

# Effects of angiotensin converting enzyme inhibition on left ventricular dimensions and hemodynamics in systemic hypertension: A radionuclide and Echocardiographic study

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*The aim of this study was to assess the effects of angiotensin converting enzyme (ACE) inhibition on cardiac systolic and diastolic parameters and left ventricular muscle mass in hypertensive patients. For this purpose thirty patients (22 female and 8 male) with mild to moderate essential hypertension, aged  $47 \pm 2$  years, were treated with enalapril maleate (MK 421, an ACE inhibitor) for six weeks. They underwent M-mode and Doppler echocardiography and radionuclide ventriculography at the beginning and after six weeks of enalapril treatment. A significant reduction in left ventricular systolic and diastolic diameters, left ventricular mass, total peripheral resistance, end-systolic stress was shown after treatment. Ejection fraction increased in both examinations after six weeks of therapy with enalapril treatment. We conclude that enalapril improves diastolic and systolic parameters in left ventricle function but causes slight decreases in cardiac output and stroke volume in addition to lowering blood pressure. [Turk J Med Res, 1995; 13(1): 16-20]*

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Cardiac death is the most common mode of death in patients with hypertension (1). Hypertensive heart disease can be defined as the response of the heart to the hemodynamic overload imposed on the left ventricle by the progressively increasing arterial pressure and total peripheral resistance produced by hypertensive vascular disease (2,3). Cardiac involvement is usually evident long before heart failure or infarction occur. In addition to the hemodynamic factors of pressure and volume overload, new non-hemodynamic concepts are recently being considered. After angiotensin converting enzyme (ACE) inhibition introduced molecular biology into clinical medicine, new frontiers have been opened and future progress is promised in this area (4,5).

However, in the selection of antihypertensive medications, relatively, little attention has been paid to the hemodynamic effects associated with their use. Recent emphasis has been placed on assessing left ventricular function in patients with hypertension and in matching therapy with the hemodynamic profile exhibited by the patient (2).

Previous studies have shown cardiac effects of some antihypertensive agents by means of either echocardiographic or radionuclide examinations (6-11). The aim of our study was to assess the behavior of left ventricle systolic and diastolic functions and cardiac structure after treatment with the ACE inhibitor, enalapril, by both radionuclide and echocardiographic methods in hypertensive patients.

## MATERIALS AND METHODS

### Patients

Thirty patients (22 female and 8 male) with essential hypertension were studied. Inclusion criteria were male and female outpatients with essential hypertension, aged 22-70 years old, with diastolic blood pressure (DBP) >95 mmHg or systolic blood pressure >160 mmHg. Other antihypertensive drugs, if any, were discontinued 2 weeks before treatment with enalapril.

### Study design

All patients were given placebo for two weeks, no statistically significant blood pressure (BP) changes occurred during this placebo period. Then enalapril 2.5 mg/day was given orally as a test dose and 5 mg/day for the first week of treatment. A dose of 10 mg/day was given in the second week if BP did not decline to the normal range. Average enalapril dose to make suf-

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ficient BP control was 20 mg/day. The duration of study was six weeks after wash-out period.

### Echocardiography examination

Echocardiograms were obtained using standart techniques with a Toshiba Sonolayer SSH 60 echocardiography and a 2.25 MHZ transducer, 1 cm in diameter. Echocardiography views and simultaneous electrocardiographic tracings were recorded on video tape and interpreted at the end of the study by a blinded reviewer. Echocardiography data were determined from stop frames recorded at the equivalent of 100 mm/sec paper speed.

Measurements pertaining to M-mode echocardiography were done according to the recommendations of the American society of Echocardiography and used to calculate the left ventricular (LV) fractional shortening, end-diastolic volume, end-systolic volume and stress, ejection fraction as well as the stroke and cardiac index and total peripheral resistance with the help of standart formulae (12-14). The Penn convention formula was used to determine LV mass; the value indicating hypertrophy was accepted as 135 gr in men and 110 gr in woman. Two-dimensional echocardiography was performed to detect structure and motion abnormalities of the heart. Doppler echocardiographic views were obtained at the level of the mitral and aortic valves with the pulsed-wave method.

### Radionuclide examination

Radionuclide ventriculography was performed after labeling red blood cells with the modified invivo method. Patients were given 400 mg potassium perchlorate at the time of 500 microgram of stannous pyrophosphate injection. Thirty minutes later 20 mCi Tc-99m pertechnenate was injected into each patient (15). Imaging was performed at 10 minutes where images were taken at left anterior oblique projection to get the best ventricular separation. Five to 15° of caudal angulation were added to minimize LV-left atrial overlap. The data were digitized into a 64x64 pixel matrix for subsequent analyses, and the cardiac cycle was formatted into 32 frames.

LV regions of interest were derived for each frame by a semiautomatic second derivative edge-detection routine applied to temporally and spatially smoothed data. The time-activity curves were generated using these regions and applied to the raw data, after subtraction of a mean paraventricular background value. These curves were then subjected to a 5-point smoothing routine. The ejection fractions (EF) were calculated from the time-activity curves in the standart manner. The peak LV filling rate (PFR) was computed by taking the first derivation of the smoothed LV time-activity curve. The time to PFR was measured from the end-systolic point to the point at which the PFR occurred.

*Turk J Med Res 1995; 13 (1)*

### Statistical analysis

Statistical evaluation of the results was carried out using paired Student's t test and Wilcoxon matched-pairs signed-ranks test. A P value of <0.05 level was considered statistically significant. All data are expressed as mean±SEM (standart error of the mean).

### RESULTS

During two weeks of placebo period, no statistically significant changes occurred in blood pressure values. After six weeks of therapy, the mean arterial pressure was significantly decreased from 126.26±1.38 to 91.38±1.15 mmHg as well as systolic and diastolic blood pressures. The heart rate at the end of the enalapril period was 87±3 beats/min. and not different from placebo (Table 1).

A significant reduction in left ventricular end-diastolic and end-systolic diameters were determined by echocardiographic examinations (p<0.001, Table 2). Other cardiac diameters and ventricular mass also decreased after six weeks of treatment with enalapril (p<0.001, Table 2).

The increases in ejection fraction in both echocardiographic and radionuclide examinations is not statistically significant. But the decreases in total peripheral resistance and end-systolic stress were found to be significant after treatment with enalapril (p<0.001, Table 2,3).

In radionuclide examinations; peak ejection rate and peak filling rate slightly increased but these changes were within intraobserver variations. But time to peak filling rate decreased significantly after six weeks of enalapril therapy (Table 3).

Despite these improvements in cardiac systolic and diastolic parameters and hemodynamics, cardiac outp and stroke volume slightly decreased after enalapril (p<0.01, Table 2).

### DISCUSSION

In systemic hypertension, left ventricular changes, occur to provide physiological and structural adaptation

Table 1. Arterial blood pressure (BP) and heart rate, before and after placebo and enalapril

	Before placebo (beginning)	After placebo (No difference)	After enalapril P<0.001
Systolic BP (mmHg)	166.72±2.22	167.12±1.95	124.48±1.56
Diastolic BP (mmHg)	105.86±1.56	106.72±2.10	75.17±1.22
Mean BP (mmHg)	126.18±1.50	<u>126.33</u> ±1.38	91.38±1.15
Heart rate (/min)*	86±3	86±2	87±3

**Table 2.** Echocardiographic parameters before and after treatment with enalapril

Parameter	pre-Enalapril	post-Enalapril	P
Left ventricle enddiastolic diameter (LVEDD) (mm)	52.2±1.04	47.92±1.02	<0.001
Left ventricle endsystolic diameter (LVESD) (mm)	33.07±1.17	28.64±1.11	<0.001
Enddiastolic posterior wall diameter (EPWD) (mm)	15.57±0.65	14.39±0.55	<0.001
Enddiastolic septum diameter (EDSD) (mm)	14.31±0.32	13.35±0.24	<0.001
Ejection fraction (%)	73.48±2.01	74.31±1.53	>0.05
Stroke volume (ml)	79.57±2.44	72.78±2.45	<0.01
Stroke index (L/min/m <sup>2</sup> )	44.68±1.22	40.88±1.23	<0.01
Cardiac output (L/min)	6.84±0.12	6.33±0.14	<0.01
Cardiac index (L/min/m <sup>2</sup> )	3.84±0.06	3.55±0.05	<0.01
Total peripheral resistance (dyn.secern <sup>-4</sup> )	1475.78±41.11	1154.88±41.88	<0.001
Endsystolic stress (mmHg)	73.56±3.19	54.73±2.12	<0.001
Ventricular mass (g)	220.62±8.26	183.31±6.62	<0.001
Ventricular mass index (gr/m <sup>2</sup> )	123.93±3.89	102.80±2.72	<0.001

to hemodynamic overload. Functionally, the ventricle remains stable in its systolic contractile actions, maintaining its pumping performance until left ventricular failure supervenes. However, diastolic dysfunction frequently precedes this deterioration (2,16,17). The factors responsible for these abnormalities can be ventricular wall thickness above normal limits, regional variations of wall thickness, changed cardiac geometry, interstitial fibrosis, collagen accumulation, disposition of collagen tissue, fibroblast proliferation, loss of myocardial contractile elements and loss of normal intracellular connections (15,18,19,21).

As hypertensive cardiac remodeling is not totally explainable hemodynamically, it is suggested that non-hemodynamic factors -including myocytic growth factors, circulating and local tissue renin-angiotensin system (RAS), intrinsic myocardial RAS, adrenergic system- may contribute to this process (18-24).

Circulating and local tissue RAS located in kidney, suprarenal gland, blood vessels, brain especially myocardial RAS have each been demonstrated to participate in maintenance of blood pressure homeostasis (25-32). Intracardiac generation of Angiotensin-II, the active factor of RAS, induces cardiac myocyte necrosis (20,33). This vasoconstrictive, vasculotoxic, necrotic, cardiotoxic agent also interacts with adrenergic system and plays a key role in cardiac pathophysiological adaptive changes (19-21, 24,33-35).

The emerging data demonstrating that RAS is a local tissue system with autocrine, paracrine, and intracrine functions raise interesting issues regarding its role in hypertension and ACE inhibitors have beneficial effects on cardiac structure and hemodynamics not only by decreasing blood pressure simply but also by inhibiting the effects of circulating, local and myocardial RAS mentioned above.

In this study all patients treated with the ACE inhibitor enalapril responded with a significant decrease in mean arterial pressure ( $p<0.001$ ). A significant reduction in left ventricular systolic and diastolic

**Table 3.** Radionuclide parameters before and after treatment with enalapril

Parameter	Before Treatment	After Treatment	P
Ejection fraction (EF) (%)	51 ±2	54±1	<0.062
Peak ejection rate (PER) (EDV/sn)	2.4±0.09	2.57±0.08	<0.034
Time to PER (tPER) (msn)	156.82±6.06	158.96±5.68	>0.05
Peak filling rate (PFR) (EDV/sn)	2.05±0.96	2.35±0.61	<0.032
Time to PFR (tPFR) (msn)	152.55±9.3	128.41±5.71	<0.021

diameters, wall thickness of the left ventricle and mass index were shown after six weeks of treatment with enalapril. Total peripheral resistance and end-systolic stress decreased at the same time course ( $p<0.001$ ) (Table 2). In radionuclide examinations, time to peak filling rate decreased significantly after six weeks of enalapril therapy (Table 3). Previous workers have shown similar improvements in cardiac systolic and diastolic parameters after treatment with some ACE inhibitors, in hypertension by either echocardiographic or radionuclide methods (6,7,36-38).

In our study; despite these beneficial effects on cardiac systolic and diastolic parameters, cardiac output and stroke volume slightly decreased after enalapril ( $p<0.01$ ). The main factors responsible for these changes may be peripheral pooling of blood in the venous capacitance beds because of vasodilatation induced by enalapril, withdrawal of venous sympathetic tone, removal of the synergistic effects of angiotensin-II on peripheral sympathetic activity and removal of the direct (+) inotropic effects of locally synthesised angiotensin-II in myocardium by ACE inhibition. In previous studies (6,7), it had been usually found that cardiac output and stroke volume was not

• ficantly altered by ACE inhibition in patients with moderate to-severe hypertension. But in an experimental study performed in hypertensive rats by Frohlich and Unger (39), it was shown that CGS-16617, a con-vert of benazapril, reduced cardiac output and stroke volume significantly. At the same study; enalapril, also reduced cardiac index but this change was not statistically significant.

The results of this study suggest that enalapril has beneficial effects on both left ventricular systolic and diastolic performance except cardiac output and stroke volume as discussed above. These differences are likely to result both from prevention of adverse ventricular remodeling induced by angiotensin peptides and from ongoing effects on ventricular systolic and diastolic load. Additional investigation is needed to gain further insight into the mechanisms by which ACE inhibition achieves these effects and into the relation among the effects of ACE inhibitors on ventricular performance, symptoms, functional capacity and survival.

#### **Sistemik hipertansiyonda ACE inhibisyonunun sol ventrikül çapları ve hemodinamisine etkileri: Radyonüklid ve ekokardiyografik bir çalışma**

*Bu çalışmanın amacı, hipertansif hastalarda angiotensin konvertir enzim (ACE) inhibisyonunun kardiyak sistolik ve diastolik parametrelere ve sol ventrikül kas kitlesi üzerine etkilerini incelemektir. Bu amaçla hafif-orta hipertansiyonu olan, ortalama 47±2 yaşlarında 30 hasta (22 kadın ve 8 erkek), altı hafta boyunca enalapril maleate (MK421, bir ACE inhibitörü) ile tedavi edildi. Bu hastalara başlangıçta ve altı haftalık enalapril tedavisi sonrası M-mode ve Doppler ekokardiyografi ve radyonüklid ventrikülografi uygulandı. Bu çalışmada ACE inhibitörü, enalapril ile tedavi edilen tüm hastalarda ortalama kan basıncında belirgin bir düşme gözlemlendi. Sol ventrikül kas kitlesi de altı haftalık enalapril tedavisi sonrası belirgin azaldı. Aynı süre içinde total periferik rezistans ve end-sistolik streste de azalma oldu. Her iki incelemede de altı haftalık enalapril tedavisi sonrası ejeksiyon fraksiyonu artmış olmasına karşın bu artışlar istatistiksel olarak anlamlı değildi. Radyonüklid incelemede, tepe doluş hızına ulaşım zamanında altı haftalık enalapril tedavisi sonrası kısalma gözlemlendi. Kardiyak sistolik ve diastolik parametrelerdeki bu gelişmelere karşın, enalapril tedavisi sonrası kardiyak output ve strok volümde bir miktar azalma gözlemlendi. Sonuçta enalaprilin kan basıncını düşürmesi yanısıra sol ventrikül diastolik ve sistolik parametrelerini düzelttiği, ancak kardiyak output ve strok volümde bir miktar azalmaya yol açtığı belirlendi. [Turk J Med Res 1995; 13(1): 16-20]*

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