EFFECT OF ACE INHIBITION ON EXERCISE CAPACITY IN PATIENTS WITH CHRONIC CONGESTIVE HEART FAILURE DUE TO CORONARY HEART DIESASE

O. ERGENE, M.D.,*
Ö. KOZAN, M. D.,*
İ. DİNDAR, M. D.,*
A. R. KAZAZOĞLU, M.D.,*
N. ÇAĞLAR, M.D.,*
A. DİRİCAN, M.D.,**
F. TURAN, M. D.,*
O. PEKTAŞ, M.D.*

From: *Koşuyolu Heart and Research Hospital
**University of İstanbul Cerrahpaşa Medical School Division of Biostatistics

Adress for reprints:
O. ERGENE, MD.
Koşuyolu Heart and Research Hospital
İstanbul, TÜRKİYE

Fourty-two patients with chronic congestive heart failure (NYHA Class III-IV) due to coronary artery disease were studied within a period of twenty- two months. Enalapril was administered randomly to 23 of the patients who had been already given digitalis and diuretics (Group A). Nineteen patients were continued to their prior medication throughout the study (Group B).

Maximal symptom-limited treadmill exercise tests were performed to all patients before treatment, between 4th and 6th months of treatment and between 15th and 19th mouhts of treatment according to a modified Naughton protocol. Exercise duration was increased from 352±164 seconds to 442±125 seconds at 6th month of treatment and it was 399±116 seconds at 18th month of treatment in enalapril group and the difference was statistically significant ($p< 0.05$). In group B these values were 377±142, 344±146 and 296±118 seconds respectively and the difference was significant at 18th months of treatment ($p< 0.05$).

This study indicated that angiotensin converting enzyme inhibition can improve the clinical condition of patients and increase their exercise tolerance probably by unloading and remodelling of the left ventricule and more efficient distribution of the peripheral circulation.

Key words: Angiotensin converting enzyme, exercise testing.

Congestive heart failure (CHF) is a common condition reported to effect 1 percent of the population with an annual incidence of apporoximately 3 per 1000[1]. The prognosis of congestive heart failure is relatively poor[2,3]. Vasodilator

therapy for severe CHF induces hemodynamic effects that are believed to be beneficial and it has become widely accepted during the past decade[4-7]. Of the vasodilators, the angiotensin -converting enzyme (ACE) inhibitors appear to be the most promising.

The left ventricle begins to dilate soon after myocardial infarction, and in the acute phase, such chamber enlargament is caused primarily by expansion of the infarct. However lengthening of the zone without an infarct also contributes to the overall increase in ventricular size[8-10]. During the late convalescent phase that follows myocardial infarction (after healing of the infarct region), enlargement of the ventricular chamber continues, and depends on the size of the infarct[11-15]. This time dependent further increase in ventricular cavitary size has deterimental effects on ventricular pump function. The clinical presentation of this depressed ventricular performance is decreased exercise tolerance and poor life quality.

The objective of the present study is to determine whether ACE inhibitor enalapril therapy improves exercise capacity in patients with severe left ventricular dysfunction in the more chronic phases of coronary heart disease.

Patients and Methods

Thirty-six men and six women with chronic congestive heart failure due to coronary artery disease and myocardial infarction completed the study within a period of 22 months. Mean age was 53±14 years (range 21-68). Sixty-six patients entered the study but 24 of them did not complete it. Ten of them died during follow up, two underwent a coronary bypass operation, and three stopped the treatment with enalapril because of side effects. Nine other patients were also excluded; four because of active ischemia and/or arrhythmias causing termination of exercise testing and the remaining five patients chose not to participate in the trial. All patients consented to undergo baseline and control catheterization. Inclusion criteria were cardiac failure class III-IV (NYHA), and a left ventricular ejection fraction less than 40% at rest, as measured by left ventriculography. Stable angina and mild mitral regurgitation secondary to ventricular dilatation or papillary muscle dysfunction were not a reason for exclusion. Exclusion criteria were severe hypertension, diabetes mellitus, chronic renal failure, valvular or congenital heart disease and myocardial infarction less than four months before.

All patients underwent randomization. The first dose of study medication (2.5 mg enalapril) was administered in a blinded fashion (to patients with odd numbers) and titrated to an in hospital maximal tolarable dose (average 20 mg/day). Prior medication was continued througout the study. All patients were taking digitalis. Other drugs that had been given to patients were long acting nitrates, diuretic and anti-arrhythmic agents. (Table 1). Ambulatory visits were conducted, weekly in the first month, monthly in the first 6 mounths and every 2 months thereafter.

Maximal symtom limited treadmill exercise tests were performed according to a modified Noughton protocol (Appendix). All patients were undergone treadmill exercise testing at base line; between 4th and 6th months of treatment and between 16th and 19th months of treatment. Exercise capacity was assesed by comparing the duration of exercise in patients who performed exercise tests with no limitations atributed to myocardial ischemia and/or arrhythmia.

All patients were admitted to the cardiology ward once before treatment and again between 4th and 6th months of treatment. During each admission a left heart catheterization was performed to determine left ventricular volume and pressure. A 7F Cordis pigtail catheter was introduced percutaneously into the femoral artery and advanced into the left ventricle. It was used for left ventricular angiography and simultaneous pressure measurements. Left ventricular angiograms were filmed in two directions the 30° right anterior oblique and the 60° left anterior oblique positions. Left ventricular end-diastolic and end-systolic volumes were estimated by single-plane method from 30° right anterior oblique position[16,17]. Correction for magnification and for pincushion distorsion was carried out with calibrated gride[18]. Left ventricular volume indices were

Table 1. Baseline clinical characteristics of patients in the two treatment groups.

Characteristics	Treatment Group	
	Group A (n= 23)	Group B (n= 19)
Age (yr) (±SEM)	51±13	54±6
Gender (no of patients)		
Male	19	17
Female	4	2
Blood pressure (mmHg) (±SEM)		
Systolic	136±17	132±9
Diastolic	83±13	82±8
Heart rate (beats/min)	96±13	91±7
Current smoking (no of patients)	11	11
Hypertension	—	—
Diabetes Mellitus	—	—
Renal failure	—	—
Drug therapy (no of patients)		
Digitalis	23	19
Diuretic	18	15
Anti-arrhytmic	5	4
Long-acting nitrate	14	11
Duration of heart failure (month)		
< 12	21	18
> 12	2	1

calculated according to patients body surface area. For statistical analysis, student- t test was used.

Results

Of the 42 consenting eligible patients, 23 were randomly assigned to enalapril (Group A) and 19 to conventional therapy (Group B). The clinical characteristics of the two groups were comparable at baseline (Table 1). Patients with severe hypertension, diabetes mellitus, chronic renal failure and valvular heart disease were excluded; hence factors that could be operative in ventricular dilation and exercise capacity were minimized in both groups. Medication other than enalapril were similar in two groups. Baseline systemic arterial pressure, heart rate, left heart filling pressure and volume indices were similar in two groups. (Tables 1 and 2) All patients underwent repeat catheterization and followed by regular ambulatory visits. In both groups (Group A, B) mean arterial pressure and heart rate did not change significantly during follow-up (127 ± 11/77±10; 131±12/80±8 mmHg and 90±14, 87±9 beats/min). In group B patients filling pressures, end-systolic and end-diastolic volume indices did not change significantly between baseline and follow-up (25±7 to 23±5 mmHg; 81±13, 123±16 to 84±17, 127±21 ml/m^2, respectively). In contrast, patients treated with enalapril had a reduction in filling pressure from their baseline levels, end-diastolic pressure decreased from 25±7 to 18±6 mmHg($p< 0.05$). Similarly, end-systolic and end-diastolic volume indices reduced in group A from 86±20, 122±28 to 79±21, 117±29 ml/m^2, respectively) and it was statistically significant for end-systolic volume ($p< 0.05$).

Table 2. Findings of pre-treatment left heart catheterization

	Group A (n= 23)	Group B (n= 19)
Sistolic (±SEM) Volume indexes (ml/m^2)	86±20	81±13
Diastolic (±SEM) Volume indexes (ml/m^2)	122±28	123±16
Ejection fraction (%)	30±6	33±8
Mitral regurgitation (No. of patients)		
1+	3	2
2+	1	±
Left ventricular end diastolic pressure (mmHg)	25±6	25±7

Comparison of the change in ejection fraction values revealed no statistically significant difference for group A and B (30±6 to 32±6 and 33±8 to 33±12, respectively).

Fourty-two patients participated in all three scheduled exercise studies. As quoted before, there were no statistically significant differences between the treatment groups at baseline clinical, hemodynamic or quantitative ventriculographic variables. At baseline exercise duration was 352±164 seconds for patients treated with enalapril (Group A) and 376±142 seconds for group B. At baseline both group had a capacity of similar metabolic equivalents (METS) (3.3± 1.1 METS for group A and 3.5±1 METS for group B).

The exercise duration in the enalapril group consistently exceded that in group B at 6 and 18 months ($p< 0.05$). (Figure 1). There was prolongation of exercise duration in the enalapril -treated patients, from 352±164 sec. at baseline to 442±125 sec. at 6th month and to 399±116 sec at 18th month, and differences were statistically significant ($p< 0.05$). There was a slight reduction of exercise duration in group B patients from 376±142 sec. at baseline to 343±146 sec. at 6th month and to 296±118 sec. at 18th month. The reduction was statistically significant at 18th month ($p< 0.05$)

Discussion

Expansion of the infarct during the acute phase of myocardial infarction has been described as thinning and dilatation of the necrotic zone, resulting in enlargament of the ventricular chamber[8,9]. However, data from both clinical and experimental studies suggest that the myocardium without an infarct is also involved in the overall pattern of enlargement of the left ventricular chamber[10,12-14]. It has been postulated that ventricular dilatation must occur if twenty percent or more of contractile myocardium is lost, in order to restore, stroke volume[19]. The increase in ventricular volume during the first two weeks after myocardial infarction has been associated with a restoration of systemic hemodynamic function, including an improvement in stroke volume and a reduction in ventricular filling pressure[10,20].

Although early cavitary enlargement tends to restore normal or nearly normal systemic hemodynamic function it has shown that ventricular dilatation is a progressive process in the more chronic phases of infarction and a further increase in ventricular cavitary size has detrimental effects on ventricular performance [11,13]. In the chronic phase, patients with infarctions that produced extensive wall motion abnormality often had ventricular volumes that

Appendix Modified Naughton Protocol

Stage	Speed (mph)	Grade (%)	Duration (Min:sec)	Mets
Rest/Recov	1.0	0.0	—	1.8
1	1.0	0.0	2:00	1.8
2	2.0	0.0	2:00	2.5
3	2.0	3.5	2:00	3.4
4	2.0	7.0	2:00	4.4
5	2.0	10.5	2:00	5.3
6	2.0	14.0	2:00	6.3
7	2.0	17.5	2:00	7.3

were two to three times greater than normal [21,22]. Indeed, data from the Framingham study indicate that the development of the clinical syndrome of congestive heart failure increases progressively during a ten-year period after myocardial infarction[23]. These anatomic and hemodynamic alterations give rise to reductions in exercise capacity and have detrimental effects on quality of life.

The addition of an angiotensin converting enzyme inhibitor such as enalapril to the conventional treatment of rest, salt restriction and a diuretic has become an established approach in the treatment of patients with severe congestive cardiac failure. We found longer exercise duration in the enalapril treated patients and the difference was statisticaly significant. The two treatment groups were well

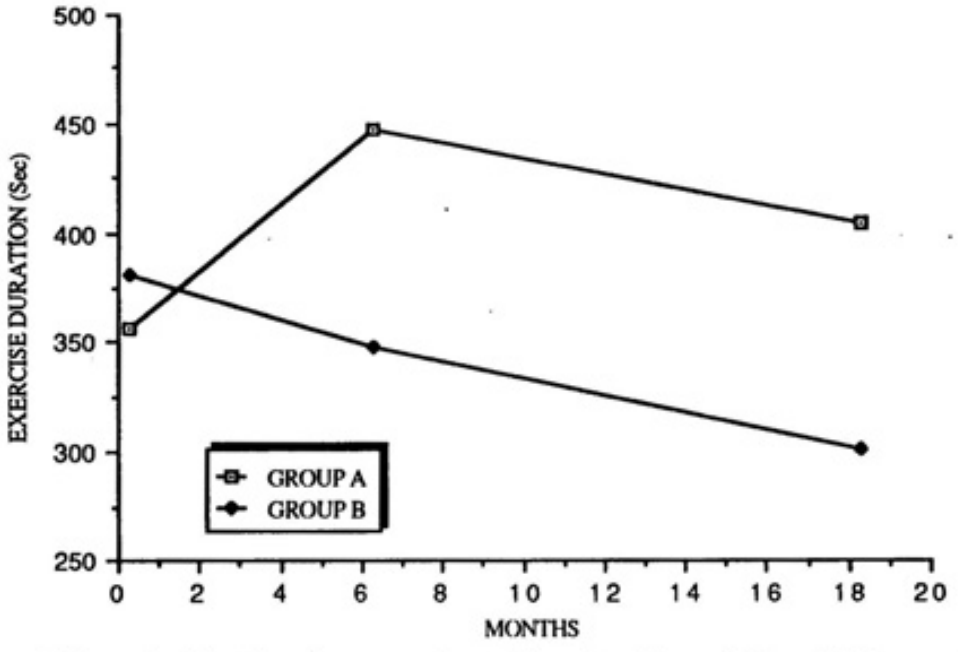

Figure 1:Exercise durations for group A and B at base-line,at 6th and 18th months of treatment

matched for base-line left ventricular dysfunction, nevertheless the enalapril treated patients exercised approximately 100 seconds longer then the patients who were treated conventionally at 6th at 18th months. Both pre-treatment and post-treatment avarage exercise duration of the two groups were under 8 minutes and were almost the same with that reported in patients with congestive heart failure [24-29].

Although the post-treatment exercise duration in enalapril treated patients were still extremely low it was significantly higher than the pre-treatment levels. This difference lasted for a relatively long period (up to 18 months). As in other reported studies, these finding indicated that the clinical condition of the patients improved and their exercise tolerance increased [25, 26, 28, 29].

The beneficial effects of angiotensin converting enzyme inhibition on exercise tolerance is due probably to several factors. The prolongation of exercise duration in the enalapril treated patients may reflect an increase in the functional reserve capacity of a reduced ventricular volume with lower filling pressure due to unloading of the heart[15,28,30,31]. Moreover, it is obvious that the observed improvement in exercise tolerance is due not only to better pump function but also to a more efficient distribution of the peripheral circulation. A newer concept, "remodelling" of the heart contributes to improvement of pump function of left ventricle[32]. Remodelling of the heart will occur only if the heart is unloaded while the plazma concentrations of angiotensin II are simultanously reduced[33]. Treatment with a vasodilator that unloads the heart but activates the renin-angiotensin aldosterone system did not reduce heart size[34]. Unloading of the heart may have a beneficial effect on its metabolism by reducing oxygen consumption.

In conclusion, whatever the operating mechanism, this study indicated that angiotensin converting enzyme inhibition can improve the clinical condition of patients and increase their exercise tolerance and should be used as a standart medication in the treatment of congestive heart failure.

References

1- McFate Smith W: Epidemiology of congestive heart failure. Am J Cardiol 1985: 55: Suppl A; 3A-8A

2- The SOLVD ınvestigators: Studies of left ventricular dysfunction (SOLVD) -Rationale, desing and methods: Two trials that evaluate the effect of enalapril in patients with reduced ejection fraction. Am J Cardiol 1990: 66;315-318

3- Applefeld MM: Chronic congestive heart failure:Where have we been?Where are we heading? Am J Med 1986: 80;Suppl 2B:73

4- Chatterjee K,Parmley W W, Massie B, et al: Oral hydralazine therapy for chronic refractory heart failure.Circulation 1976: 54;879-884

5- Levine TB: Role of vasodilators in the treatment of congestive heart failure. Am J Cardiol 1985: 55:Suppl A; 32A-35A

6- Braunwald E, Colucci WS:Vasodilator therapy of heart failure:has the promissory note have been paid:N Engl J Med 1984: 310;459-463

7- Abrams J:Vasodilatory therapy for chronic congestive heart failure:JAMA 1985: 254;3070-3075

8- Hutchins GM,Bulkley BH: Infarct expansion versus extension:two different complications of acute myocardial infarction Am J Cardiol 1978: 41;1127-1135

9- Eaton LW,Weiss JL,Bulkley BH: Garrison JB,Weisfeldt ML:Regional cardiac dilatation after acute myocardial infarction:recognition by two dimentional echocardiography N Engl J Med 1979: 300; 57-62

10- McKay RG,Pfeffer MA,Pasternak RC, et al: Left ventricular remodelling after myocardial infarction:a corollary to infarct expansion.Circulation 1986:74;693-696

11- Pfeffer MA,Pfeffer JM:Ventricular enlargement and reduced survival after myocardial infarction.Circulation 1987: 75:Suppl IV; IV 93-97

12- Weisman HF,Bush DE,Manissi JA, Bulkley BH: Global cardiac remodelling after acute myocardial infarction: a study in the

rat model.J Am Coll Cardiol 1985: 5;1355-1359
13- Erlebacher JA,Weiss JL,Eaton LW, Kallman I ,Weisfeldt ML,Bulkley BH:Late effects of acute infarct dilation on heart size:a two dimentional echocardiographic study. Am J Cardiol 1982: 49;1120-1124
14- Anversa P,Loud AV,Levicky V,Guideri G:Left ventricular failure induced by myocardial infarction.I.Myocyte Hypertrophy.Am J Physiol 1985: 248;H876
15- Pfeffer MA,Lamas GA,Vaughan DE,Parisi AF,Braunwald E:Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction.N Engl J Med 1988: 319;80-85
16- Greene DG,Carlisle R,Grant C,Bunnel IL:Estimation of left ventricular volume by one-plane cineangiography Circulation 1967: 35;61-65
17- Sandler H, Dodge HT:The use of single-plane angiocardiograms for the calculation of left ventricular volume in man.Am Heart J 1968: 75;325-328
18- Kasser IS, Kennedy JW:Measurement of left ventricular volumes in man by single-plane cineangiography. Invest Radiol 1969: 4; 83-88
19- Herman MV,Gorlin R:Implications of left ventricular asynergy.Am J Cardiol 1969: 23; 538-542
20- Gaudron PJ,Eilles C,Ertl G:Subacute adaptation to loss of contractile myocardium by left ventricular dilatation (remodilling) in patientswith myocardial infarction: Circulation1987: 76;Suppl IV:IV-402-408
21- Kitamura A,Kay JH,Krahn BG, Magidson O, Dunne EF:Geometric and functional abnormalities of the left ventricule with a chronic localized non-contractile area. Am J Cardiol 1973: 31;701-707
22- Lamas GA,Pfeffer MA:Increased left ventricular volume following myocardial infarction in man.Am Heart J 1986: 111; 30-38
23- Kannel WB,Sorlie P,McNamara PM: Prognosis after initial myocardial infarction:the Framingham study. Am J Cardiol 1979: 44;53-57
24- Franciosa JA: Exercise testing in chronic congestive heart failure. Am J Cardiol 1984: 53; 1447-1451
25- Captopril Multicenter Research Group: A placebo controlled trial of captopril in refractory chronic congestive heart failure. J Am Coll Cardiol 1983: 2;755-761
26- The Captopril-Digoxin Multicenter Research Group: Comperative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure JAMA 1988: 259; 539-547
27- Bruce RA: Exercise testing for evaluation of ventricular function. N Engl J Med 1977: 296;671-677
28- Sharpe DN: Enalapril in patients with chronic congestive heart failure: a placebo controlled randomized double blind study. Circulation 1984: 70; 271-276
29- Franciosa JA: Effects of enarapril a new angiotensin converting enzyme inhibitor in a controlled trial in heart failure. J Am Coll Cardiol 1985: 5;101-107
30- Sharpe N,Smith H, Murfhy J,Hennan S: Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. Lancet 1988: 1; 255-258
31- Kramer EP:Effectiveness of converting enzyme inhibition (enalapril) for mild congestive heart failure. Am J Cardiol 1986: 57; 459-464
32- Weber KT, Janicki JS: Angiotensin and the sevedalling of the myocardium Br J Clin Pharmacol 1989: 28; 141-145
33- Baur LHB, Schipperheyn JJ, Baan J, Laarse A, Buis B et al:Influence of angiotensin corverting enzyme inhibition on pump function and cardiac contractility in patients with chronic congestive heart failure. Br. Heart J 1991: 65;137-142
34- Raya TE, Gay RG,Aguirre M, Goldman S: Importance of venodilation in prevention of left ventricular dilatation after chronic large myocardial infarction in rats: a comparison of captopril and hydralazine.Circ Res 1989: 64;330-337