Effect on Exercise Performance of Enalapril Therapy Initiated Early After Myocardial Infarction

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Objectives. The Nordic Enalapril Exercise Trial was a multicenter subtrial of the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II) designed to evaluate the effect on maximal exercise performance of a 6-month period of enalapril treatment initiated early after myocardial infarction.

Background. When begun early after myocardial infarction, converting enzyme inhibition therapy has been shown to attenuate infarct expansion and reduce left ventricular volume. Therapy has been associated with improved exercise performance.

Methods. Three hundred twenty-seven men (mean age 63.3 ± 10.9 years) with documented acute myocardial infarction were randomized to treatment with enalapril or placebo on a double-blind basis. Intravenous enalaprilat or placebo therapy was initiated within 24 h after the onset of symptoms. Oral therapy was continued at a target dose of 20 mg/day. Patients exercised maximally at 1 month and 6 months after infarction to symptom-limited end points on a cycle ergometer with a 20 W/min incremental protocol.

Results. The treatment and control groups were comparable in patient age, concurrent therapy and type and site of infarction. At 1 month, for all patients, mean total work performed was 34.9 ± 10.9 years) with documented acute myocardial infarction were randomized to treatment with enalapril or placebo on a double-blind basis. Intravenous enalaprilat or placebo therapy was initiated within 24 h after the onset of symptoms. Oral therapy was continued at a target dose of 20 mg/day. Patients exercised maximally at 1 month and 6 months after infarction to symptom-limited end points on a cycle ergometer with a 20 W/min incremental protocol.

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vention (22). Therapy with inotropic agents (23), diuretic drugs (24), vasodilators (25) and exercise training programs (26) has demonstrated improvement in peak and submaximal exercise variables in patients with symptomatic heart failure.

The Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II) (27) was a multicenter trial designed to evaluate the effect on mortality at 6 months of enalapril administered early after myocardial infarction. The Nordic Enalapril Exercise Trial was a CONSENSUS II subtrial designed to test the hypothesis that long-term converting enzyme inhibition initiated in patients early after myocardial infarction would improve exercise performance. Three hundred twenty-seven men with documented acute myocardial infarction were randomized in a double-blind manner to enalapril or placebo according to the CONSENSUS II protocol previously reported (27). Patients were tested at 1 and 6 months using a maximal, symptom-limited, incremental exercise protocol.

Methods

Study protocol. The Nordic Enalapril Exercise Trial was prospectively designed in connection with the CONSENSUS II study. Eleven hospitals in Scandinavia participated in this subtrial (Appendix). Patients randomized into the CONSENSUS II study were invited to participate.

Myocardial infarction was confirmed by conventional clinical, electrocardiographic (ECG) and biochemical criteria. Therapy was initiated within 24 h after the onset of chest pain with intravenous enalapril (1 mg/250 ml, 5% dextrose in water) or placebo administered over 3 h. Arterial blood pressure was monitored continuously, and therapy was discontinued if systolic blood pressure decreased to <90 mm Hg. Oral therapy was initiated 6 h after the completion of the infusion with 2.5 mg of enalapril or placebo. The dosage was titrated to 20 mg daily in the absence of possible drug-related side effects, symptomatic hypotension or a substantial increase in serum creatinine. Other therapy, administered concurrently as clinically indicated for the management of acute myocardial infarction, included thrombolytic therapy and intravenous administration of nitroglycerin and beta-adrenergic blocking agents. The protocol specified that patients whose clinical condition deteriorated to New York Heart Association functional class IV should be withdrawn from the trial and placed on open label therapy.

Patients were included consecutively in the exercise trial 1 month after myocardial infarction. However, we excluded candidates who were considered to be in clinically unstable condition or were unable to perform a maximal, symptom-limited exercise test. Concurrent medication at 1 month is listed for both the treatment and the placebo groups in Table 1.

Study patients. Patients with an onset of chest pain <24 h before hospital admission were screened for possible inclusion into the CONSENSUS II study. Eligible patients with significant aortic stenosis, hypotension (systolic blood pressure <105 mm Hg), cardiogenic shock or need for inotropic support were not randomized. Patients considered by the investigator to be unable to perform maximal exercise at 1 month were not included in the trial.

Three hundred twenty-seven men with documented myocardial infarction were included in the study. The mean age was 63.3 ± 10.9 years. Patients were concurrently treated with all other clinically indicated medication apart from converting enzyme inhibition therapy. Two hundred nine patients had ECG evidence of Q wave myocardial infarction, and 136 patients showed evidence of anterior myocardial infarction. Eighty-four patients had previous confirmed myocardial infarction, and 105 patients were ≥70 years old.

A detailed description of the clinical characteristics of the study group according to randomization is provided in Table 1.

Exercise testing protocol. The exercise protocol employed an upright, electronically braked cycle ergometer and was based on an initial work load of 20 W, with stepwise 20-W increments at 1-min intervals. Testing occurred approximately 2 h after a light meal and always between 2 and 6 h after ingestion of the test medication. Patients were instructed to maintain a pedaling rate of approximately 65 rpm and to exercise maximally to symptomatic end points, resulting in the inability to maintain constant pedal speed. A 12-lead ECG was interfaced, and heart rate was recorded continuously.

Total exercise duration was recorded from the start of exercise to the point where the patient was unable to maintain a constant pedaling speed. Total work performed was calculated in joules. Peak heart rate and the magnitude of ST segment depression were recorded. The primary symptom causing the patient to discontinue exercise and other concurrent symptoms were noted.

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<th>Table 1. Clinical Characteristics at 1 Month</th>
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*p < 0.01. †p < 0.001. ‡p < 0.05. Data are presented as percent of patients or mean value ± SD. CK-MB = creatine kinase, MB fraction; DBP = diastolic blood pressure; MI = myocardial infarction; SBP = systolic blood pressure.
**Statistical methods.** The Fisher exact test was used to compare the treatment groups with respect to dichotomous variables. The Wilcoxon rank sum test was used to compare treatment groups with respect to ordinal variables. Differences between the treatment groups with respect to continuous variables were tested using nonparametric analysis of covariance models. The rank sum test was used to compare the treatment groups and the signed rank test to test within-group differences.

**Results**

Three hundred twenty-seven men were included in the exercise trial. One hundred sixty-nine patients were randomized to enalapril and 158 patients to placebo. The average long-term dose of enalapril was 18.7 mg and of placebo, 19.1 mg. Five hundred forty-one men were randomized into the CONSENSUS II study at the 11 centers during the period of inclusion into the Nordic Enalapril Exercise Trial. One hundred forty-seven patients were considered by the investigator unable to perform maximal exercise at 1 month largely because of unstable angina pectoris, advanced age or orthopedic conditions. Sixty-seven patients (37 receiving enalapril, 30 receiving placebo) died before the first exercise test, and 22 patients died between 1 and 6 months (10 receiving enalapril, 12 receiving placebo). Sixteen patients (6 receiving enalapril, 10 receiving placebo) underwent coronary artery bypass grafting or percutaneous transluminal coronary angioplasty between 1 and 6 months and were excluded from the 6-month Nordic Enalapril Exercise Trial test as per protocol.

The treatment groups were comparable with regard to age, concurrent therapy at 1 month and type and site of myocardial infarction (Table 1). Both mean systolic and diastolic blood pressure at rest were significantly lower in the enalapril group (p < 0.01). A small but significant difference (p < 0.05) in thrombolytic therapy during the acute phase of infarction was noted. The mean peak creatine kinase, MB fraction was 172 ± 134 U/liter in the placebo group and 173 ± 143 U/liter in the enalapril group.

**Exercise performance.** Peak heart rate during exercise at 1 month in the placebo group was 128 ± 22 versus 132 ± 24 beats/min in the enalapril group (p = NS). At 6 months, peak heart rate in the placebo group was 132 ± 22 versus 130 ± 26 beats/min in the enalapril group (p = NS). There were no significant between group differences at either 1 or 6 months with regard to the major limiting symptom at the termination of exercise (Table 2). At 1 month for all patients, mean total work performed in the enalapril group was 34.9 ± 20.9 versus 28.5 ± 20.6 kJ in the placebo group (difference = 18.4%, p < 0.01). At 6 months, mean total work performed in the enalapril group was 35.4 ± 23.8 versus 34.0 ± 23.9 kJ in the placebo group (difference = 4.1%, p = NS). The results are shown for both work performed and total exercise duration in Tables 3 and 4.

**Subgroup analysis.** Four subgroups were prospectively defined for analysis. Patients were classified into groups according to myocardial infarction type (Q wave vs. non-Q wave), site of myocardial infarction (anterior vs. nonanterior), age (<70 vs. ≥70 years) and heart failure, as indicated by the presence of at least two of the following criteria at 1 month: diuretic therapy, pulmonary rales, peripheral edema or cardiomegaly by two-plane chest X-ray film (28) (relative volume >600 ml/m²).

The percent between-group differences at 1 and 6 months...
in work performed for patients with anterior myocardial infarction were 23.2% (enalapril > placebo, p = NS) and 5.8% (enalapril > placebo, p = NS), respectively. The corresponding percent differences for nonanterior myocardial infarction were 21.4% (enalapril > placebo, p < 0.05) and 1.8% (enalapril > placebo, p = NS) (Fig. 2).

The percent between-group differences at 1 and 6 months in work performed for patients with Q wave myocardial infarction were 9.0% (enalapril > placebo, p = NS) and 1.8% (placebo > enalapril, p = NS), respectively. The corresponding differences for non-Q wave myocardial infarction were 46.3% (enalapril > placebo, p < 0.01) and 20.2% (enalapril > placebo, p = NS) (Fig. 3).

The percent between-group differences at 1 and 6 months in work performed for patients <70 years old were 14.4% (enalapril > placebo, p = NS) and 2.7% (placebo > enalapril, p = NS), respectively. The corresponding percent differences for patients ≥70 years old were 41.4% (enalapril > placebo, p < 0.01) and 16.9% (enalapril > placebo, p = NS) (Fig. 4).

The percent between-group differences at 1 and 6 months in work performed for patients with clinical evidence of heart failure were 33.0% (enalapril > placebo, p < 0.01) and 2.7% (placebo > enalapril, p = NS), respectively. The corresponding percent differences for patients without heart failure were 18.0% (enalapril > placebo, p = 0.05) and 8.7% (enalapril > placebo, p = NS) (Fig. 5).

Possible subgroup interactions (myocardial infarction type, localization, age and heart failure) were tested with a nonparametric analysis of variance model and none were significant, indicating that the effect of enalapril versus placebo was consistent across the subgroups.

### Discussion

Maximal exercise testing has been shown to be a valuable tool in the clinical assessment of functional capacity (21) and prognosis (20). It has been demonstrated that peak exercise performance with metabolic evidence of anaerobiosis can be achieved reliably in patients with coronary artery disease (29,30). The results are highly reproducible in such patients 1 month after myocardial infarction (31). Measurements of exercise capacity provide clinically relevant information with regard to functional status and should not be considered as surrogate end points in cardiac evaluation.

**Converting enzyme inhibition and exercise capacity.** Convincing evidence exists confirming symptomatic and functional improvement in patients with New York Heart Association functional class III and IV heart failure treated with converting enzyme inhibitors (32). The renin-angiotensin
system is markedly activated during both moderate and strenuous exercise in patients with heart failure (33,34). This response may contribute substantially to the attenuated vasodilator reserve in skeletal muscle observed in patients with heart failure (35,36). Converting enzyme inhibition may partially correct this pathophysiologic response, improve vasodilator reserve and increase muscle blood flow (37-39). Long-term therapy has been shown to attenuate the marked increase in adrenergic tone that accompanies maximal exercise in patients with left ventricular dysfunction (40).

The results of this trial indicate that enalapril therapy initiated early after myocardial infarction is associated with improved exercise capacity during the convalescent phase. The difference in work performed at 1 month was 18.4% (p < 0.01) between the active and control group for all patients. The difference was greatest for patients ≥70 years old (41.4%, p < 0.01), for patients with non-Q-wave myocardial infarction (46.3%, p < 0.01), and for patients with clinical evidence of heart failure (33.0%, p < 0.01). The difference in work performed at 6 months was 4.1% (p = NS) for all patients.

The results are expressed in units of work performed because testing involved a rapidly increasing incremental protocol, as opposed to an endurance protocol in which exercise duration would be the most appropriate variable. Differences between the treatment groups were tested using nonparametric analysis of covariance models, so that the statistical significance of observed differences is identical for both time and work. The four subgroups were identified prospectively in an attempt to identify the group most likely to profit from intervention. Although no subgroup interactions were found to be significant, the power of tests for interaction was limited, and the data do suggest a degree of subgroup interaction.

**Potential mechanisms.** The potential mechanisms responsible for these observations are not known, and we can only speculate about the possible physiologic factors involved. This trial did not measure central or peripheral hemodynam-
ics, and neurohumoral status was not assessed. It is postulated that the findings in this trial probably result from both an attenuation of ventricular dilation after myocardial infarction and a reduction of the increased peripheral vascular resistance associated with deconditioning and left ventricular dysfunction.

Several studies have demonstrated that converting enzyme inhibition initiated early after myocardial infarction attenuates left ventricular dilation by means of reduction of infarct expansion and improved remodeling of noninfarcted myocardium (15,16,41). A subtrial of the CONSENSUS II study also confirmed that enalapril therapy initiated during the acute phase after myocardial infarction was associated with reduced left ventricular volumes at both 1 and 6 months (42). The largest difference in volumes was observed at 1 month. It is certainly conceivable that attenuated left ventricular dilation during the convalescent phase may be relevant to the interpretation of the results.

The convalescent phase after acute myocardial infarction is associated with reduced exercise performance due to both a reduction in cardiac reserve and prolonged inactivity with deconditioning (43). Deconditioning is associated with attenuated vasodilator capacity in skeletal muscle. This is largely due to interstitial and intramural salt and water retention, as well as a reduction in vessel size resulting from reduced muscular blood flow (44,45). In the presence of heart failure, neurohumoral activation also contributes to elevated peripheral vascular resistance (35).

It has been demonstrated that activation of the renin-angiotensin-aldosterone system is largely limited to the acute and early convalescent phase and persists only in patients with sustained left ventricular failure after myocardial infarction (46). No data are available that describe the degree of activation during the later convalescent phase (47). We did not measure plasma renin activity during this trial because half of the patients were randomized to an angiotensin-converting enzyme inhibitor. Considering the selection bias in this trial, it is reasonable to postulate that most patients...
did not have substantial neurohumoral activation at the 6-month test.

The improved exercise performance in the placebo group at 6 months is compatible with previous reports demonstrating improvement in exercise performance observed during the 1st 6 months after myocardial infarction (43, 48). This is probably the result of both improved ventricular performance and reversal of the modest deconditioning process associated with the convalescent phase after myocardial infarction. The similarity in performance between groups at 6 months was due to improvement in the placebo group and not to deterioration in the enalapril group.

Limitations of the study. The trial has some important limitations. The patient group was selected both by protocol design and by practical considerations. The CONSENSUS II protocol excluded patients with hypotension, cardiogenic shock, need for inotropic support or concurrent converting enzyme inhibitor therapy. Patients who developed symptoms of heart failure at rest were withdrawn from the trial in favor of open label therapy. Furthermore, the NEET protocol excluded patients considered unable to perform a maximal exercise test at 1 month. These considerations would tend to exclude the patients most likely to develop sustained left ventricular dysfunction, that is, the subgroup most likely to profit from intervention.

Most trials demonstrating improvement in exercise performance with converting enzyme inhibition have shown the greatest improvement in the most symptomatic patients receiving long-term therapy (17,49). Information regarding ejection fraction or the severity of focal hypokinesia and left ventricular dilation was not available in the present trial. Assessment of the presence of heart failure was based on commonly available clinical criteria. Considering that both the CONSENSUS II and NEET protocols excluded the most seriously ill patients, it is likely that most patients in this trial were comparatively well compensated hemodynamically with only mild left ventricular dysfunction. Therefore, this selection bias would suggest that therapy might be even more efficacious when the more symptomatic postinfarction patients are targeted. This hypothesis deserves further investigation.

Trials evaluating acute therapy after myocardial infarction cannot establish a stable baseline before intervention. Assessment of the comparability between the randomized groups is therefore essential. In this trial, the groups were comparable with regard to age, concurrent therapy and type and site of myocardial infarction. There was a small but significant difference with regard to thrombolytic therapy during the index infarction. The enalapril group contained the larger percentage (66% vs. 54%); however, the mean peak myocardial creatine kinase release was identical for the two groups. Theoretically, thrombolytic therapy might reduce infarct size and permit improved peak exercise performance. A recent report (50) did demonstrate a 15% (p < 0.05) improvement in exercise performance at 3 months. However, the similarity in exercise performance in our trial at 6 months suggests that the groups were comparable and that the difference in performance observed at 1 month was therefore not the result of selection bias.

This trial does not address the issue of the optimal timing of initiation of converting enzyme inhibition therapy after myocardial infarction. All patients were randomized according to the CONSENSUS II protocol with therapy initiated within the 1st 24 h. It may be that the improved performance at 1 month would have been observed had oral therapy been initiated at a late stage during the convalescent phase. Such an approach would permit inclusion of the considerable group of patients with hypotension obviating initiation of therapy in the acute phase.

Implications. Improvement in exercise capacity during the early convalescent phase after acute myocardial infarction has practical clinical consequences. Such improvement would serve to facilitate rehabilitation aimed at reversal of the deconditioning process and permit earlier resumption of normal physical activity. However, the cost and potential adverse effects of generalized use of converting enzyme inhibition after myocardial infarction are substantial. Further research should attempt to elucidate the physiologic mechanisms involved, profile the patient group most likely to profit from early therapy and establish the optimal timing and duration for intervention. The advantages of a more rapid recovery after myocardial infarction are considerable.

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Appendix

Nordic Enalapril Exercise Trial

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