Plasma Levels of Enalaprilat in Chronic Therapy of Heart Failure: Relationship to Adverse Events

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ABSTRACT

Angiotensin-converting enzyme (ACE) inhibitors are established as first-line therapy in chronic heart failure (CHF). However, little is known about the dosage-plasma-level relationship of ACE inhibitors in CHF and its relation to drug-induced adverse effects. We investigated 45 patients (age 55 ± 10 years) with stable CHF who presented with a maintenance dosage of enalapril of either 5 mg b.i.d. (E10, n = 16), 10 mg b.i.d. (E20, n = 18), or 20 mg b.i.d. (E40, n = 11). This dosage was changed three times to treat all patients with lower, higher, and, finally, the initial dosage for 4 weeks each. Patients were examined clinically, by questionnaire, and by spiroergometry. In addition, neurohormones (atrial and brain natriuretic peptide and norepinephrine), enalaprilat trough levels, and serum potassium and creatinine were measured. Enalaprilat trough levels differed significantly between the three groups at study entry but also varied markedly within each group. In addition to the dose of enalapril, serum creatinine, severity of CHF, basal metabolic rate, and body weight significantly influenced enalaprilat trough levels (R² = .84, p < .001). Within-patient comparisons revealed that serum creatinine (107 ± 26 versus 102 ± 20 μmol/liter) and potassium (3.8 ± 0.4 versus 3.7 ± 0.3 mmol/liter) were higher, cough was more common (scored on a scale of 0–8: 1.7 ± 2.1 versus 1.4 ± 1.8), and blood pressure was lower (systolic, 112 ± 14 versus 117 ± 13 mm Hg; diastolic, 66 ± 9 versus 69 ± 11 mm Hg) on the highest than on the lowest enalaprilat trough level (all p < .05). Highly variable enalaprilat trough levels and the fact that adverse effects were more common on high enalaprilat trough levels provide a rationale for individually adjusting ACE-inhibitor dose in case of adverse effects.

Despite the clear evidence that angiotensin-converting enzyme (ACE) inhibitors improve survival, only 30 to 50% of patients with chronic heart failure (CHF) actually receive these drugs (Philbin et al., 1996; Stafford et al., 1997; Barron et al., 1998). Of those receiving ACE inhibitors, the majority in clinical practice receive doses lower than the dosage used in the large clinical trials (Luzier et al., 1998). The reasons for this underuse are not clear but may be related to a lack of familiarity with the use of ACE inhibitors in CHF and concerns about their safety and adverse reactions, especially hypotension, renal failure, hyperkalemia, and cough (Bart et al., 1997; Deedwania, 1997; Houghton and Cowley, 1997). Similar concerns seem to be the reason for the use of low doses of ACE inhibitors, even though this has not yet been addressed directly.

One possible reason for ACE-inhibitor intolerability may be higher plasma levels in some patients than in others because of differences in pharmacokinetics. It is well known that renal function is a major determinant of plasma levels for most ACE inhibitors and their active metabolites, which are excreted mainly by the kidneys (Kelly et al., 1986). In addition, age may play an important role in the elimination of ACE inhibitors (Hockings et al., 1986).

However, it is largely unknown whether there is a relationship between plasma levels of ACE inhibitors and their adverse events during chronic therapy of patients with CHF. In recent years, some studies found a relationship between blood pressure and ACE-inhibitor dosage even though orthostasis was not related to dosage in these studies (Davidson et al., 1996; Pacher et al., 1996). Creatinine clearance was lower on a high dose than on a low dose of lisinopril (Davidson et al., 1996). On the other hand, changes in serum creatinine were not related to dosage in long-term treatment with enalapril (Pacher et al., 1996). Similarly, reports on the dose-effect relationship of ACE inhibitors with respect to cough are conflicting (Yesil et al., 1994; Yeo et al., 1995).

Therefore, we conducted a within-patient, crossover study with different doses of enalapril in patients with stable, mild to moderate CHF who had been treated previously with the

ABBREVIATIONS: ACE, angiotensin-converting enzyme; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CHF, congestive heart failure; E10, patients initially treated with 5 mg b.i.d.; E20, patients initially treated with 10 mg b.i.d.; E40, patients initially treated with 20 mg b.i.d.
drug for at least 3 months. It was investigated whether plasma trough levels of enalaprilat could be predicted by different clinical and biochemical variables. Additionally, we tested whether there was a relationship between enalaprilat plasma level and adverse effects.

Materials and Methods

Patient Population. The study comprised 45 patients (43 male, 2 female) aged 33 to 74 years (mean, 55 ± 10 years) with mild to moderate CHF secondary to coronary artery disease in 26 (58%), dilated cardiomyopathy in 16 (35%), and valvular heart disease in 3 (7%) patients. All patients had an ejection fraction ≤40% (mean 28 ± 7%) and were in stable condition for at least 3 months. ACE inhibition had been started at least 3 months before inclusion into the study. Drug therapy was unchanged for at least 1 month. Serum creatinine level had to be lower than 150 μmol/liter to be included in the study. The protocol was approved by the local Ethics Committee, and patients gave informed consent to participate in the study.

Study Design. Patients were divided into three groups according to the dose of enalapril they were receiving before inclusion into the study: the first group (E10, n = 16) was receiving 5 mg enalapril b.i.d., the second (E20, n = 18) was being treated with 10 mg b.i.d., and the third (E40, n = 11) was on 20 mg b.i.d. As illustrated in Fig. 1, patients were assessed four times by clinical examination, and serum levels of creatinine, electrolytes, and enalaprilat were determined. Additionally, spirometry and measurement of various neurohormones were performed. Thus, the first examination (baseline) was carried out while patients received their initial enalapril dose. Thereafter, the dosages were changed twice in a single blinded manner using identical-looking capsules prepared by the hospital pharmacy to treat all patients with the two other dosages for 4 weeks each (Fig. 1). At the end of each period, examinations were repeated. Finally, the initial dose was restored, and, after another 4 weeks of open therapy, the last examination was performed.

All patients were on frusemide (n = 42) or torasemide (n = 3); 28 received digitalis and 22 received amiodarone. All but 10 patients were on phenprocoumon, and 8 were on aspirin. The doses of concomitant medication remained unchanged unless clinically indicated. No concomitant medication was stopped during the study. Neither concomitant therapy nor its dosage influenced the results (data not shown).

Evaluation Criteria. Patients were examined in the morning between 7 and 9 AM. All drugs were withheld on the morning of examination. Patients were advised to take enalapril in the morning between 7 and 9 AM. All drugs were withheld on the morning of examination. Cough (dry and productive) and orthostasis defined as dizziness felt by the patients upon standing were considered to be ACE inhibition-related adverse events. Cough was rated by the patients (questionnaire) on an arbitrary scale from 0 (no) to 8 (very severe).

Angioedema was not observed. Blood pressure was measured while supine and standing. Blood samples were taken in the supine position.

Ergospirometry. Exercise testing was performed on a treadmill using a ramp protocol. ECG was monitored continuously with a CASE 12 monitor (Marquette Corporation, Milwaukee, WI), and blood pressure was measured before, during, and after the exercise test by standard sphygmomanometer. Gas exchange was assessed, breath by breath, using a CPX/D system (Medical Graphics Corporation, St. Paul, MN). Oxygen was analyzed by a rapidly responding zirconia fuel cell and carbon dioxide was analyzed by an infrared analyzer. Flow measurements were performed using a disposable pneumotachograph.

Patients started walking after reaching a steady state of gas exchange for at least 1 min while standing quietly on the treadmill. Initially, they walked at a speed of 1.0 mph with an elevation of 6% for 6 min corresponding to approximately 0.5 W/kg b.wt. Thereafter, both speed and elevation were increased to augment work load by 0.15 W/kg b.wt./min until exhaustion. Work load was assessed by calculating the power to overcome the elevation (speed × tan [grade]) × g and to cover the distance. Horizontal energy exposure was estimated by rearrangement of the formula by the American College of Sports Medicine (American College of Sports Medicine, 1986).

Laboratory Measurements. Venous blood was collected into chilled tubes containing EDTA and aprotinin (500 kU/ml blood) for measurement of natriuretic peptides and into tubes containing lithium-heparin for determination of potassium, creatinine, norepinephrine, and enalaprilat. Plasma was separated immediately using a refrigerated centrifuge and stored at −80°C until measurement. Potassium and creatinine were measured within 1 h after blood had been taken. All analyses were performed by individuals who were blinded to the treatments.

Atrial natriuretic peptide (ANP) was determined directly, i.e., without prior extraction, in duplicate by a competitive radioimmunoassay with 125I as tracer (Eiken Chemical, Tokyo). Brain natriuretic peptide (BNP) likewise was determined directly in duplicate by a solid-phase immunometric radioimmunoassay with 125I as tracer (Shionogi Chemical, Osaka).

Norepinephrine was measured by means of HPLC separation after solvent extraction as described in detail elsewhere (Bauch et al., 1986). In brief, the extraction system makes use of the complex formation in alkaline medium between diphenylborate and the dioxane group of norepinephrine in combination with ion-pair formation. The concentration of plasma norepinephrine was determined by HPLC using a nucleoside 7-C18 column and electrochemical detection.

Enalaprilat Assay. Analysis of enalaprilat was performed by the Clinical and Biochemical Pharmacology Laboratory (University of Glasgow, Glasgow, Scotland). Enalaprilat was measured by means of a nonspecific, indirect HPLC-UV method. The endogenous ACE activity of 100 μl of plasma was inactivated by heating at 60°C for 1 h. Then, 50 μl of diluted rabbit sera, i.e., exogenous ACE, was added and the mixture was incubated with 400 μl of the ACE substrate hippuryl-histidyl-leucine (5 mM in 100 mM phosphate buffer, pH 8.3). After 45 min of incubation at 37°C, the enzymatic reaction was terminated by the addition of 100 μl of HCl. The hippuric acid produced was extracted using 1 ml of ethyl acetate, after the addition of 100 μl of internal standard (500 μM phthalic acid) and 50 mg NaCl. After centrifugation, 500 μl of the organic phase was separated into clean tubes and evaporated to dryness at 50°C under a stream of air. The desiccated extracts were reconstituted with 150 μl of mobile phase consisting of 20 mM KH2PO4, pH 4.0, and methanol, in a ratio of approximately 95:5, transferred to appropriate vials, and injected into HPLC for analysis.

The compounds of interest were separated on an analytic cartridge column (10 cm × 4.6 mm i.d.) packed with Spherisorb ODS 1, with a particle size of 5 μm. The system was fitted with a precolumn packed with Lichroprep RP-18, with a particle size of 25 to 40 μm. Eluted

Fig. 1. Schedule of changes of enalapril doses. * Examinations. E40, group initially treated with 20 mg of enalapril b.i.d.; E20, treated with 10 mg b.i.d.; E10, treated with 5 mg b.i.d.
compounds were monitored by UV at 228 nm. UV absorption to the compounds was recorded by a Shimadzu CR-3A Integrator.

**Statistical Analyses.** Values are expressed as frequencies and means ± S.D. or S.E. as indicated. To evaluate dose dependence of enalaprilat plasma levels, multifactorial ANOVA using a hierarchical method was performed. Pearson correlation was used for comparison between continuous variables, and Spearman rank was used for ordinal variables. Comparisons between two groups were performed using unpaired Student’s t test or Mann-Whitney U test, as appropriate. Within-patient comparison was performed using paired t test, or Wilcoxon rank-sum test for two measurements, and ANOVA for repeated measurements or Friedman ANOVA, as appropriate.

A two-tailed significance level of 0.05 was considered to be statistically significant. All analyses were performed using a commercially available statistical package (SPSS for Windows 6.0).

**Results**

The baseline characteristics are summarized in Table 1. Exercise capacity and left ventricular ejection fraction were moderately impaired and neurohormones were elevated. There were no statistically significant differences between the three groups.

**Relationship Between Enalapril Dosage and Enalaprilat Trough Level**

As expected, enalaprilat trough levels differed significantly between the three groups at study entry (E10: 20.7 ± 21.9 ng/ml; E20: 25.0 ± 12.0 ng/ml; E40: 48.1 ± 33.9 ng/ml; p < .01). However, as shown in Fig. 2, enalaprilat levels varied markedly within each group. This was also true when only 40 (89%) patients were considered in whom enalaprilat trough levels followed the direction of dosage change.

ANOVA revealed that various factors influenced the enalaprilat trough level in addition to the dosage of enalapril (Table 2). Age did not influence enalapril serum levels (p > .1).

Together with dosage of enalapril, ANOVA including covariates (p < .1 in former model) explained 84% of the variance of enalaprilat levels in these patients (R² = .84, p < .0001). Apart from dosage of enalapril (F = 30.0, p < .001), serum creatinine (increase in plasma enalaprilat of 0.74 ng/ml per 1 μmol), oxygen consumption at rest per kg body weight (decrease in plasma enalaprilat of 10.0 ng/ml per 1 ml/kg per min), body weight (decrease in plasma enalaprilat of 0.38 ng/ml per 1 kg), BNP level (increase in plasma enalaprilat of 0.23 ng/ml per 10 pg/ml), and physical signs of CHF (increase in plasma enalaprilat of 16.0 ng/ml if present) independently influenced plasma enalaprilat levels. Mean enalaprilat trough level after consideration of covariates was 14.2 ng/ml in patients taking 10 mg enalapril daily, 31.8 ng/ml in patients taking 20 mg enalapril daily, and 54.3 ng/ml in patients taking 40 mg enalapril daily (Fig. 2).

**Enalapril Dosage and Adverse Effects**

At baseline, there was no relationship between dosage of enalapril and blood pressure in supine or standing position, and orthostasis was equally common in all three groups. Subjective severity of cough as assessed by cough score was highest in the E40 group and lowest in the E10 group (E40: 3.1 ± 3.0; E20: 1.8 ± 1.8; E10: 0.9 ± 1.0; p < .05).

Within-patient comparisons of blood pressure, renal function, and adverse effects were performed when enalapril doses were 40 mg and 10 mg. There was no significant difference in the change of cough throughout the study on various enalapril doses; 16% of the patients had more cough on low dose and 28% had more cough on high dose of enalapril (p > .1). Orthostasis was more common on enalapril 40 mg daily. Systolic blood pressure in supine position was slightly lower on enalapril 40 mg daily than on 10 mg (Table 3).

Changes in serum creatinine and potassium levels are depicted in Fig. 3. Doubling of enalapril (i.e., 10 mg to 20 mg and 20 mg to 40 mg) did not result in a significant increase in serum potassium or creatinine. However, quadrupling of the dose from 10 to 40 mg per day resulted in a significant reduction of renal function in the E40 group. Reduction of enalapril decreased serum potassium significantly.

Thirty-seven patients completed the whole protocol. Three patients needed early restoration of initial high dose of enalapril because of worsening of CHF. In addition, five patients had to be withdrawn from the study for various reasons: worsening of CHF in three, two after up- and one after tablet.

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**Table 1**

Baseline characteristics of study population

| Age (yr) | 55 ± 10 |
| Diagnosis | 26 |
| Coronary artery disease (n) | 16 |
| Dilated cardiomyopathy (n) | 3 |
| NYHA class | 2.1 ± 0.4 |
| Systolic blood pressure (mm Hg) | 117 ± 15 |
| Diastolic blood pressure (mm Hg) | 67 ± 10 |
| Heart rate (beats per min) | 70 ± 12 |
| Ejection fraction (%) | 28 ± 7 |
| Exercise time (s) | 299 ± 262 |
| Peak VO₂ (ml/kg/min) | 21.3 ± 4.8 |
| Creatinine (μmol/l) | 102 ± 18 |
| Potassium (mmol/l) | 3.8 ± 0.4 |
| ANP (pg/ml) | 170 ± 143 |
| BNP (pg/ml) | 188 ± 239 |
| Norepinephrine (nmol/l) | 3.7 ± 1.6 |

Values are numbers or means ± S.D.
down-titration; temporary anuria in one after up-titration and concomitant use of nonsteroidal anti-inflammatory drug; exercise-induced ventricular tachycardia in one after down-titration. Accordingly, when considering all up-titrations, 3 of 74 (4%) were not tolerated whereas 5 of 50 (10%) down-titrations were accompanied by serious adverse events \( (p = 0.08) \). Enalaprilat trough levels at study entry were significantly higher in patients not tolerating up-titration in the E10 and E20 groups \( (52 \pm 30 \text{ ng/ml versus } 20 \pm 13 \text{ ng/ml}, p < 0.05) \) whereas this was not the case in patients not tolerating down-titration in the E40 group \( (51 \pm 48 \text{ versus } 46 \pm 28 \text{ ng/ml}, p > 0.1) \).

### Relationship Between Enalaprilat Trough Level and Adverse Effects

#### Baseline Measurements

There was a weak negative correlation between enalaprilat trough level and diastolic blood pressure \( (r = -0.38, p = 0.01, \text{supine and standing}) \) whereas systolic blood pressure was not significantly correlated to enalaprilat trough level. Patients complaining about orthostasis tended to have higher enalaprilat trough levels \( (44.4 \pm 33.4 \text{ ng/ml versus } 24.2 \pm 19.0 \text{ ng/ml}, p = 0.06) \). There was a significant relationship between cough and enalaprilat trough level \( (r = 0.42, p < 0.01) \). Patients without cough had significantly lower enalaprilat trough levels than patients with cough \( (\text{any cough: } 18.3 \pm 15.3 \text{ versus } 34.2 \pm 27.3 \text{ ng/ml}, p < 0.05; \text{dry cough: } 18.3 \pm 14.4 \text{ versus } 36.7 \pm 28.3 \text{ ng/ml}, p < 0.01; \text{productive cough: } 19.4 \pm 15.1 \text{ versus } 42.4 \pm 29.7 \text{ ng/ml}, p < 0.01) \). These differences were independent of other parameters, although there was a significant correlation between the symptoms and physical signs of CHF and cough. Although two-thirds of the patients \( (n = 30) \) coughed, only one third of those with cough \( (n = 10) \) felt disturbed by it.

#### Effects of Changes in Enalaprilat Trough Level

Within-patient comparisons of blood pressure, renal function, and adverse effects were performed when enalaprilat trough level was lowest \( (15.1 \pm 16.0 \text{ ng/ml}) \) and highest \( (56.2 \pm 29.7 \text{ ng/ml}, p < 0.001) \). Orthostasis and cough were more common on the highest than on the lowest enalaprilat trough level. Only 12% reported more cough on the lowest level whereas 40% had less cough \( (p < 0.05) \). Interestingly, neurohormones and exercise capacity changed the most between lowest and highest enalaprilat trough levels in those 12% of patients who showed a decrease in cough score on the highest enalaprilat trough level compared with the other patients \( (\text{ANP: } -136 \pm 146 \text{ versus } -8 \pm 82 \text{ pg/ml}, p = 0.08; \text{BNP: } -127 \pm 152 \text{ versus } -21 \pm 84 \text{ pg/ml}, p = 0.05; \text{norepinephrine: } -2.3 \pm 3.1 \text{ versus } -0.5 \pm 1.8 \text{ nmol/liter}, p = 0.20; \text{peak VO}_2: 2.1 \pm 2.0 \text{ versus } 0.2 \pm 1.9 \text{ ml/kg/min}, p < 0.05), \) indicating that the effect of enalaprilat trough level on severity of cough possibly was attenuated by improved cardiac function.

Serum potassium was higher on the highest than on the lowest enalaprilat trough level. Although no hyperkalemia was observed, hypokalemia \( (i.e., <3.5 \text{ mmol/liter}) \) was less common on the highest than on the lowest enalaprilat trough level. Table 3 summarizes the results.

### Table 2

<table>
<thead>
<tr>
<th>Variables influencing baseline enalaprilat trough levels in addition to dosage of enalapril (including all ( p &lt; .1 ))</th>
<th>One Covariate</th>
<th>Multiple Covariates*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( F ) Value</td>
<td>Significance</td>
</tr>
<tr>
<td>Body weight</td>
<td>3.7</td>
<td>.06</td>
</tr>
<tr>
<td>Physical sign of CHF (yes/no)</td>
<td>4.0</td>
<td>.05</td>
</tr>
<tr>
<td>NYHA class</td>
<td>4.1</td>
<td>.05</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>21.0</td>
<td>.001</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>9.5</td>
<td>.01</td>
</tr>
<tr>
<td>ANP</td>
<td>8.2</td>
<td>.01</td>
</tr>
<tr>
<td>BNP</td>
<td>3.0</td>
<td>.09</td>
</tr>
<tr>
<td>Peak VO(_2) ( b )</td>
<td>3.0</td>
<td>.09</td>
</tr>
<tr>
<td>( \text{VO2}_{at\ rest} )</td>
<td>3.0</td>
<td>.09</td>
</tr>
</tbody>
</table>

ANOVA including one or multiple covariates in addition to enalapril dosage.

* NYHA class, systolic blood pressure, and peak VO\(_2\) did not independently influence plasma enalaprilat levels in this model \( (p > .05) \).

* Oxygen consumption.

### Table 3

Renal function, blood pressure, and adverse events at enalapril 10 and 40 mg daily as well as at lowest and highest enalaprilat trough level

<table>
<thead>
<tr>
<th>Enalapril</th>
<th>Enalapril Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>100 ( \pm 14 \text{ mmol/liter} )</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>3.7 ( \pm 0.3 \text{ mmol/liter} )</td>
</tr>
<tr>
<td>Systolic BP supine</td>
<td>116 ( \pm 15 \text{ mm Hg} )</td>
</tr>
<tr>
<td>Diastolic BP supine</td>
<td>67 ( \pm 10 \text{ mm Hg} )</td>
</tr>
<tr>
<td>Systolic BP standing</td>
<td>110 ( \pm 14 \text{ mm Hg} )</td>
</tr>
<tr>
<td>Diastolic BP standing</td>
<td>66 ( \pm 10 \text{ mm Hg} )</td>
</tr>
<tr>
<td>Orthostasis</td>
<td>12%</td>
</tr>
<tr>
<td>Cough score ( c )</td>
<td>1.2 ( \pm 1.5 )</td>
</tr>
</tbody>
</table>

BP, blood pressure.

* \( \text{Significance, } p < .05 \) between 10 and 40 mg enalapril.

* \( \text{Significance, } p < .01 \) between 10 and 40 mg enalapril.

* \( \text{Significance, } p < .05 \) between lowest and highest enalaprilat trough level.

* \( \text{Significance, } p < .01 \) between lowest and highest enalaprilat trough level.

* \( \text{Cough score on a scale of } 0 \text{ to } 8 \).
of enalaprilat level. In spite of lack of evidence in the literature, it cannot be excluded completely that BNP has a direct effect on enalaprilat excretion. However, the relation between other variables associated with the severity of CHF and serum enalaprilat levels as well as the relation between signs of CHF and BNP in this model (data not shown) support the former assumption. This finding is in agreement with previous studies showing a slower clearance of ACE inhibitors in patients with CHF (Dickstein et al., 1987; Gerckens et al., 1989; Cody, 1993).

Oxygen consumption at rest was an additional factor determining enalaprilat trough level in the study patients. Although we did not use standardized conditions for indirect calorimetry, an effect of basal metabolic rate on enalaprilat plasma levels might be a cause for this relationship. To our knowledge, this was neither described nor investigated in the past. In addition, our study design did not allow to investigate directly such a relationship. Although a fortuitous finding cannot be excluded, our results may be interpreted as metabolism of enalapril and/or elimination of enalaprilat being related to basal body metabolism. Whether this is a result of hemodynamic changes associated with CHF remains to be investigated.

In contrast to our results, previous studies found age to be related to enalaprilat excretion (Hockings et al., 1986). However, it has been suggested that this relation mainly reflects decreased renal function in older age. That most of our patients were less than 65 years of age and there was no relationship between age and serum creatinine might be the reason why we did not find any influence of age on enalaprilat trough levels.

### Relationship Between Enalaprilat Trough Level and Adverse Effects.

Apart from angioneurotic edema and other rare adverse effects, ACE inhibition can cause hypotension with associated symptoms, cough, renal dysfunction, and hyperkalemia (Moyses and Higgins, 1992; Messner Pellenc et al., 1995). Hypotension is observed particularly during initiation of therapy. Originally, initiation of ACE inhibition with high doses in patients with CHF had led to major concerns about tolerability of these drugs in CHF (Packer et al., 1986). In spite of lower incidence of first-dose hypotension with low doses and avoidance of excessive water and salt depletion (Flapan et al., 1992; Hasford et al., 1993), these concerns may have contributed to the underuse of ACE inhibitors in patients with CHF (Deedwania, 1997) despite the clear benefit of these agents regarding survival (The SOLVD Investigators, 1991; Pfeffer et al., 1992; Garg and Yusuf, 1995). Although hypotension is widely accepted to be dose-related for the first dose (The CONSENSUS Trial Study Group, 1987), this relationship is less well defined during long-term therapy. Our data suggest that there is a relationship between resting blood pressure and enalaprilat trough level and enalapril dosage, respectively, during chronic therapy. This is in agreement with other studies: 20 mg of lisinopril led to 3- to 6-mm Hg lower supine blood pressure than 5 mg in a recent crossover trial (Davidson et al., 1996), and 20 mg b.i.d. enalapril lowered the supine diastolic blood pressure more than 5 mg b.i.d. in a parallel trial (Pacher et al., 1996).

In addition, orthostatis was more common in patients with high enalaprilat trough levels and on high enalapril dose, respectively. Although it might be confusing that there was only a trend toward lower standing blood pressure whereas...
orthostasis was influenced by enalapril dosage and enalaprilat trough level, respectively, orthostatic responses may vary and patients on high enalapril dosage and enalaprilat level, respectively, may tend to have a greater decrease in blood pressure under certain circumstances whereas the blood pressure decrease under standardized conditions may be small. Thus, these findings may not be contradictory, in particular, because orthostasis was assessed by questionnaire and patients were blinded to the treatment. However, it is important to note that none of our patients fainted and blood pressure was not a limiting factor to increase enalapril dosage up to 40 mg per day.

Persistent repetitive dry cough, which occurs in bouts and is prominent at night (Yeo et al., 1991), is another limiting factor for the use of ACE inhibitors. Reported frequencies varied from less than 1% to more than one-fourth of the study population (Fuller, 1989; Israili and Hall, 1992), and 3 to 6% discontinued therapy because of cough (Yeo et al., 1991; Desche et al., 1993; Fletcher et al., 1994; Pitt et al., 1997). The underlying mechanism is probably the inhibition of kininase II with accumulation of kinins, Substance P, and prostacyclin and, therefore, a class effect (Overlack, 1996). However, the dose-effect relationship is not well defined: although a small study reported the severity of cough being dose-related (Yeo et al., 1995), others did not find such a relationship (Yesil et al., 1994). In our study, cough occurred in two-thirds of the patients and was related to enalapril dosage and enalaprilat trough level and changed with changes in enalapril dosage and enalaprilat trough levels. However, the finding of a relationship between cough and the severity of CHF suggests that CHF is an important contributor to coughing even in patients under stable conditions. Thus, an increase in the dose of ACE inhibitor may diminish cough by improvement of CHF in some patients whereas ACE-inhibitor-induced cough may be decreased by a dose reduction in others. It is important to note that in our study population, the type of cough did not allow distinction of the underlying cause because dry and productive cough was equally affected by enalapril dosage and enalaprilat trough level.

Serum potassium and serum creatinine were slightly, although significantly, higher at high than at low enalaprilat levels, which is in agreement with some (Davidson et al., 1996) but not all previous studies (Pacher et al., 1996). However, despite a significant worsening of renal function in up to one-third of patients with CHF after initiation of ACE inhibitor therapy, most patients show a only mild increase in serum creatinine, and ACE inhibitor therapy does not have to be discontinued in these patients (Sica and Deedwania, 1997). In fact, a recent randomized, placebo-controlled study showed that renal function may be significantly improved by ACE inhibition in patients with renal dysfunction over a course of 3 years despite an initial increase in serum creatinine of 10 to 15% (Maschio et al., 1996). In our study, severe renal failure was observed in only one patient with concomitant use of nonsteroidal anti-inflammatory drug, with prompt recovery after cessation of this drug and enalapril. Nevertheless, quadrupling the dose within 1 week led to a significant increase in serum creatinine and doubling was generally well tolerated. An increase in enalapril dose did not lead to hyperkalemia. In contrast, hypokalemia was more common on the lowest than on the highest enalaprilat level, thereby possibly augmenting the risk of serious tachyarhythmias (Packer and Lee, 1986). Although concomitant therapy with diuretics can explain the relatively high frequency of hypokalemia, reduction of ACE inhibitor doses further increased the risk of hypokalemia in our patients.

Limitations. There are several limitations of our study. First, our patients entered into the trial on different dosages of enalapril. Thus, it could be argued that clinical indications led to different dosages. However, baseline data were comparable between the three groups.

Second, our study was single-blinded only. However, those who performed analysis of plasma samples were unaware of the actual dose of enalapril. In addition, the patients filled out the questionnaires without being influenced by study personnel.

Third, it is known that basal metabolic rate is increased in patients with severe CHF (Obisesan et al., 1997). Because we investigated only patients with mild to moderate chronic CHF, it cannot be excluded that the relationship between basal metabolic rate as well as CHF and enalaprilat trough level may be different in patients with more advanced or acute CHF. Additionally, it remains unknown whether these relations are independent of renal function because we determined serum creatinine only rather than creatinine clearance. Nevertheless, our results suggest that enalaprilat serum levels are predictable to a certain extent, making dose-finding of enalapril in patients with CHF easier.

Conclusions. Our data show a relationship between enalapril dosage and enalaprilat trough level and side effects in patients with CHF under chronic ACE inhibition. Despite that, an enalapril dose of 40 mg daily was well tolerated by most patients, and serious adverse events (i.e., worsening of CHF, anuria, serious arrhythmia) tended to be more common after downward than after upward titration of enalapril. Some of these adverse effects observed during up-titrations seem to be related to high enalapril trough levels.

The results, therefore, support an approach of individual adjustment of ACE-inhibition dosage in the chronic CHF therapy rather than discontinuation in patients suffering from ACE-inhibitor-induced adverse events, in particular, in those with an expectedly high plasma level.

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