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Treatment with Ramipril Improves Systolic Function Even in Patients with Mild Systolic Dysfunction and Symptoms of Heart Failure after Acute Myocardial Infarction

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Summary

Background: Clinical signs of heart failure such as pulmonary rales and dyspnea, ventricular dysfunction, and ventricular arrhythmia are independent predictors of a poor prognosis after acute myocardial infarction (AMI).

Hypothesis: The study aimed to assess the effect of ramipril treatment on mildly depressed left ventricular (LV) systolic function, assessed by atrioventricular (AV) plane displacement in patients with congestive heart failure after AMI.

Methods: The study was a substudy in the Acute Infarction Ramipril Efficacy Study, a double-blind, randomized, placebo-controlled trial of ramipril versus placebo in patients with symptoms of heart failure after AMI. In all, 56 patients were included in the main study, 4 refused to participate in the substudy, and 4 were excluded for logistical reasons. Echocardiography was performed at entry and after 6 months. Patients who underwent coronary artery bypass grafting during the follow-up period were excluded.

Results: At baseline, the patients had modest LV dysfunction, and mean AV plane displacement of 9.7 mm. During follow-up, AV plane displacement increased in ramipril-treated patients from 9.5 to 10.9 mm ($p < 0.01$). No statistically significant changes were seen in the placebo group.

Conclusions: Ramipril improves LV systolic function in patients with clinical signs of heart failure and only modest systolic dysfunction after AMI. Measurement of AV plane displacement is a simple and reproducible method for detection of small changes in systolic function and may be used instead of ejection fraction in patients with poor image quality.

Key words: myocardial infarction, heart failure, left ventricular systolic function, ramipril

Introduction

Clinical signs of heart failure such as pulmonary rales and dyspnea, ventricular dysfunction, and ventricular arrhythmia are independent predictors of a poor prognosis after acute myocardial infarction (AMI).[1,2]

Diuretics are extensively used in the treatment of heart failure, and their efficacy is well established. However, they have a tendency to increase afterload and deplete sodium and potassium while having no effect on progressive left ventricular (LV) dilatation and dysfunction seen in many patients, especially after large Q-wave infarctions.[3] Angiotensin-converting enzyme (ACE) inhibitors reduce afterload, preserve electrolytes, and reduce ventricular remodelling after AMI.[3,4] Major trials have shown beneficial effects with regard to survival and/or development and progression of cardiac failure, and on the treatment with ACE inhibitors in symptomatic patients with severe[5] and moderate heart failure.[6] Similar effects have been noted in asymptomatic patients with LV dysfunction.[7,8] In the Acute Infarction Ramipril Efficacy (AIRE) Study, ramipril improved survival after a mean follow-up of 15 months in patients with clinical signs of heart failure during the first 10 days after AMI.[9]

The present work was a substudy of the AIRE study. The aim was to investigate the effect of treatment with ramipril on LV systolic function, during the first 6 months of follow-up.

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Methods

Patients

Fifty-six patients at our hospital were included in the AIRE study, a multicenter, multinational, double-blind, randomized, placebo-controlled trial studying the effects of ramipril on mortality in patients with AMI and clinical evidence of heart failure. Heart failure was defined as showing at least one of the following: basal bilateral post-tussive crackles over the lung fields in the absence of significant chronic pulmonary disease, and/or signs of pulmonary congestion on erect chest x-ray, and/or evidence of a third heart sound with persistent tachycardia.

Acute myocardial infarction was defined as an evolving electrocardiogram diagnostic of myocardial infarction (progressive changes in the ST segment and T waves with or without the presence of pathologic Q waves) and elevation of cardiac enzymes to more than twice the upper limit of the laboratory reference range.

Details concerning inclusion criteria, titration, and dosage of ramipril have been published previously.[9]

Patients were examined by echocardiography at entry and after 6 months of follow-up while still on study medication. Those who underwent coronary artery bypass grafting during the follow-up period were excluded from the substudy.

Four patients refused to participate and four patients could not be included in the substudy for logistic reasons. All patients gave their informed consent to participate in the trial, which was approved by the local Ethics Committee of the University of Linköping.

Thus, 48 patients, 32 men and 16 women, with a mean age of 68 years (range 43–83) were included. Of these, 29 had a Q-wave and 19 a non-Q-wave infarction. The location was anterior in 31 patients and inferior in 17. The median peak creatine kinase myocardial band was 204 mKat/l (range 20–1070, reference level < 10). Thrombolytic treatment was given to 23 of the patients, 40 were on beta blockers, 14 on calcium-channel blockers, and 9 on long-acting nitrates. At entry, 39 patients were treated with furosemide (median dose 40 mg, range 0–160 mg), 19 patients had potassium-sparing diuretics, and 3 patients were treated with digoxin.

Twenty-five patients were randomized to ramipril treatment and 23 to placebo. Clinical characteristics were the same in the two subgroups except for gender, with significantly more women in the ramipril-treated group ($p < 0.05$) (Table I).

Echocardiography

The same two examiners conducted all examinations. Two-dimensional (2-D) echocardiography was performed in the left recumbent position using six standard views (apical two-, three- and four-chamber views, parasternal long-axis and short-axis views at papillary muscle and chord level). Images were obtained using a combined 3.25 MHz tissue imaging and 2.5 MHz pulsed Doppler device (Vingmed CFM 750, Vingmed Sound A/S, Horten, Norway). The recordings were stored on videotapes, external digital hard disks, and paper printouts.

Displacement of the atrioventricular (AV) plane was recorded using the M-mode technique from the apical four- and two-chamber views.[10] The M-mode cursor was placed perpendicular to the septal, anterior, lateral, and posterior borders of the AV plane, and the total amplitude of motion was measured at each location with calculation of a mean value. Ejection fraction measurement was not part of the study protocol but was estimated afterward from available cine-loops of apical four- and two-chamber views using the biplane method of discs and modified Simpson's rule. Every registration was traced three times and the average value was calculated. Because of suboptimal image quality in several patients, ejection fraction measurements were not optimal and the available cine-loop registrations did not fulfill the quality needed for scientific purpose; they were intended as a frame of reference to those not familiar with displacement of the AV plane (AVPD). Ten consecutive tracings of the AVPD and ejection fraction were independently analyzed by two observers and by the same observer on two different days to assess inter- and intraobserver variability.

Statistics

Data are presented as means and standard deviations (SDs). Reproducibility was expressed in relative terms as the coefficient of variance, which was calculated by use of the formula

$$SD_{diff} \times 100 / \text{mean value}$$

TABLE I Baseline clinical characteristics of patients in the two treatment groups

	Ramipril group (n=25)	Placebo group (n=23)
Mean age (years)	69	67
Gender (F/M)	12/13	4/19
Q-wave/non-Q-wave infarction	16/9	13/10
Anterior	14	17
Inferior	11	6
Median peak CK-MB (mKat/l)	168	240
No. receiving thrombolytic treatment	11	12
No. with previous myocardial infarction	6	5
No. with previous heart failure	3	1
Hypertension	8	4
Angina pectoris	8	12
Diabetes mellitus	5	3
HR (beats/min)	68 (12)	65 (8)
Systolic blood pressure (mmHg)	127 (18)	121 (15)
Diastolic blood pressure (mmHg)	71 (9)	72 (11)

Abbreviations: F = female, M = male, CK-MB = mean peak creatine kinase (reference level < 10 mKat/l), HR = heart rate.

The Mann-Whitney rank sum test was used for comparisons between groups and Wilcoxon's signed rank test for comparisons within groups for continuous variables. Fisher's exact test was used for nominal variables. Simple regression was used to test linearity between variables. Differences were considered significant at the 5% ($p < 0.05$) level. All analyses were performed with a Macintosh computer using StatView® 4.02 software (Abacus Concepts Inc., Berkeley, Calif.).

Results

Forty-eight patients were examined at baseline, and 38 at 6-month follow-up. Four patients, one in the placebo group and three in the ramipril group, died during follow-up. Five underwent coronary artery bypass grafting and were therefore excluded and one patient was unable to undergo echocardiographic examination due to intercurrent disease (severe stroke). Five patients in each group suffered a new AMI within the 6 months. One in each group of patients underwent percutaneous transluminal coronary angioplasty. There was no difference between groups regarding mortality, stroke, new AMI, or revascularization.

Of the 38 patients examined at 6 months, all placebo-treated patients remained on study medication, whereas ramipril had been withdrawn in three patients; one patient developed progressive heart failure and was treated with open-label ACE inhibitor. The other two were withdrawn because of intolerance to study medication. Concomitant medication was similar in both treatment groups at baseline and during follow-up.

Table II shows AVPD and ejection fraction with corresponding volume measurements at baseline. At baseline, no difference was seen between patients in the two treatment groups. Examinations were carried out on average 5 days after index AMI in both treatment groups. After 6 months of treatment, the ramipril-treated patients showed an improvement in AVPD and a reduction in heart rate and systolic volume index, whereas the same parameters in the placebo-treated patients remained unchanged; however, no difference was seen between groups. Systolic and diastolic blood pressures increased significantly ($p<0.05$) in both treatment groups. No difference was seen between groups at baseline or after 6 months. Neither diastolic volume index, stroke volume index, nor ejection fraction changed between inclusion and follow-up (Table III).

There was a significant correlation between AVPD and ejection fraction, $r = 0.56$, $p < 0.0005$ at baseline, and $r = 0.40$, $p < 0.02$ at follow-up (Fig. 1). Correlation was also seen between AVPD and stroke volume index, $r = 0.44$, $p < 0.01$ at baseline, and $r = 0.38$, $p < 0.05$ at follow-up.

There was a weak but significant negative correlation between AVPD and New York Heart Association class at follow-up ($r = -0.39$, $p = 0.01$).

In spite of poor 2-D image quality in some patients, AVPD values were obtained in all patients and reproducibility was good. The coefficient of variation for AVPD was 8.8% between two observers, and 9.8% for the same observer. For ejection fraction, coefficient of variation was 17.1% between observers and 15.6% for the same observer.

Discussion

In this study, we found an improvement in AVPD in patients treated with the ACE inhibitor ramipril after a recent AMI, even though LV dysfunction at baseline was only mild to moderate.

Several studies,[5–9] although not all,[11] have shown that ACE inhibitors have beneficial effects on mortality and/or morbidity in patients with recent AMI and/or depressed LV systolic function.

Improvement in systolic function in patients with recent AMI has been shown by Sharpe *et al.*,[3] Gøtzsche *et al.*,[12] and in 512 patients from the Survival and Ventricular Enlargement (SAVE) study by Sutton *et al.*[13] In the latter study, the LV end-diastolic area was smaller and the relative change in area was greater in the captopril group than in the placebo group after 1

TABLE II Systolic function measurement in the two treatment groups

Parameter	Ramipril group (n = 25)	Placebo group (n = 23)
AVPD (mm)	9.8 (2.4)	10.0 (2.0)
LVEDVi (ml/m²)	56 (24.2)	60 (22.8)
LVESVi (ml/m²)	32 (22.1)	33 (14.5)
SVi (ml/m²)	24 (10.0)	27 (12.2)
EF (%)	46 (14.9)	45 (11.0)

Abbreviations: AVPD = displacement of the atrioventricular plane; EF = ejection fraction; LVEDVi and LVESVi = left ventricular end-diastolic and end-systolic volume index, respectively; SVi = stroke volume index.

TABLE III Changes in systolic function parameters from baseline to 6 months follow-up in 38 patients examined at both occasions

Parameter	Ramipril group (n=18)	p Value	Placebo group (n=20)	p Value
AVPD (mm)	1.4	<0.01	0.12	NS
LVEDVi (ml/m²)	−5.9	NS	−6.0	NS
LVESVi (ml/m²)	−4.5	<0.05	−5.1	NS
SVi (ml/m²)	−1.4	NS	−0.9	NS
EF (%)	0.8	NS	4.3	NS
Heart rate (beats/min)	−4	<0.05	−5	NS
Systolic blood pressure (mmHg)	13	<0.05	21	<0.005
Diastolic blood pressure (mmHg)	9	<0.01	9	<0.005

Abbreviation: NS = not significant. Other abbreviations as in Table II.

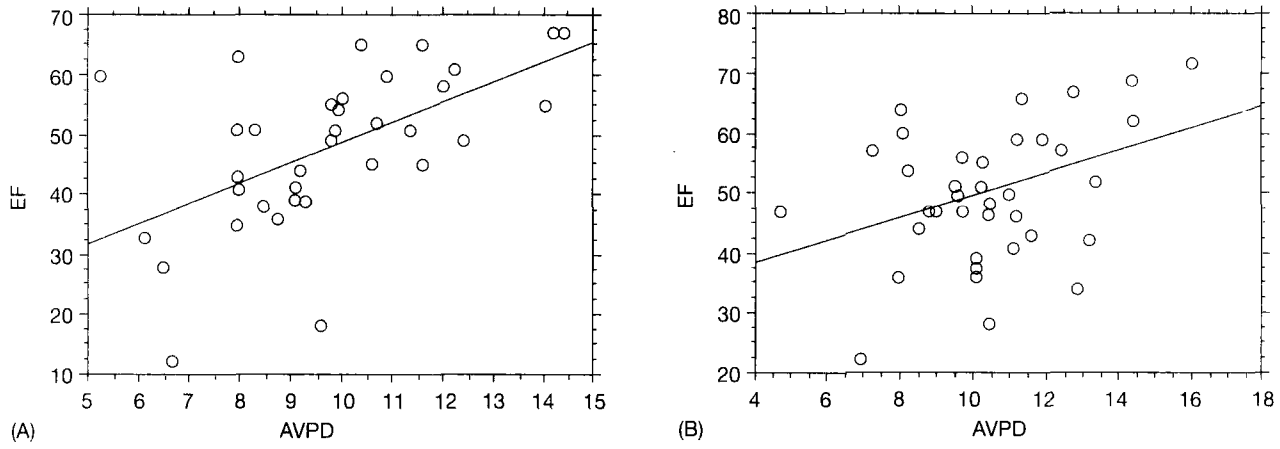

Fig. 1 Scattergram of atrioventricular plane displacement and ejection fraction at baseline (A) and at 6 months follow-up (B). EF = ejection fraction, AVPD = displacement of atrioventricular plane.

year, whereas within-group comparison showed no difference in either group.

Compared with these studies, our patients on average had milder LV dysfunction and, in contrast to these studies, all our patients had symptoms of heart failure. The number of patients in the present study was smaller, which may explain why improvement was seen only in the within-group comparison.

The increase in blood pressure during follow-up is a common finding after AMI and was observed in both groups. The decrease in heart rate seen in the ramipril group is probably secondary to the improvement in systolic function.

Our finding of only mild LV dysfunction in most of our patients, despite clinical symptoms of heart failure, is in accordance with studies showing that clinical signs of heart failure and depressed LV ejection fraction are independent risk factors after AMI.[1,2] The importance of symptoms both for risk of progression and degree of improvement achieved by ACE inhibition has previously been demonstrated in the Studies of Left Ventricular Dysfunction (SOLVD),[5,6,14,15] in which mortality and morbidity were most prevalent in symptomatic patients (in the treatment trial), and significant reduction in mortality was seen only in the treatment and not in the prevention trial.[6,7] Improvement in LV function was only seen in symptomatic patients, despite a similar degree of systolic dysfunction and ejection fraction 25 versus 29%.[14,15]

The finding of a negative correlation between functional class and AVPD shows that this measurement of LV systolic function correlates with clinical symptoms. In the spirit of the AIRE study, using simple and inexpensive methods to select high-risk patients, we used AVPD to measure LV function because it is an easily applicable method that can be performed in most hospitals, even with less advanced echocardiographic equipment and at a small expense. It takes only a few minutes to perform an examination, and highly reproducible results can be achieved even by persons without much experience.[16] In contrast, ejection fraction measurement by 2-D echocardiography is dependent on image quality, with good definition of the endocardial border, and it must be possible to find the true long axis both in the two- and four-chamber views with high reproducibility if serial measurements are to be made. Ejection fraction measurement using radionuclide scans is most often of good quality and is probably the most reproducible method, but it is costly because of the expense of equipment and isotopes and is therefore not available in small hospitals. Furthermore, if serial measurements are needed, exposing patients to increasing doses of radiation may be a matter of concern.

Studies by Alam and Rosenhamer[16,17] and Pai *et al.*[18] have shown that there is good correlation between ejection fraction assessed by radionuclide scans and AVPD in patients with AMI and in those with congestive heart failure. This is not unexpected, as part of the systolic reduction in LV volume occurs in the longitudinal plane of the heart. In patients with AMI, decreased AVPD has been seen in the part which corresponds to the infarcted area.[17]

In the present study, the coefficient of variation between individuals was 9%, similar to that found in previous studies,[10] and better than for ejection fraction 17%. Similar results have been observed in previous studies.[16,18,19] There could be several reasons for that; AVPD is an M-mode measurement having a higher resolution (1000 frames/s) compared with ejection fraction which is a 2-D measurement (25–50 frames/s). In contrast to ejection fraction, AVPD measurements do not depend on lateral resolution with poor image quality, which is often a major problem in older patients. However, this study was not designed for evaluation of the two methods, and the measurements of ejection fraction were not performed as carefully as AVPD measurements, which may account for the difference favoring the latter. However, in the study by Pai *et al.*,[18] the correlation between ejection fraction measured by radionuclide scans and AVPD was better than between ejection fraction estimated from 2-D echocardiography and radionuclide scans. The correlation between AVPD and ejection fraction and stroke volume in the present study was not as good as previously reported,[16–18] probably due to suboptimal image quality. In clinical practice, however, it is our experience that it is often possible to measure AVPD in patients with

very poor 2-D images where ejection fraction or wall motion is impossible to obtain. Therefore, in patients with poor image quality, changes in LV function should be detected more easily by measurement of AVPD than by ejection fraction.

Conclusion

Treatment with an ACE inhibitor may improve systolic function even in patients with mildly depressed LV systolic function and symptoms of heart failure. We found that AVPD measurement can be performed easily and reproducibly in post AMI patients and that the method may be as good as ejection fraction, especially in older patients in whom only poor image quality is obtained.

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