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Effects of Long-Term Transdermal Nitrate Treatment on Left Ventricular Function in Patients Following Myocardial Infarction

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Summary

Background: Nitrates are widely used for the treatment of myocardial infarction (MI). The large megatrials (GISSI-3 and ISIS-4) did not in fact demonstrate a significant decrease in mortality in the nitrate-treated group. However, examination of the number of postinfarction angina episodes and the occurrence of cardiogenic shock in the GISSI-3 study did reveal significant decreases.

Hypothesis: It was hypothesized that chronic nitrate treatment after an MI preserves left ventricular systolic and/or diastolic functions.

Methods: Patients were divided into two groups: those receiving chronic nitrate treatment for 6 months after an MI (n = 30), and those without such treatment (n = 29). Echocardiography was performed 3, 14, 42, and 180 days after the infarction. The changes in early diastolic and atrial contraction-related mitral valve inflow pattern and deceleration time were assayed. Alterations in systolic, diastolic, and atrial reverse flow velocities in the pulmonary vein were measured, as were ejection fraction (EF), the number of registered angina episodes, and the maximal ST-segment depression in response to the stress test.

Results: During the 6-month study period, the increase in systolic pulmonary venous flow velocity was significantly larger in the nitrate group than in the controls. The decreases in the velocities of the diastolic and the atrial reverse flow were also more pronounced in the nitrate group than in the controls. The EF was improved only in the nitrate group. Examination of the maximal ST-segment depression in response to the stress test revealed a significant decrease in the nitrate group only. There were no significant differences between the two groups in the number of registered angina episodes or mitral inflow pattern.

Conclusions: The study showed that prolonged nitrate treatment after an MI may help preserve diastolic left ventricular function.

Key words: nitrate, myocardial infarction, diastole, pulmonary veins

Introduction

The administration of nitrate compounds for the treatment and prevention of angina pectoris has been known for more than 100 years. The vasodilatory effects of such compounds are more pronounced on the venous system. Consequently, they reduce preload more substantially than afterload. The vasodilatory effects lead to reductions in (1) left ventricular (LV) filling pressure, (2) dilatation of the ventricle, and (3) systolic wall tension.[1] These hemodynamic changes result in reduced energy and oxygen demands of the myocardium and improve the subendocardial blood flow. When administered in an acute myocardial infarction (MI), the nitrates reduce pulmonary congestion, complaints about dyspnea, and arterial blood pressure, and simultaneously increase cardiac output.[2–5] Consequently, nitrates are widely used for the treatment of MI in forms ranging from sublingual to transdermal and intravenous.[6–8] Two large multicenter studies, Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico (GISSI-3) and the Fourth International Study of Infarct Survival (ISIS-4), dealt with the effects of nitrates on mortality following MI.[9,10] These two megatrials, in fact, demonstrated no significant decrease in mortality in the nitrate-treated group; merely a small decrease was noted in 6-week mortality, which did not reach a level of significance (for 1,000 patients, this decrease was 2.1 in ISIS-4, and 3.9 in GISSI-3). However, examination

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of the number of postinfarction angina episodes and the occurrence of cardiogenic shock in the GISSI-3 study did reveal significant decreases ($p = 0.03$ and $p = 0.009$, respectively). These data may be indicative of the advantageous effects of nitrates in patients post infarction.

During the development of the ischemic cascade, damage to the diastolic function precedes the onset of the impairment of the systolic function.[11] Consequently, identification of impaired diastolic and systolic functions has been considered to be an important prognostic factor in heart disease.[12] For assessment of diastolic function, the most appropriate technique is traditional Doppler echocardiography, by virtue of its ready availability and simplicity. The principle of "diastology" was initiated more than a decade ago, and large numbers of studies have been performed with the aim of determining diastolic function with the aid of Doppler echocardiography.[13–17] A characteristic echocardiographic sign of diastolic dysfunction is a decrease in the E wave (passive filling), and an increase in the A wave (atrial contraction) of the mitral valve inflow, which result in a decreased E/A ratio. Besides these alterations, a prolongation of the deceleration time (DT) has been reported. The Norwegian Tromso study, which was based on more than 3,000 examinations, concluded that determinations of E/A and DT are not suitable for the diagnosis of diastolic dysfunction.[18] However, comparison of the values observed for the same patient at different times may reveal changes in diastolic function. On the other hand, Garcia *et al.*[19] found that conventional echocardiographic parameters (E, A, and E/A), together with certain complementary parameters (e.g., pulmonary venous flow velocities and isovolumetric relaxation time) can be reliable indicators of diastolic function. Most normal adult patients have a prominent systolic (S) versus diastolic (D) pulmonary venous flow velocity and a ratio of $S/D > 1$. In patients with elevated LV filling pressure, severe mitral regurgitation, or reduced LV compliance, there is a decrease in S flow and an increase in D flow. This typical pattern, in addition to high atrial reverse (AR) flow velocity, has been used to differentiate between normal and pseudonormal transmitral Doppler filling.[16, 20]

Since the data available on clinical effectiveness of prolonged nitrate treatment in stable patients post infarction are conflicting,[9, 10] a clinical study was organized to characterize the effects of prolonged transdermal nitrate treatment on (1) diastolic and systolic LV functions evaluated by echocardiography and (2) various other clinical parameters (blood pressure, heart rate, number of angina episodes during the treatment period, and maximal ST depression in response to the stress test). The aim of the study was to examine whether chronic nitrate treatment in stable patients post infarction is associated with any improvement in these clinical endpoints.

Patients, Materials and Methods

Patients aged between 18 and 85 years, with a diagnosis of MI and who were in stable clinical condition, were enrolled in the study. Enrollment was carried out between March 1, 2000, and October 31, 2000. The diagnosis of MI was based on troponinT (Qualitative, Roche Diagnostic Corporation, Indianapolis, Ind., USA) positivity and the presence of at least two of the following conditions: (1) Chest pain lasting for > 20 min and no reaction to sublingual nitrate; (2) creatine kinase (CK) and/or CK-MB level increase to more than double the upper limit of normal range; (3) ST elevation of ≥ 1 mm in at least two connected standard leads (representing the same area), or of ≥ 2 mm in at least two thoracic leads; and (4) development of a new left bundle-branch block.

Patients were regarded as clinically stable if (1) there were no recurring angina episodes, (2) there was no pulmonary congestion, (3) no invasive intervention was planned, and (4) blood pressure was in the range 100–150/65–90 mmHg. The exclusion criteria were as follows: (1) chest pain requiring sublingual nitrate within 14 days of the onset of MI; (2) pulmonary congestion requiring diuretic treatment; (3) a coronary intervention (percutaneous coronary intervention or aortocoronary bypass surgery); (4) severe hypotension or hypertension; (5) right ventricular infarction; (6) intolerable side effects in response to nitrate (headache or allergy); (7) the presence of a clinically significant aortic or mitral insufficiency; and (8) molsidomine treatment. During the 8-month enrollment period, 92 patients were screened for eligibility for inclusion. In 33 cases, conditions necessitating exclusion were observed (in 8 cases, recurring angina within the first 2 weeks after the infarction; in 6 cases, pulmonary congestion requiring diuretics; in 7 cases, coronary intervention; in 2 cases, severe hypotension; in 3 cases, severe hypertension; in 5 cases, intolerable nitrate-induced headache; and in 2 cases, nitrate-related skin allergy). Finally, 59 patients were enrolled in the study and the data on these cases have been analyzed. All patients received intravenous nitroglycerin within the first 48 h after the infarction. Two therapy groups were then formed: one (the nitrate group, comprising 30 patients) received transdermal nitroglycerin treatment (0.2 mg/h) for 6 months from Day 3 after the infarction. The other group was regarded as the control group (consisting of 29 patients) and received nitrate-free treatment for 6 months after Day 2 of the MI (sublingual nitrate was allowed at the onset of angina in both groups). To avoid the development of nitrate resistance, the patch was applied at 7 A.M. and was removed at 7 P.M. each day (except on the days of the visits, when the patch was employed after the examinations). All concomitant treatments with aspirin, beta blockers, and angiotensin-converting enzyme (ACE) inhibitors corresponded to the usual clinical practice, and there was no significant difference between the two groups either at baseline or at the end of the study (Table I). During the randomization period, patients who received odd numbers were enrolled into the nitrate group, while those with even numbers entered the control group. Before randomization, all patients provided their written consent to the study, which was performed with the approval of the local Ethics Committee. The study visits were performed on Days 3, 14, and 42 (± 2 days) and at 6 months (± 2 weeks) following the infarction (Visits 1, 2, 3 and 4, respectively), and included a detailed physical examination, a 12-lead electrocardiogram (ECG)

TABLE I Concomitant medication in the two groups (% of patients)

	BB	ACE-I	AngIIb	ASA	Diuretics	CAA	AC	Statin
Basal treatment								
Nitrate group	90	87	7	73	37	10	10	30
Control group	93	83	7	79	34	10	14	34
Treatment at the end of the study								
Nitrate group	90	82	5	70	33	8	8	26
Control group	93	83	5	79	30	10	12	30

Abbreviations: BB = beta blocker, ACE-I = angiotensin-converting enzyme inhibitor, AngIIb = angiotensin II receptor blocker, ASA = aspirin, CAA = calcium antagonist, AC = oral anticoagulant.

and Doppler echocardiography. The E and A waves of the mitral inflow as well as DT were measured by continuous-wave Doppler echocardiography (at all four visits). Moreover, pulmonary venous flow velocities (pulsed-wave Doppler) and ejection fraction (EF) were also determined. Wall motions, cavity diameters, and valve functions were established according to the usual clinical practice. Two independent experts performed echocardiography without knowledge of the treatment of the patient (single-blinded), using an HP (Hewlett-Packard Co., Andover, Mass., USA) SONOS 2000 device equipped with a 2.5 MHz transducer. The results of the two examinations were averaged and used for further evaluation. The mean intra- and interobserver differences ± standard deviation (SD) of the measurements were as follows: (1) EF -0.30 ± 2.29 and -0.76 ± 3.65%, respectively; (2) S wave of the pulmonary flow 0.20 ± 2.33 and 0.40 ± 5.87 cm/s, respectively; and (3) D wave of the pulmonary flow: -0.95 ± 2.25 and 1.45 ± 5.30 cm/s, respectively. The Doppler sample volume was situated caudally to the mitral annulus, between the tips of the mitral leaflets, where the peak inflow velocity in early diastole was recorded. Deceleration time was measured as the time between the peak E wave and the deceleration slope extrapolated to the baseline. Pulmonary venous flow recordings were obtained from the four-chamber view directed to the right upper pulmonary vein. The sample volume was obtained 1–2 cm into the pulmonary vein. The modified biplane Simpson formula was administered to define EF.[21] No automatic border detection was used for the measurements. All examinations were performed between 10 and 12 A.M.

Exercise tests were performed during Visits 2 and 3, with a Marquette (ACU 002C Milwaukee, Wisc., USA) treadmill. The first test was carried out according to the Naughton protocol (as is usual with early infarctions—Day 14), and the second test according to the Bruce protocol.[22] Both tests were carried out between 10 and 12 A.M., without interrupting the concomitant medical therapy and without knowledge of the treatment of the patient (single-blinded). ST segment depression was measured automatically on averaged QRST complexes. No patient had a left bundle-branch block or atrial fibrillation during the study.

All patients recorded the number of angina episodes requiring nitrate in a specially issued patient's diary. Blood pressure was measured with a mercury manometer in a sitting position after a 5-min period of resting, according to the method of Korotkoff. Pulse was checked at the same time on the radial artery by counting for 1 min.

Statistical Analysis

All data are reported as means ± SD. Categorical data were compared by means of Fischer's exact test. For continuous independent variables such as age and angina pectoris, Student's *t*-test was used. Analysis of variance was applied for E, A, E/A, S, D, AR, EF, the stress test, blood pressure, and heart rate variables. Post hoc analysis was carried out with the Tukey test. Two-sided statistical tests were performed at a level of significance of 5%. Statistical analyses were performed with the SAS statistical software package (version 6.12) (SAS, Cary, N.C., USA.).

Results

First, the homogeneity of the two groups was examined. There was no statistical difference between the groups regarding the risk factors examined (Table II), that is, age, gender, hy-

TABLE II Patient characteristics in the two groups

Variable	Nitrate group (n = 30)	Control group (n = 29)	p Value
Age (years)	66.7 ± 9.6	65.7 ± 10.4	NS
Male/female	18/12	16/13	NS
Hypertension	7	8	NS
Smoking	10	10	NS
Elevated total cholesterol level (>5.0 mmol/l)	9	7	NS
Diabetes mellitus	4	7	NS
Previous MI	5	6	NS
Location of current MI (anterior/inferior)	17/13	15/14	NS

Abbreviations: MI = myocardial infarction, NS = not significant.

pertension, smoking, total cholesterol level, diabetes mellitus, previous MI, and location of current infarction. Subsequently, the outset values for the two treatment groups at Visits 1 to 4 were compared. As to mitral inflow velocities (E and A waves, E/A, and DT), there was no difference between the two groups throughout the treatment period (Table III). Moreover, there was no significant difference in the different mitral inflow parameters within the individual groups at the different times (Table III). The outset values of the pulmonary flow velocities (S and D waves) were not significantly different for the two groups at the time of Visit 1. Examination of the changes in the value of S during the period of the study revealed a gradual and significant increase in both groups, which was more pronounced in the patients who received nitrate (Table IV, Fig. 1). The D value, on the other hand, displayed a gradual and significant decrease in both groups during the study period. This decrease, similar to that in S, was more pronounced in the nitrate group (Table IV, Fig. 1). The AR wave was identical in the two groups at Visit 1 and subsequently declined significantly in both groups. For this parameter as well, the changes were larger in the nitrate group (Table IV, Fig. 1).

Ejection fraction was statistically identical in the two groups at Visit 2. However, the nitrate group exhibited a gradual and significant increase in this parameter (Table V), and at Visit 4 it exceeded the value for the control group significantly (nitrate group 52.6 ± 7.4% and control group 47.4 ± 7.3%). Examination of LV end-diastolic diameter revealed no statistically significant difference between the two groups. Moreover, there was no significant difference in this parameter within the individual groups at the different times. The maximal ST depression during the exercise test was statistically identical in the two groups at Visit 2. At Visit 3, the maximal ST depression was significantly reduced in the nitrate group compared with the value measured at Visit 2, while the ST depression observed in the control group did not change significantly between Visits 2 and 3. The decrease in the ST-segment depression in the nitrate-treated group during the study resulted in a significant difference between the two groups at Visit 3 (Table V).

No statistically significant difference between the two groups was noted in the number of angina episodes during the study period. Moreover, the two treatment groups did not differ significantly in systolic and diastolic blood pressures and heart rate (Table V); because of the small number of mortalities, no statistical analysis was carried out in this respect. In the nitrate group, two patients died (one sudden death at home, and one traffic accident), while in the control group three patients died (one apoplexy, one pneumonia, and one acute LV failure).

Discussion

The data of this trial have demonstrated that long-term nitrate treatment after an MI is associated with (1) a slightly, but significantly improved LVEF; (2) a greater increase in S; (3)

TABLE III Doppler values of mitral flow in the two groups

	Nitrate group (n = 30)				Control group (n = 29)				
Variable	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	p Value
Early mitral inflow velocity (E, cm/s)	56.6 ± 10.6	56.3 ± 9.1	58.2 ± 9.1	56.5 ± 10.3	55.9 ± 9.7	54.0 ± 7.7	57.1 ± 8.0	55.1 ± 9.2	NS [a] NS [b] NS [c] NS [d]
Atrial inflow velocity (A, cm/s)	63.2 ± 9.6	60.0 ± 9.2	63.4 ± 7.7	60.8 ± 7.9	63.1 ± 7.8	59.1 ± 8.7	63.1 ± 7.8	58.7 ± 8.2	NS [a] NS [b] NS [c] NS [d]
Ratio of E/A	0.92 ± 0.22	0.95 ± 0.16	0.92 ± 0.13	0.93 ± 0.14	0.90 ± 0.21	0.93 ± 0.16	0.91 ± 0.13	0.95 ± 0.17	NS [a] NS [b] NS [c] NS [d]
Early inflow deceleration time (DT, ms)	219 ± 16	219 ± 16	216 ± 18	221 ± 21	215 ± 16	220 ± 15	216 ± 16	221 ± 18	NS [a] NS [b] NS [c] NS [d]

[a] Difference between nitrate and control groups at the beginning of the study (Visit 1).
[b] Difference between nitrate and control groups at the end of the study (Visit 4).
[c] Difference within nitrate group between Visits 1 and 4.
[d] Difference within control group between Visits 1 and 4.
Abbreviations: DT = deceleration time, NS = not significant.

TABLE IV Doppler values of pulmonary venous flow in the two groups

	Nitrate group (n = 30)				Control group (n = 29)				
Variable	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	p Value
									NS [a]
Systolic pulmonary									0.010 [b]
venous flow	35.1	34.8	44.2	54.9	35.4	35.4	43.6	47.8	0.002 [c]
velocity (S, cm/s)	± 12.0	± 9.7	± 9.5	± 10.9	± 11.8	± 10.6	± 8.7	± 9.3	0.002 [d]
									NS [a]
Diastolic pulmonary									0.001 [b]
venous flow	51.6	46.0	41.7	37.9	53.7	55.5	46.9	47.8	0.0002 [c]
velocity (D, cm/s)	± 8.0	± 7.7	± 9.8	± 11.9	± 7.1	± 9.1	± 8.4	± 9.5	0.0002 [d]
									NS [a]
Ratio of S/D	0.68	0.76	1.06	1.45	0.66	0.64	0.93	1.0	0.001 [b]
	± 0.08	± 0.09	± 0.11	± 0.12	± 0.08	± 0.08	± 0.10	± 0.11	0.0002 [c]
									0.0002 [d]
									NS [a]
Pulmonary venous									0.01 [b]
atrial reverse flow	41.6	41.3	36.5	26.8	42.7	43.0	38.3	32.9	0.0002 [c]
velocity (AR, cm/s)	± 10.0	± 10.3	± 10.7	± 8.4	± 9.7	± 10.0	± 10.3	± 8.8	0.0002 [d]

[a] Difference between nitrate and control groups at the beginning of the study (Visit 1).
[b] Difference between nitrate and control groups at the end of the study (Visit 4).
[c] Difference within nitrate group between Visits 1 and 4.
[d] Difference within control group between Visits 1 and 4.
Abbreviations as in Table III.

a greater decrease in D and AR; (4) a larger ratio of S/D; and (5) a decrease in the maximal ST depression in response to the stress test, compared with the control group. The pulmonary venous flow (S, D, and S/D) changes, together with the alterations in EF, suggest better-preserved diastolic and systolic functions of the left ventricle in response to nitrate treatment following an MI. It is interesting that examination of the conventional echocardiographic parameters (E/A and DT) characterizing LV diastolic function revealed no statistical difference between the nitrate-treated and control groups. Explanations for this discrepancy could be that (1) the transmitral inflow pattern was not a reliable indicator because of relatively preserved (only mildly reduced) LV systolic function (EF), (2) the pulmonary venous flow indices are more sensitive indicators of diastolic function than is E/A or DT,[19] and (3) the nitrates exert a more pronounced effect on the preload than on the afterload.

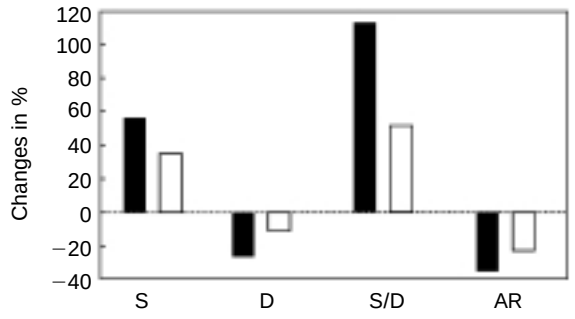

FIG. 1 Percent changes in pulmonary venous flow velocities in the nitrate-treated and control groups during the study (between Visits 1 and 4). The negative values reflect a decreasing tendency, and the positive values an increasing tendency of the different parameters. S = systolic pulmonary flow velocity, D = diastolic pulmonary flow velocity, S/D = ratio of systolic and diastolic flows, AR = atrial reverse flow velocity. ■ = Nitrate treated, □ = control.

Due to the relatively low numbers of enrolled patients and deaths during the study period (two deaths in the nitrate group and three in the control group), statistical evaluation of the mortality data was not carried out. However, no sign of an excess mortality was observed upon nitrate treatment.

Opinions differ concerning the effectiveness of prolonged nitrate treatment following an MI. Although large multicenter randomized studies (GISSI-3 and ISIS-4) have reported a minor effect of nitrate treatment on decreasing mortality, this effect did not reach the level of statistical significance.[9, 10] However, in order to promote a better quality of life (symptom relief) for the patients, in the absence of any contraindications, prolonged transdermal or oral formulations of nitrates may be applied after an infarction (even if there are no complaints).[6]

Earlier clinical studies on patients post infarction suggested that ACE inhibitors prevent the development of LV remodel-

TABLE V Effects of nitrate treatment on left ventricular ejection fraction, left ventricular end-diastolic diameter, maximal ST depression in response to stress test, number of angina episodes, blood pressure, and heart rate in the two groups

	Nitrate group (n = 30)				Control group (n = 29)				
Variable	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	p Value
Left ventricular systolic EF (%)		50.6 ± 7.0	50.8 ± 7.6	52.6 ± 7.4		48.5 ± 6.0	49.7 ± 6.1	47.4 ± 7.3	NS [a] 0.01 [b] 0.03 [c] NS [d]
LVEDD (mm)		55.8 ± 8.2	54.9 ± 9.1	53.6 ± 8.4		56.6 ± 7.4	56.1 ± 7.9	55.5 ± 7.5	NS [a] NS [b] NS [c] NS [d]
Maximal ST depression in response to stress test (mm)		0.76 ± 0.46	0.60 ± 0.44			0.82 ± 0.38	0.90 ± 0.38		NS [a] 0.01 [b] 0.003 [c] NS [d]
Number of angina episodes requiring sl. nitrates/6 months				1.86 ± 1.6				2.62 ± 1.8	0.11 [b]
Blood pressure (mm Hg)	118 ± 12/ 74 ± 8	118 ± 12/ 74 ± 5	118 ± 10/ 74 ± 6	119 ± 12/ 74 ± 6	123 ± 11/ 75 ± 6	122 ± 12/ 75 ± 5	121 ± 10/ 76 ± 5	122 ± 10/ 76 ± 6	NS [a] NS [b] NS [c] NS [d]
Heart rate (beats/min)	76 ± 7	77 ± 7	77 ± 5	79 ± 7	75 ± 6	75 ± 5	73 ± 5	75 ± 7	NS [a] NS [b] NS [c] NS [d]

[a] Difference between nitrate and control groups at the beginning of the study (Visit 1; Visit 2 for EF and the stress test).
[b] Difference between nitrate and control groups at the end of the study (Visit 4; Visit 3 for the stress test).
[c] Difference within the nitrate group between Visits 1 and 4 (Visits 2 and 4 for EF and Visits 2 and 3 for the stress test).
[d] Difference within the control group between Visits 1 and 4 (Visits 2 and 4 for EF and visits 2 and 3 for the stress test).
Abbreviations: Sl = sublingual, EF = ejection fraction, LVEDD = left ventricular end-diastolic diameter, NS = not significant.

ing.[1] In the present study, the changes observed in LV function could not be mediated by ACE inhibition, since there was no statistical difference in concomitant medical treatment (ACE inhibitors, angiotensin II receptor blockers, beta blockers, etc.) during the trial between the nitrate-treated and control groups. Moreover, no significant change occurred in the degree of hypertension, diabetes control, and smoking habits of the patients during the 6 months of the study. How can nitrates preserve LV function following MI? The beneficial effects are most probably complex. The histological recovery after an MI involves collagen deposition and the formation of strong scar tissue in the infarcted zone to resist distension and wall dilation. However, the insufficiency of these defensive mechanisms in a majority of cases means that early remodeling leads to local dilation and expansion of the involved area within a few days after the infarction.[23, 24] This process can eventually give rise to overall ventricular dilation and an elevated diastolic wall tension in both the infarcted zone and the intact area. Nitrates protect LV function and prevent the extension of the infarcted area (and the development of an aneurysm) by lowering the ventricular wall tension and preserving the collagen matrix in the necrotic zone.[7, 8, 23, 24] Moreover, it has been shown that nitrates exert a protective effect on the myocardium following stunning and reperfusion damage.[25] The anti-ischemic properties of nitrates have also been demonstrated in our study, since a significant reduction was noted in the maximal ST-segment depression in response to the stress test in the nitrate group compared with the controls.

Limitations of the Study

No placebo treatment and double-blind approach was used in the trial (only the echocardiographic examinations and the treadmill test were carried out single-blinded); consequently, some experimental bias cannot be excluded. Furthermore, only a limited number of conventional echocardiographic parameters (E/A, DT, S, D, and AR) characterizing LV diastolic function were utilized.

Conclusion

Prolonged nitrate treatment following a myocardial infarction results in better-preserved left ventricular diastolic function, as evidenced by echocardiography. These limited observations justify further studies on the beneficial effects of nitrates on left ventricular function, and the authors plan to extend this examination to a larger number of patients in the future, employing novel echocardiographic techniques (e.g., tissue Doppler echocardiography).

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