EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITION ON MORTALITY IN PATIENTS WITH SEVERE CONGESTIVE HEART FAILURE DUE TO CORONARY HEART DISEASE

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Fifty-six patients with chronic congestive heart failure (NYHA Class III-IV) caused by coronary artery disease were studied within a period of twenty- two months. Enalapril was administered randomly to 31 of them who had been already given digitalis and diuretics (Group A). Twenty-five patients were continued to their perior medication throughout the study (Group B).

For baseline charecterization and follow-up, ventricular volume and volume index, ejection fraction, left ventricular end diastolic pressure and effort capacity were evaluated by left heart catheterization and maximal symptom limited exercise tests. There were five deaths among 31 group A patints compared to five among 25 group B patients. The difference was statistically insignificant.

This study indicated that angiotensin converting enzyme inhibition can improve the clinical condition of patients with chronic congestive heart failure but life expectancy does not differ significantly.

Key words: Angiotensin converting enzyme, congestive heart failure.

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 mortality among CHF patients is reported to be between 10 and 50%/year[2,3]. The median survival for individuals in the Framingham Study with newly diagnosed CHF was between 2 and 4 years (4). Worldwide the number of deaths may be between 1 and 2 million/year.

Despite the use of digitalis and diuretic in patients with overt CHF the outlook continues to be grim, with a median survival often measured in months rather than years[5,6]. After the introduction of vasodilator therapy, as a component of CHF, treatment it was shown that there are beneficial effects on its symptomatology. Of the vasodilators, the angiotensin-converting enzyme inhibitors appear to be the most promising since they relieve symptoms, diminish cardiac dilatation after myocardial infarction and improve exercise capacity in controlled, randomized double blind studies[7-11]. On the other hand, the effect of these agents on survival in CHF, however is equivocal.

Present study was designed to evaluate the effect of angiotensin converting enzyme inhibitor, enalapril on mortality as compared with conventional therapy in severe CHF.

Patients and Methods

Forty-seven men and nine women with chronic congestive failure caused by coronary artery heart disease and myocardial infarction completed the study within a period of 22 months. Mean age was 53±15 years (range 21-68 years). Sixty-six patients entered the study but 10 of them did not complete the study. Two underwent a coronary bypass operation, three stopped the treatment with enalapril because of side effects and five patients could not be followed-up. 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. Mild mitral regurgitation secondary to ventricular dilatation or papillary muscle dysfunction were not a reason for exclusion. Exculusion criteria were severe hypertension, diabetes mellitus, chronic renal failure, valvular or congenital heart disease and myocardial infarction less than four months before.

All patients urderwent randomization. The first dose of study medication (2.5 mg enalpril) was administered in a blinded fashion to an inhospital maximal tolerable dose (average: 20 mg/day). Prior medication was continued througout the study. All patients were taking digitalis. Other drugs that have 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. Exercise tests were reperated at sixth and 18th (average) months.

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. 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[12,13]. Left ventricular volume indices were calculated according to the patients body surface area. For statistical analysis student- t test, Kaplan-Meier survival curves and log-rank chi-square tests were used.

Results

Of the 56 consenting eligible patients, 31 were randomly assigned to enalapril (Group A) and 25 to conventional therapy (Group B). The clinical characteristics of the two groups were comparable at baseline (Table 1). By excluding patients with severe hypertension, diabetes mellitus, chronic renal failure and valvar heart

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

Characteristics	Treatment Group	
	Group A (n= 31)	Group B (n= 25)
Age (yr) (±SEM)	52±12	54±8
Gender (no of patients)		
Male	25	22
Female	6	3
Blood pressure (mmHg) (±SEM)		
Systolic	131±16	130±10
Diastolic	84±13	82±9
Heart rate (beats/min)	93±16	91±9
Current smoking (no of patients)	15	13
Hypertension	—	—
Diabetes Mellitus	—	—
Renal failure	—	—
Drug therapy (no of patients)		
Digitalis	31	25
Diuretic	24	19
Anti-arrhytmic	6	4
Long-acting nitrate	18	15
Duration of heart failure (month)		
< 12	28	24
> 12	3	1

disease; factors that could be operative in ventricular dilation and hence exercise capacity were tried to minimize 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 (126 ± 13/77±11; 131±14/79±9 mmHg and 89±15, 89±11 beats/min respectively). In group B patients filling pressures, end-systolic and end-diastolic volum indices did not change significantly between baseline and follow-up (25±6 to 23±5 mmHg; 82±13, 122±15 to 85±16, 126±20 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 26±7 to 19±6 mmHg($p< 0.05$). Similarly, end-systolic and end-diastolic volume indices reduced in group A from 86±19, 119±26 to 79±18, 115±26 ml/m^2, respectively) and the difference was significant for end-systolic volume index ($p< 0.05$).

Comparison of the change in ejection fraction values revealed no statistically significant difference for group A and B (29±5 to 31±6 and 32±6 to 32±11, respectively).

At baseline exercise duration was similar in the two treatment groups (359±142 seconds and 371±152 seconds for group A and B, respectively). At sixth month these values were 434±135 seconds and 348±144 seconds respectively.

As quoted before, there were no statistically significant differances between the threatment groups at baseline clinical hemodynamic and quantitative ventriculographic variables.

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±19	82±13
Diastolic (±SEM)		
Volume indexes (ml/m^2)	119±26	122±15
Ejection fraction (%)	29±5	32±6
Mitral regurgitation (No. of patients)		
1+	5	3
2+	1	±
Left ventricular end diastolic pressure (mmHg)	26±7	25±6

During follow-up period (average: 18 months), there were five deaths in each group (Total 10 deaths). In group A patients deaths occured at third, seventh, eighth, nineth and fourteenth months of treatment. In group B patients deaths occured at seventh (2 patients), nineth, tenth and thirteenth months of follow-up. At baseline 4 of the 5 patients were in NYHA functional class IV, in group A and 2 of the 5 patients were in NYHA functional class IV in group B; remaining patients were in NYHA functional class III. As shown in Figure 1 there was no difference in the survival rate between the two treatment groups (Figure 1).

Discussion

Congestive heart failure is a serious and relatively common condition with a high mortality rate (1-4,14). It was believed that patients with advanced heart failure are so ill and have such extensive myocardial damage that no important prolangation of survival by any medical treatment can be expected. The recognition that patients with CHF often have elavated peripheral vascular resistance has led to the introduction of vasodilator therapy, which has emerged as an important component of its treatment. Symtomatic improvement of CHF by addition of ACE inhibitors has been demonstrated in numereous studies (7-11). The positive influence of ACE inhibitors on CHF pathophysiology and symptomatology might favorably affect the prognosis, as well. In 1985 an overview of several small short-term randomized trials about the impact of any long-term drug treatment with ACE inhibitors on survival; suggested a favorable trend toward a lover mortality but the data were too limited to allow reliable conclusions. In 1987 the results of the Cooperative North Scandinavian Enalapril Survival Study (16) (CONSENSUS) showed that enalapril given to patients with severe congestive heart failure was associated with a considerable reduction in mortality. This trial was stopped after 253 of the 400 planned patients were enrolled because of a significant decrease in 6 month mortality in the enalapril group. It is likely that the study was stopped at a time when the results were exaggerated, so that it is possible that the real effect may well be more modest. In this trial 102 patients followed beyond 1 year and the proportion of deaths after the first 3 months appeared to be similar in the enalapril and control groups. Therefore, data on long-term effects of ACE inhibitors on mortality beyond 6 months are lacking. On the other hand patient selection was based on clinical and radiologic criteria at base-line, and for this reason it is debatable that the two treatment groups were

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

well matched. Both survival and ventricular enlargement trial (SAVE) (17) and studies of left ventricular dysfunction (SOLVD)[2,18] have rendomized a lot of patients and found statistical difference between the treatment groups. The risk reduction was 19 percent in SAVE and 16 percent in SOLVD study. In CONSENSUS trial 50 percent risk reduction was in patients with NYHA functional class IV but in SOLVD trial there were more deaths in the enalapril group among those with ejection fractions of 0.30 to 0.35 and among those in

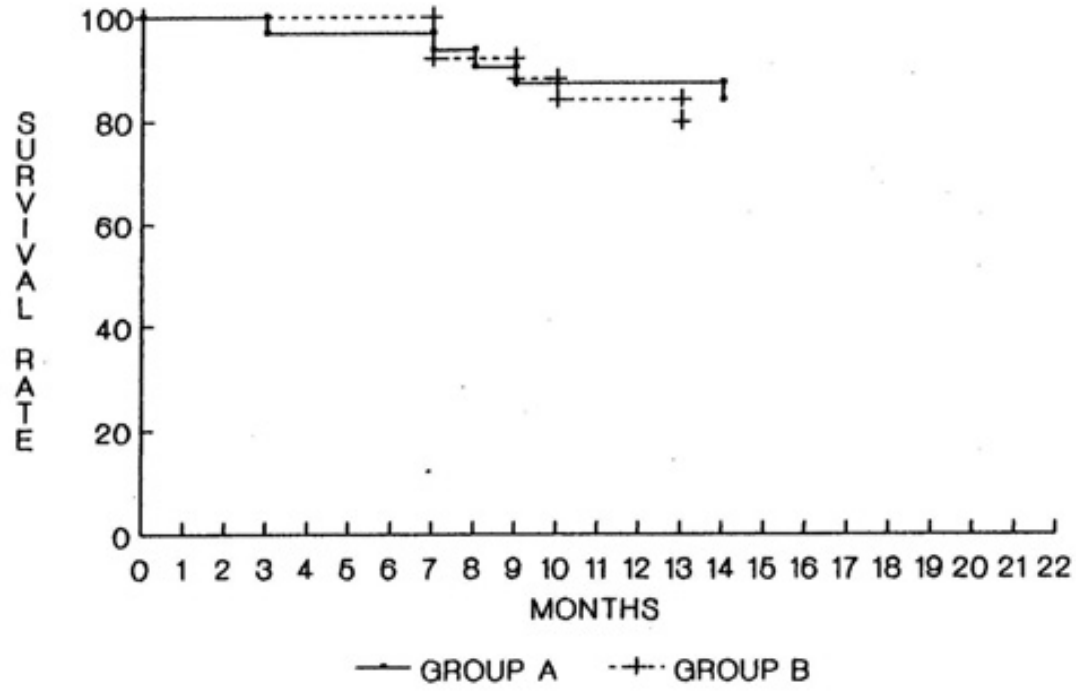

Fig 1: Survival rates of the two treatment groups.

NYHA functional class IV. On the other hand, of the patients alive after 24 months, those receiving placebo and those treated with enalapril had the same montality rate.

In the present study the two treatment groups are well matched at baseline by means of more objective criteria such as left heart cathaterization, left ventriculography and maximal symptom limited exercise tests. More over the ethiologic factor for CHF was CHD for all patients in the two treatment groups. As in other reported studies follow-up showed that the clinical condition of the enalapril treated patients improved, exercise tolerance increased and ventricular volumes decreased significanly. In view of these findings we aticipated a lower mortality rate in the enalapril treated patients but the statistical analysis demonstrate no difference between the two treatment groups.There were 5 deaths out of 31 patients in enalapril group and 5 deaths out of 25 patients in group B; demonstrating a trend toward a lower mortality following the ACE inhibitor therapy, which however did not reach statistical significance.

In summary we conclude that there are beneficial effects of ACE inhibitors on symptomatology and effort capacity in patients with congestive heart failure and as a result quality of life is better; but the effect on survival may well be more modest.

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