important directions: 1) decrease pulmonary capillary wedge pressure with reduction of left ventricular filling pressure; 2) normalize parameters of diastolic function.

After 6 months of antihypertensive therapy, parameters of diastolic function such as: E/A ratio, isovolumic relaxation time and deceleration time measuring by transmitral Doppler echocardiography was significantly improved in the eprosartan group. Increased E/A ratio with 68,5% ($P < 0,0001$) eprosartan vs 56,0% ($P < 0,0001$) ramipril group, preponderant on account prologation time of precocious diastolic filling which improves left ventricular filling during rapid filling and increases atrial contribution; IVRT was reduced with 24,5% ($P < 0,0001$) in the eprosartan group vs 20,5% ($P < 0,0001$) in patients receiving treatment with ramipril. There were more patients in the eprosartan group (60,0%) than in the ramipril group (48,0%) that achieved a deceleration time of less than 220 msec at 6 months follow-up period, and the difference was statistically significant ($P = 0.02$, Fisher's exact test). There were no statistically significant changes in E/A ratio and IVRT among the eprosartan and enalapril groups that achieved normal indices at finally follow-up period.

Improvement of ventricular filling relation and diastolic distensibility prevent diastolic heart failure suggesting favorable prognosis. The beneficial effects of AT1 antagonism and ACE inhibition would therefore appear to be mediated principally through blocking the effect of angiotensin II.

These findings suggest that eprosartan, an AT1 receptor inhibitor, effectively reduces systemic blood pressure and, compared with ramipril, suggests additional benefits in the diastolic function by inhibiting left ventricular hypertrophy.

CONCLUSION

The diastolic function in patients with moderate to severe hypertension was affected predominantly by the "relaxation abnormality" type in 89,0%, sometimes - "restrictive physiology" - 9,0% and insignificant - "pseudonormalization" type in 2%.

Eprosartan, a novel angiotensin II receptor antagonist, is effective and well tolerated for the treatment of moderate to severe hypertension and results in better systolic and diastolic BP control than does ramipril.

Combination of antihypertensive agents is efficient in moderate to severe hypertensive patients, with median doses which contribute to increase treat-

ment compliance and minimize side effects.

In hypertensive patients with diastolic dysfunction, regimen treatments with Ramipril and Eprosartan resulted in a significant improvement, but the best results was better in Eprosartan group. Improvement of ventricular filling, relaxation and myocardial distensibility prevent diastolic heart failure and, as a result, congestive heart failure, suggesting favorable prognosis.

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