Cilazapril Treatment in a Cohort of Seven Patients with Congestive Heart Failure: A Seven-Year Follow-Up Study

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ABSTRACT

Background: Although angiotensin-converting enzyme inhibitors (ACEIs) have been shown to prolong life in patients with congestive heart failure (CHF), the prognosis of these patients remains poor.

Objective: The purpose of the study was to reevaluate a cohort of patients with CHF after 7 years of follow-up with cilazapril therapy to assess the renin-angiotensin system (RAS), anatomic and functional capacity of the heart, and aldosterone escape.

Methods: Surviving patients from a cohort hospitalized for CHF between January 1994 and December 1994 who were treated with cilazapril in our center were included in this study. Exercise testing was carried out using the Kattus protocol, and breath-by-breath oxygen analysis, echocardiography, and hormonal analysis were done.

Results: Seven patients (5 men, 2 women; mean [SD] age, 70.6 [4.4]) were included in the study. Compared with the early effects (at 15 days) of cilazapril therapy, only mean (SD) peak exercise time decreased significantly at the 7-year follow-up (8.9 [2.4] minutes vs 5.1 [1.9] minutes; $P = 0.02$). Mean (SD) anaerobic threshold (AT) oxygen consumption and AT ratio increased slightly from 15 days, although these changes were not statistically significant (12.86 [3.5] mL/kg · min vs 13.57 [2.6] mL/kg · min; 70.3% [7.7%] vs 78.9% [9.8%], respectively). Compared with the early effect of therapy, patients had slightly lower mean (SD) ejection fractions (EFs), but the decrease did not reach statistical significance (52% [4%] vs 48% [4%]). Aldosterone levels were within normal limits in all patients, and 2 patients had increased RAS activity.

Conclusions: In this study, the observed lack of aldosterone escape, as well as patient survival during ACEI therapy, may be due to selection bias of the surviving patients, who had better EFs and lack of aldosterone escape.

Therefore, the remaining issue seems to be the selection of patients who will not show aldosterone escape during chronic ACEI treatment. (*Curr Ther Res Clin Exp.* 2003;64:167–175) Copyright © 2003 Excerpta Medica, Inc.

Key words: cilazapril, congestive heart failure, long-term follow-up.

INTRODUCTION

Large, randomized studies^{1,2} have shown that angiotensin-converting enzyme inhibitors (ACEIs) prolong life in patients with congestive heart failure (CHF) and appear to be useful in patients at risk for cardiovascular events and those with diabetes mellitus.³ However, despite the ability to prolong life in patients with CHF, the prognosis of these patients remains poor. Data from other large, randomized studies^{4,5} also indicate that major determinants of CHF progression are increased renin-angiotensin system (RAS) activity and activation of the sympathetic nervous system. Several studies^{6,7} reported loss of potency for RAS inhibition during long-term therapy with ACEIs in CHF, even when used at the highest recommended doses.⁸ Some data⁹ indicate that this escape phenomenon can become apparent as soon as 1 year after treatment.

The purpose of this study was to reevaluate survivors of a cohort of patients with CHF after 7 years of follow-up with cilazapril therapy to assess the RAS, functional and anatomic capacity of the heart, and aldosterone escape.

PATIENTS AND METHODS

The survivors of the cohort of patients who had been hospitalized for CHF in our center (Cardiovascular Diseases Research Center, Istanbul, Turkey) between January 1994 and December 1994 and who had been treated with cilazapril at the same center were included in this study. After the termination of the study, patients were followed up outside the study protocol at 3-month intervals at the center's outpatient clinic. After 7 years of follow-up, the patients' records were extracted from the files and the surviving patients were reassessed for changes in the anatomic and functional capacity of the heart and for aldosterone escape. Coronary angiography and endomyocardial biopsy were used to verify all diagnoses of cardiac conditions.

Written informed consent was obtained from all patients. Declaration of Helsinki guidelines¹⁰ for physicians performing biomedical research involving human subjects were followed.

Exercise Testing

Exercise testing was carried out using a Quinton 5000® exercise system (SunTech Medical Instruments, Raleigh, North Carolina) and the Kattus protocol,¹¹ which progresses in 1-MET (minimum activity at which CHF symptoms appear) increments. At the end of each stage, heart rate (HR); blood pressure

(BP); and, for ischemic patients, the deepest ST-segment depression and its derivation were recorded. Breath-by-breath oxygen analysis was carried out using the SensorMedics 2900 metabolic measurement system (SensorMedics, Yorba Linda, California). Spirometric examination was done using the Sensor Medics 2400 respiratory function system (SensorMedics). Ten-second averages were used to calculate breath-by-breath oxygen consumption (VO_2). For the entire test, total exercise and anaerobic threshold (AT) times; peak and AT VO_2 ; and resting, AT, and peak HR were recorded.

Echocardiography

Echocardiographic examination was carried out on a Hewlett-Packard Sonos 1000 (Hewlett-Packard Co., Palo Alto, California) echocardiography system using a 2.5-MHz probe according to the standards of the American Society of Echocardiography.^{12,13}

Hormonal Analysis

Hormonal analysis was carried out after an overnight fast. After 2 hours of bed rest, an antecubital vein was catheterized; 45 minutes later, blood samples were drawn to measure plasma renin activity and plasma aldosterone concentration. Samples were collected and kept on ice, as described elsewhere.¹⁴ The tubes were centrifuged (3000 rpm) at -4°C , and the plasma was frozen at -30°C until assayed.

Statistical Analysis

On statistical analysis, all numeric variables are expressed as mean (SD). Numeric variables were compared using the Student *t* test. $P < 0.05$ was considered significant.

RESULTS

The characteristics and early findings during cilazapril treatment of the patients in this study have been reported elsewhere.¹⁵ Briefly, the mean (SD) age of our cohort of 20 patients (17 men, 3 women) was 66.7 (9.4) years (range, 49 to 88 years) (Table I). Sixteen patients had ischemic CHF, 3 had idiopathic dilated cardiomyopathy, and 1 had alcoholic cardiomyopathy. The mean duration of CHF was 7.8 (2.2) years.

Nine patients (45%; 8 men, 1 woman) died. Of these, 4 died suddenly and 1 each died of cerebrovascular accident, sepsis, pulmonary embolism, abdominal aortic aneurysm rupture, and CHF progression. Three of these 9 patients had diabetes mellitus and 3 had atrial fibrillation. All 9 patients had relatively lower ejection fractions (EFs) than did the survivors.

Two of the 11 patients who survived were lost to follow-up, 1 of whom was known to have survived a recurrence of myocardial infarction and stent implantation 1 month previously.

Patient No.	Sex and Age, y	Duration of Treatment, y	EF, %	CHF Type	Concomitant Diseases or Conditions	AI Level, ng/mL	Aldosterone Level, pg/mL	Cilazapril Dose, mg	Status at 7-Year Follow-Up
1	M, 61	10	36	Alcoholic	AF	N/A	N/A	2.5	Cerebrovascular death
2	M, 51	3	30	Ischemic	DM	N/A	N/A	2.5	Sudden death
3	M, 63	11	40	Ischemic	DM	N/A	N/A	2.5	Diabetic foot sepsis death
4	M, 67	7	23	Ischemic	AF	N/A	N/A	2.5	Sudden death
5	M, 58	6	17	Ischemic	DM	N/A	N/A	2.5	CHF progression death
6	M, 56	10	42	Ischemic	–	N/A	N/A	2.5	Sudden death
7	F, 74	7	44	Ischemic	–	N/A	N/A	2.5	Pulmonary embolism death
8	M, 88	10	53	Ischemic	AF	N/A	N/A	2.5	Sudden death
9	M, 71	3	47	Ischemic	AAA	N/A	N/A	2.5	Aneurysm rupture death
10	M, 59	6	36	Ischemic	–	N/A	N/A	2.5	Lost to follow-up last year
11	M, 77	7	53	Dilated	PrCa	N/A	N/A	2.5	Suprapubic catheter
12	M, 60	9	54	Ischemic	DM, CABG	N/A	N/A	2.5	Dialysis
13*	M, 49	7	57	Ischemic	–	N/A	N/A	2.5	Coronary stent implantation
14	M, 67	9	55–38	Dilated	AF	1.1	256.5	5.0 + HCT 12.5 mg	Alive
15	M, 68	8	39–45	Ischemic	COPD, CABG	13.4	109.7	2.5	Alive
16	M, 73	9	57–56	Ischemic	PuCa, DM	2.7	193.4	2.5	Alive
17	M, 68	7	63–33	Ischemic	MDS, DM	0.4	27.1	2.5	Alive
18	M, 77	9	50–48	Ischemic	–	4.2	158.6	2.5	Alive
19	F, 75	8	39–58	Dilated	DM	3.8	60.0	5.0 + HCT 12.5 mg	Alive
20	F, 66	9	62–58	Ischemic	CABG	12.8	76.3	5.0 + HCT 12.5 mg	Alive

EF = ejection fraction; CHF = congestive heart failure; AI = angiotensin I; M = male; AF = atrial fibrillation; N/A = not available; DM = diabetes mellitus; F = female; AAA = abdominal aortic aneurysm; PrCa = prostate cancer; CABG = coronary artery bypass grafting; HCT = hydrochlorothiazide; COPD = chronic obstructive pulmonary disease; PuCa = pulmonary cancer; MDS = myelodysplastic syndrome.
 *This patient could not be followed up regularly because he lived far from the study site.

Two of the 9 remaining patients were excluded: 1 had been receiving dialysis 3 times a week for the previous 2 years, and the other had been diagnosed with prostate cancer and had a suprapubic catheter. Of the 20 patients in the original cohort, only 1 (the patient who died of CHF progression) had required hospitalization during the 7-year follow-up period.

Seven patients (5 men, 2 women; mean [SD] age, 70.6 [4.4] years) were included in the reevaluation. Five of these patients each had at least 1 concomitant condition (atrial fibrillation, pulmonary carcinoma, myelodysplastic syndrome, atrial fibrillation, diabetes mellitus, or chronic obstructive pulmonary disease). None of the 7 patients had obvious symptoms of CHF or were experiencing treatment-related adverse events. Only 3 of the surviving patients had needed titration of the dose from cilazapril 2.5 mg to cilazapril 5.0 mg + hydrochlorothiazide 12.5 mg due to lack of symptom relief. In addition to the ACEIs, 5 patients had also used aspirin and nitrates; 2, beta-blockers; and 1 each, spironolactone, digitalis, and an anticoagulant.

After 15 days of treatment with cilazapril 2.5 mg/d, no significant improvement in peak VO_2 or peak and AT HR was found, but peak exercise time and AT exercise time, AT VO_2 , and AT ratio increased (Table II).¹⁵ Compared with the early effect of therapy, peak exercise time decreased significantly at the 7-year reevaluation (mean [SD] from 8.9 [2.4] minutes to 5.1 [1.9] minutes; $P = 0.02$). AT VO_2 and AT ratio increased slightly, although these changes were not statistically significant (mean [SD] from 12.86 [3.5] mL/kg · min to 13.57 [2.6] mL/kg · min and from 70.3% [7.7%] to 78.9% [9.8%], respectively).

Echocardiographic analysis showed a lack of improvement in the measured parameters during the 15-day cilazapril treatment.¹⁵ Compared with the early effects of therapy, EF decreased slightly at the reevaluation, but the difference was not statistically significant (52% [4%] vs 48% [4%]).

On hormonal analysis, all patients had normal plasma aldosterone concentrations, and only 2 patients had increased plasma renin activity. Mean (SD) systolic BP was 110.4 (3.3) mm Hg, and mean diastolic BP was 77.0 (4.6) mm Hg. The mean serum potassium concentration was 4.54 (0.3) mEq/L.

DISCUSSION

Mortality and hospitalization rates in patients with CHF remain high despite advances in therapy. The annual mortality rate in France ranges from 5% to 10% in mildly symptomatic patients and from 30% to 40% in those with advanced CHF.¹⁶ In the population-based Rochester Epidemiology Project,¹⁷ survival at 1 year was 76% but at 5 years it was only 35%. The mortality rate of 45% at 7 years in our study was consistent with mortality in patients with mild CHF.

The early effect of cilazapril therapy on exercise performance was mostly on AT, which represented improved skeletal muscle performance. Treadmill time can increase after certain interventions or medications without any

Table II. Comparison of early (15 days) and late (7 years) follow-up of cilazapril treatment in the surviving patients (n = 7).¹⁵

Patient No.	Resting HR, bpm			Peak Exercise Time, min			Peak HR, bpm			Peak VO ₂ , mL/kg · min		
	Baseline	15 d	7 y	Baseline	15 d	7 y	Baseline	15 d	7 y	Baseline	15 d	7 y
14	100	90	108	9.47	11.11	5.10	185	204	207	18.91	19.27	18.53
15	120	121	115	5.40	8.53	3.25	138	142	147	14.80	16.49	13.27
16	98	93	96	4.01	5.15	4.30	132	138	126	17.63	17.88	19.55
17	62	60	97	6.15	8.30	3.57	136	143	159	12.92	17.30	14.49
18	92	76	82	10.56	12.24	7.07	124	123	117	25.13	27.32	22.66
19	63	55	56	9.28	10.15	8.25	120	100	138	14.90	13.02	16.94
20	91	84	61	7.33	7.15	4.43	137	143	113	15.17	16.14	15.32
Mean (SD)	89.4 (20.7)	82.7 (22.2)	87.8 (22.6)	7.5 (2.4)	8.9 (2.4)	5.1 (1.9)*†	138.9 (21.5)	141.8 (31.6)	143.8 (32.3)	17.1 (4.1)	18.2 (4.5)	17.2 (3.2)
Patient No.	AT HR, bpm			AT Exercise Time, min			AT Ratio, %			AT VO ₂ , mL/kg · min		
	Baseline	15 d	7 y	Baseline	15 d	7 y	Baseline	15 d	7 y	Baseline	15 d	7 y
14	175	185	185	4.15	4.30	4.01	55	59	83	10.41	11.46	15.39
15	138	133	134	3.66	6.96	2.40	68	72	89	10.09	11.87	11.88
16	121	127	112	2.00	2.37	2.10	61	78	75	10.83	13.90	14.69
17	120	115	122	1.15	2.58	0.00	74	80	62	9.53	13.80	9.00
18	97	102	104	3.20	4.50	3.49	55	71	76	13.79	19.42	17.20
19	96	80	120	6.05	6.25	5.14	58	62	76	8.65	8.13	12.90
20	134	136	109	1.66	2.28	3.20	65	70	91	9.93	11.43	13.96
Mean (SD)	125.9 (27.1)	125.4 (32.7)	126.6 (27.6)	3.1 (1.7)	4.2 (2.0)	2.9 (2.0)	62.3 (7.1)	70.3 (7.7)	78.9 (9.8)‡	10.5 (1.6)	12.86 (3.5)	13.57 (2.6)‡

HR = heart rate; AT = anaerobic threshold; VO₂ = oxygen consumption.

*P = 0.03 versus baseline.

†P = 0.02 versus 15 days.

‡P = 0.02 versus baseline.

concurrent increase in maximal VO_2 .¹⁸ The lack of concordance between peak VO_2 and exercise time is due to individual variations in mechanical efficiency in walking and VO_2 for a given workload. At the 7-year reevaluation, only peak-exercise time decreased significantly. These findings might have been due to the patients' being 7 years older and having developed concomitant diseases. Continuous activation of the RAS may have negative effects on skeletal muscle performance and hemodynamic mechanisms.¹⁹ Although not statistically significant, the increases in AT VO_2 and AT ratio may be due to continuing improvement in skeletal muscle performance.

The early and late lack of signs of improvement in exercise capacity on echocardiography in this study may be due to a lack of concordance between impaired cardiovascular function and anatomic abnormality. Some cardiac patients may have been capable of peripheral adaptations during exercise.²⁰ The relative lack of sensitivity of echocardiography in detecting the effects of subtle increases in exercise capacity might be another explanation. At the 7-year reevaluation, the decrease in EF was not statistically significant. This finding might also be due to ACE inhibition with no aldosterone escape, which has continued protective effects on the peripheral vascular system and the heart.

On hormonal analysis, all patients had normal plasma aldosterone concentrations, and only 2 had increased plasma renin activity. Unfortunately, no hormonal measurement was recorded at baseline. The Randomized Aldactone Evaluation Study²¹ concluded that aldosterone escape did occur in the cohort, which might be a reason that spironolactone therapy was effective. However, the normal BP and serum potassium concentration data may show that in surviving patients no aldosterone escape phenomenon occurs. Furthermore, the use of diuretics (3 patients) also may increase plasma renin activity, thus increasing the renin substrate for angiotensin I activation.

The first limitation of our study was the unavoidably small sample size of the surviving patients, which may have decreased the power of our conclusions. The second limitation was our inability to follow the changes in the patients during follow-up, which prevented us from making meaningful comparisons between deceased and surviving patients. A third limitation may have been the changes in drug therapy for CHF during the past decade, which caused relatively low use of beta-blockers and the use of suboptimal doses of ACEIs during follow-up. The dose was titrated to the highest recommended level in only 3 patients due to deterioration of clinical status. However, relatively low use of spironolactone was due to the mild to moderate nature of CHF in our patients.

CONCLUSIONS

In this study, the observed lack of aldosterone escape, as well as patient survival during ACEI therapy, may be due to selection bias of the surviving patients, who had better EFs and lack of aldosterone escape. Therefore, the remaining

issue seems to be the selection of patients who will not show aldosterone escape during chronic ACEI treatment.

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REFERENCES

1. Effects of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med.* 1987;316:429–435.
2. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med.* 1991;325:293–302.
3. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med.* 2000;342:145–153.
4. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med.* 1984;311:819–823.
5. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. *Circulation.* 1990;82:1730–1736.
6. Benedict CR, Francis GS, Shelton B, et al. Effect of long-term enalapril therapy on neurohormones in patients with left ventricular dysfunction. SOLVD Investigators. *Am J Cardiol.* 1995;75:1151–1157.
7. Struthers AD. Aldosterone escape during ACE inhibitor therapy in chronic heart failure. *Eur Heart J.* 1995;16(Suppl N):103–106.
8. Roig E, Perez-Villa F, Morales M, et al. Clinical implications of increased plasma angiotensin II despite ACE inhibitor therapy in patients with congestive heart failure. *Eur Heart J.* 2000;21:53–57.
9. St John Sutton M, Pfeffer MA, Moye L, et al. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: Baseline predictors and impact of long-term use of captopril: Information from the Survival and Ventricular Enlargement (SAVE) trial. *Circulation.* 1997;96:3294–3299.
10. Declaration of Helsinki. Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects. 41st World Medical Assembly; September 1989; Hong Kong.
11. Zohman LR, Young JL, Kattus AA. Treadmill walking protocol for the diagnostic evaluation and exercise programming of cardiac patients. *Am J Cardiol.* 1993;51:1081–1085.
12. Henry WL, DeMaria A, Gramiak R, et al. Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-Dimensional Echocardiography. *Circulation.* 1980;62:212–217.
13. Sahn DJ, De Maria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation.* 1978;58:1072–1083.

14. Jimenez W, Gutkowska J, Gines P, et al. Molecular forms and biological activity of atrial natriuretic factor in patients with cirrhosis and ascites. *Hepatology*. 1991; 14:601–607.
15. Demirel Ş, Akkaya V, Dinç C, et al. An open label, uncontrolled trial of the angiotensin converting enzyme inhibitor cilazapril in the treatment of patients with chronic congestive heart failure. *Curr Ther Res Clin Exp*. 1997;58:594–600.
16. Zannad F, Briancon C, Juilliere Y, et al. Incidence, clinical and etiologic features, and outcomes of advanced chronic heart failure: The EPICAL Study. *Epidemiologie de l'Insuffisance Cardiaque Avancee en Lorraine. J Am Coll Cardiol*. 1999;33:734–742.
17. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: A study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation*. 1998;98:2282–2289.
18. McKirnan MD, Sullivan M, Jensen DG, et al. Limitations in the clinical assessment of functional capacity and its relationship to ventricular function in coronary patients. *Med Sci Sports Exerc*. 1982;14:438. Abstract.
19. Vescovo G, Dalla Libera L, Serafini F, et al. Improved exercise tolerance after losartan and enalapril in heart failure: Correlation with changes in skeletal muscle myosin heavy chain composition. *Circulation*. 1998;98:1742–1749.
20. Bengt W, Litchfield RL, Marcus ML. Exercise capacity in patients with severe left ventricular dysfunction. *Circulation*. 1980;61:955–959.
21. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717.

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