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Hemodynamic Effects of Captopril and Isosorbide Mononitrate Started Early in Acute Myocardial Infarction: A Randomized Placebo-Controlled Study

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Objectives. **The aim of this study was to study the hemodynamic effects of orally administered captopril and isosorbide mononitrate in suspected acute myocardial infarction.**

Background. **Early treatment with converting enzyme inhibitors and nitrates in acute myocardial infarction may limit infarct expansion and prevent left ventricular dilation.**

Methods. **In a double-blind study, 81 patients were randomized within 36 h of the onset of symptoms of suspected acute myocardial infarction to 1 month of oral captopril (6.25 mg initial dose, followed 2 h later by 12.5 mg and continuing with 12.5 mg three times daily), isosorbide mononitrate (initial dose 20 mg followed by 20 mg three times daily) or matching placebo. The effects of treatment on changes from baseline in mean arterial blood pressure, heart rate, stroke volume, cardiac output and systemic vascular resistance were assessed noninvasively using Doppler echocardiography 1 h after the first dose, 1 week after infarction and at 6 weeks (that is, 2 weeks after the scheduled end of trial treatment).**

Results. **One hour after the start of treatment, blood pressure was reduced by ≈10% with both captopril and isosorbide mononitrate, but this difference did not persist at 1 week. Captopril was associated with a significant increase in cardiac output compared with placebo of 13 ± 3% at 1 h ($p < 0.01$), 23 ± 5% at 1 week ($p < 0.001$) and 22 ± 6% ($p < 0.05$) at 6 weeks (2 weeks after the end of trial treatment). This increase in cardiac output with captopril was mainly due to a substantial and sustained increase in stroke volume, although there was also a small increase in heart rate at 1 week. Both captopril and isosorbide mononitrate reduced systemic vascular resistance within 1 h of the start of treatment, but only the effect of captopril was sustained (perhaps because the three-times daily nitrate regimen induced tolerance). Study treatment was well tolerated, and the incidence of withdrawal of study treatment for hypotension was not significantly different from that with placebo.**

Conclusions. **This study indicates that the hemodynamic effects of both captopril and isosorbide mononitrate are well tolerated in the acute phase of myocardial infarction and that captopril favorably influences cardiac function.**

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Left ventricular dilation is a major independent predictor of poor outcome after myocardial infarction and is associated with an increased risk of congestive heart failure, ventricular aneurysm formation, cardiac rupture and death (1–6). The major cause of early ventricular dilation is infarct expansion (2,3), which can start during the first few days after the initial infarction, whereas later progressive ventricular dilation, which occurs largely during the first few months (7,8), may occur as a result of increased wall stress produced by remodeling of both infarct and noninfarct areas (3,9). In experimental infarction, increasing wall stress exacerbates infarct expansion (10), whereas converting enzyme inhibitors (11–14) and nitrates (15), which reduce wall stress, have been shown to limit infarct expansion and ventricular dilation. In patients with acute myocardial infarction, there is evidence that intravenous nitrates started early and continued for 24 to 48 h can improve ventricular remodeling (16) and reduce mortality (17). Similarly promising effects have been observed in studies of converting enzyme inhibitors started later after the acute phase of infarction (7,8,18–20). Evidence is more limited about the effects of nitrate therapy continued beyond the first few days (21) or of converting enzyme inhibitor therapy started in the acute phase of infarction (22–26). Moreover, concerns have been expressed about potential adverse effects of starting converting enzyme inhibition early in acute myocardial infarction (8,25). However, because ventricular dilation starts early after infarc-

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tion, any benefits may be greatest if treatment is started as early as possible and continued for at least the 1st month, when the majority of any dilation occurs (7,8).

The International Study of Infarct Survival (ISIS)-4 "three-way" randomized placebo-controlled pilot study was therefore set up to assess the safety and tolerability of 1 month of oral captopril therapy and 1 month of oral isosorbide mononitrate treatment started during the acute phase of suspected acute myocardial infarction. The present report describes a substudy in which the hemodynamic response to these treatments was investigated noninvasively using Doppler echocardiography.

Methods

Study patients. The study protocol was approved by the Central Oxford Research Ethics Committee, and all participating patients gave their informed consent. Patients were eligible for the ISIS-4 pilot study if the symptoms of suspected acute myocardial infarction (with or without ST elevation on the presenting electrocardiogram (ECG)) had started <36 h before and there were no clear indications for, or contraindications to, prolonged use of converting enzyme inhibitors or nitrates (for example, systolic blood pressure persistently <90 mm Hg). Patients who were to be given intravenous nitrates for just the first few days were still eligible. The intent was to randomize patients as promptly as possible after admission to the hospital, but patients who were not eligible on admission (perhaps because of some contraindication such as hypotension) could be reassessed a few hours later and entered into the study if they were still eligible and within 36 h from symptom onset.

Patients were entered into the trial by the responsible physicians, who telephoned a 24-h randomization service. After providing a few baseline details, they were randomly allocated to receive a treatment pack containing 1 month's supply of oral captopril (initial dose, 6.25 mg followed 2 h later by 12.5 mg and continuing with 12.5 mg three times daily), isosorbide mononitrate (initial dose 20 mg followed by 20 mg three times daily) or matching placebo. Apart from any planned short-term intravenous nitrate use, nonstudy nitrates and converting enzyme inhibitors were to be used only if a clear indication was thought to have developed. All other aspects of patient management were left entirely to the discretion of the responsible physician.

Hemodynamic assessment. Patients were to be included in this detailed substudy of the hemodynamic response to treatment if after randomization but before the start of placebo-controlled trial treatment, they were in sinus rhythm and it was technically possible to obtain a good quality Doppler signal. Eighty-one of the 123 patients randomized in the ISIS-4 pilot study from the John Radcliffe Hospital between August 1989 and July 1990 fulfilled these eligibility criteria and were included in the substudy. Systolic, diastolic and mean arterial (D+(S−D)/3) blood pressure (by standard sphygmomanometer), heart rate and blood velocity in the ascending aorta (by Doppler echocardiography) were recorded immediately before the start of trial treatment, 1 h after the first dose, 1 week after the start of trial treatment and at 6 weeks (that is, 2 weeks after the scheduled end of trial treatment to allow a washout period). The assessments at 1 week and 6 weeks were performed 6 h after any morning medication was taken. The recording and analysis of the Doppler signal, as well as the clinical follow-up, was performed without knowledge of the trial treatment.

Doppler echocardiography was performed by a single observer using an Alfred (Vingmed) ultrasound generator with a 2-MHz pulsed wave Doppler transducer directed from the suprasternal window with the patient supine. The sample volume was set at a level just above the aortic valve (4 to 9 cm from the suprasternal notch) and the angle adjusted to obtain the highest audible pitch and the cleanest velocity curve on the display screen. All follow-up Doppler recordings in any particular patient were performed in the same position with the same depth setting as at baseline to help ensure that the recording was from the same point in the aorta. Stroke distance (averaged over 10 beats) was obtained by fast Fourier transform spectral analysis of the signal to obtain the intensity-weighted mean velocity, which was then integrated over time to derive the velocity integral or stroke distance. This system was developed and validated in the John Radcliffe Hospital cardiac hemodynamic laboratory (27,28). It has been shown that aortic cross-sectional area can be assumed to be constant over the short term in any particular patient (29,30), so that percent changes from baseline in stroke distance accurately reflect percent changes in stroke volume (taken as stroke distance multiplied by aortic cross-sectional area). Similarly, because cardiac output is equal to stroke distance times aortic area times heart rate, percent changes in the product of stroke distance and heart rate reflect percent changes in cardiac output. Percent changes in total systemic vascular resistance were estimated using the approximation that systemic vascular resistance equals mean blood pressure divided by cardiac output. The intraobserver variability for stroke distance (expressed as the SD of the differences between repeat measurements [31]) was previously determined to be 5.6%, and the month to month reproducibility was 7.4%.

Statistical methods. On the basis of these estimates of observer variability and reproducibility, it was calculated (32) that a study with at least 25 patients in each treatment group would provide 80% power at $p < 0.05$ to detect the type of differences (i.e., 10%) in cardiac output observed in previous studies (7,8). Comparisons of the percent change from baseline in each of the treatment groups compared with the percent change in the control group were made on an intention-to-treat basis except when follow-up data were unavailable because of death or nonattendance (see Results). One-way analysis of variance was performed at each time point and, if p was < 0.05, then two-way comparisons of each treatment versus control were carried out using two-tail

Table 1. Clinical Characteristics of Patients Studied

Variable	Captopril (n = 27)	ISMN (n = 22)	Placebo (n = 32)
Before randomization			
Age (yr)	62 ± 2	62 ± 3	62 ± 2
Male/female	20/7	18/4	26/6
Hours from pain onset	13 ± 1	12 ± 2	12 ± 1
Site of infarct			
Anterior	11 (41)	7 (32)	14 (44)
Inferior	15 (56)	14 (64)	15 (47)
Other	1 (4)	1 (5)	3 (9)
Baseline hemodynamic data			
Systolic BP (mm Hg)	129 ± 3	135 ± 5	128 ± 3
Diastolic BP (mm Hg)	81 ± 2	82 ± 3	79 ± 2
Mean BP (mm Hg)	97 ± 2	99 ± 2	95 ± 2
Heart rate (beats/min)	71 ± 3	71 ± 2	71 ± 2
Stroke distance (cm)	10.5 ± 0.6	10.2 ± 0.5	9.9 ± 0.3
After randomization and before discharge			
Treatment			
Fibrinolytic	26 (96)	20 (91)	30 (94)
Aspirin	27 (100)	22 (100)	31 (97)
i.v. ISDN	7 (26)	6 (27)	12 (38)
Beta-adrenergic blocking agents	15 (56)	15 (68)	18 (56)
Calcium antagonist	3 (11)	1 (5)	5 (16)
Peak enzyme (AST, U/liter)	363 ± 42	278 ± 43	370 ± 60
Infarction confirmed	27 (100)	22 (100)	31 (97)
Cardiogenic shock	1 (4)	1 (5)	0 (0)
Heart failure requiring diuretics	3 (11)	3 (14)	6 (19)
Coronary artery surgery	1 (4)	1 (5)	2 (6)
Stroke	0 (0)	0 (0)	1 (3)
Death	1 (4)	2 (9)	2 (6)

Data are expressed as mean value ± SEM or number (%) of patients. No differences between groups were significant. AST = aspartate aminotransferase; BP = blood pressure; ISMN = isosorbide mononitrate; i.v. ISDN = intravenous isosorbide dinitrate.

Student unpaired *t* test. All data are presented as mean value ± SEM.

Results

The clinical characteristics of the 81 patients included in this hemodynamic substudy are summarized in Table 1. There was good balance between the treatment groups for the main prognostic features recorded before randomization and for the baseline hemodynamic measures. The use of nontrial treatment in the hospital was similar in the three treatment groups, with 94% of patients receiving fibrinolytic therapy, 99% aspirin, 31% intravenous nitrates and 59% oral beta-adrenergic blocking agents. The use of indomethacin or ibuprofen was very rare and, although no data were available on specific use of inotropic agents, the incidence of cardiogenic shock was very low and similar in the three groups. Peak enzyme levels did not differ significantly among the groups, and all but one patient had the diagnosis of infarction subsequently confirmed by enzyme or ECG changes, or both.

Compliance with trial treatment was high (Table 2); 80% overall continued treatment until discharge or death, and a similar number of patients in each treatment group were withdrawn from treatment because of hypotension or other reasons. The rate of use of nontrial converting enzyme inhibitors or oral nitrates during or after the scheduled treatment period was low and was also similar in the different groups.

Table 2. Compliance With Trial Treatment

Outcome	Captopril (n = 27)	ISMN (n = 22)	Placebo (n = 32)
Started trial treatment	27 (100)	22 (100)	32 (100)
Continued treatment to death or discharge	23 (85)	18 (82)	24 (75)
Withdrawn			
Because of hypotension	2 (7)	1 (5)	2 (6)
For other reason	1 (4)	1 (5)	3 (9)
Nontrial CEI or nitrate during scheduled treatment period	1 (4)	2 (9)	3 (9)
CEI or nitrate after scheduled treatment period	4 (15)	3 (14)	5 (16)

There were no significant differences between groups in any of these measures of compliance. Data are expressed as number (%) of patients. CEI = converting enzyme inhibitor; ISMN = isosorbide mononitrate.

Table 3. Percent Changes From Baseline in Hemodynamic Measures

	Captopril	ISMN	Placebo
Patients studied (no.)			
1 h	27	22	32
1 wk	22	20	26
6 wk	24	17	25
Mean arterial BP			
1 h	−10 ± 2*	−10 ± 2*	−1 ± 1
1 wk	−8 ± 3	−7 ± 3	−8 ± 2
6 wk	−1 ± 3	+1 ± 4	−1 ± 3
Heart rate			
1 h	+5 ± 3	−3 ± 2	−1 ± 1
1 wk	+6 ± 5†	−10 ± 3	−9 ± 4
6 wk	+2 ± 5	−10 ± 6	−3 ± 4
Cardiac output			
1 h	+13 ± 3‡	+1 ± 2	+1 ± 2
1 wk	+23 ± 5*	−1 ± 4	−4 ± 4
6 wk	+22 ± 6†	0 ± 5	+7 ± 4
Stroke volume			
1 h	+8 ± 2†	+4 ± 2	+2 ± 1
1 wk	+18 ± 4†	+10 ± 3	+7 ± 3
6 wk	+22 ± 4	+15 ± 6	+11 ± 3
Systemic vascular resistance			
1 h	−19 ± 3*	−10 ± 3‡	−1 ± 1
1 wk	−22 ± 4*	−3 ± 4	−1 ± 4
6 wk	−14 ± 5	+4 ± 6	−3 ± 5

*$p < 0.001$, captopril versus placebo or isosorbide mononitrate versus placebo; †$p < 0.05$; ‡$p < 0.01$. Data are presented as mean percent change ± SEM. Abbreviations as in Table 1.

Hemodynamic changes. All 81 patients who had a baseline recording were also evaluated at 1 h after the first dose, but a Doppler recording was obtained at 1 week from only 68 patients (22 patients allocated to captopril, 20 allocated to isosorbide mononitrate, 26 allocated to placebo treatment) and at 6 weeks from 66 (24, 17 and 25, respectively). Complete follow-up data could not be obtained from 15 patients: 2 (1, 0 and 1) who required coronary artery surgery, 1 (0, 0 and 1) who had a stroke, 5 (1, 2 and 2) who died, 5 (1, 2 and 2) with a technically inadequate signal and 2 (0, 1 and 1) who subsequently refused repeat assessment. None of these reasons for incomplete follow-up was significantly more common in any particular treatment group.

Percent changes from baseline in mean arterial blood pressure, heart rate, cardiac output, stroke volume and systemic vascular resistance are shown in Table 3 and Figure 1. One hour after the first dose of trial treatment, mean arterial blood pressure was reduced by 10% in the captopril and the isosorbide mononitrate groups (both $p < 0.001$ compared with placebo), with similar reductions in both systolic and diastolic pressures. By 1 week, however, the change in mean blood pressure from baseline was similar in all three groups and remained so after the scheduled end of trial treatment (Table 3, Fig. 1a). There were no significant differences in heart rate between groups at 1 h and 6 weeks, but at 1 week there was a small increase in the captopril compared with the placebo group ($p < 0.05$, Table 3).

One hour after the first dose, cardiac output increased with captopril by 13 ± 3% compared with 1 ± 2% in the placebo group ($p < 0.01$). By 1 week, captopril was associated with a significant 23 ± 5% increase in cardiac output ($p < 0.001$ vs. placebo), which persisted even after the end of trial treatment (at 6 weeks; Table 3, Fig. 1b). In contrast, no significant change in cardiac output was observed in the isosorbide mononitrate group compared with the placebo

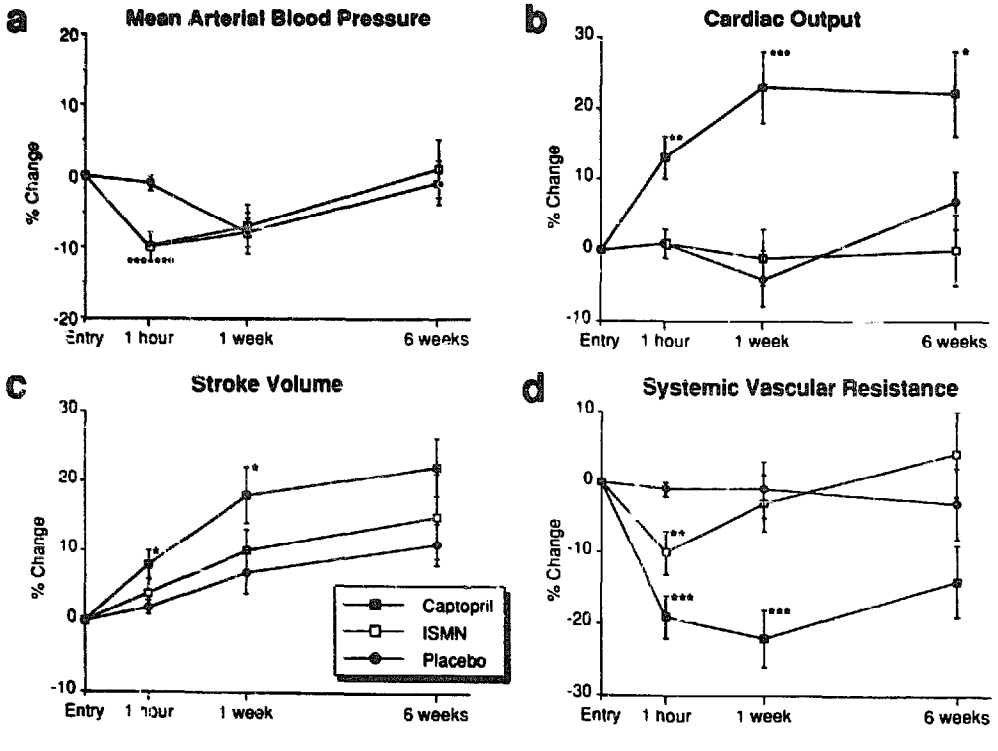

Figure 1. Percent changes (±1 SEM) from baseline in (**a**) mean arterial blood pressure, (**b**) cardiac output, (**c**) stroke volume and (**d**) systemic vascular resistance. The number of patients assessed at 1 h, 1 week and 6 weeks was 81, 68 and 66, respectively. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ comparing captopril or isosorbide mononitrate (ISMN) versus placebo.

group. The increase in cardiac output observed with captopril reflects a substantial and sustained increase in stroke volume (Table 3, Fig. 1c), with the small transitory increase in heart rate having only a small impact while captopril was being given. Both captopril and isosorbide mononitrate also significantly reduced systemic vascular resistance within 1 h of the first dose (Table 3, Fig. 1d), but, whereas this afterload reduction persisted subsequently with captopril, it did not appear to do so with isosorbide mononitrate.

The hemodynamic response to trial treatment was not apparently influenced by any of the recorded baseline characteristics, and there was no correlation between the change in blood pressure or the change in cardiac output and baseline blood pressure, heart rate, site of infarction, presence of heart failure, patient age or time delay from the onset of pain to randomization. The relation between changes in mean blood pressure and changes in cardiac output 1 h after the first dose of trial treatment for individual patients is shown in Figure 2. A decrease in blood pressure was observed in most patients with captopril or isosorbide mononitrate (that is, points to the left of the vertical zero line). But, despite this, cardiac output either increased, especially with captopril, or remained largely unchanged (that is, points between the horizontal ± 15% lines that represent ± 2 SD of the differences between repeat measurements [28]).

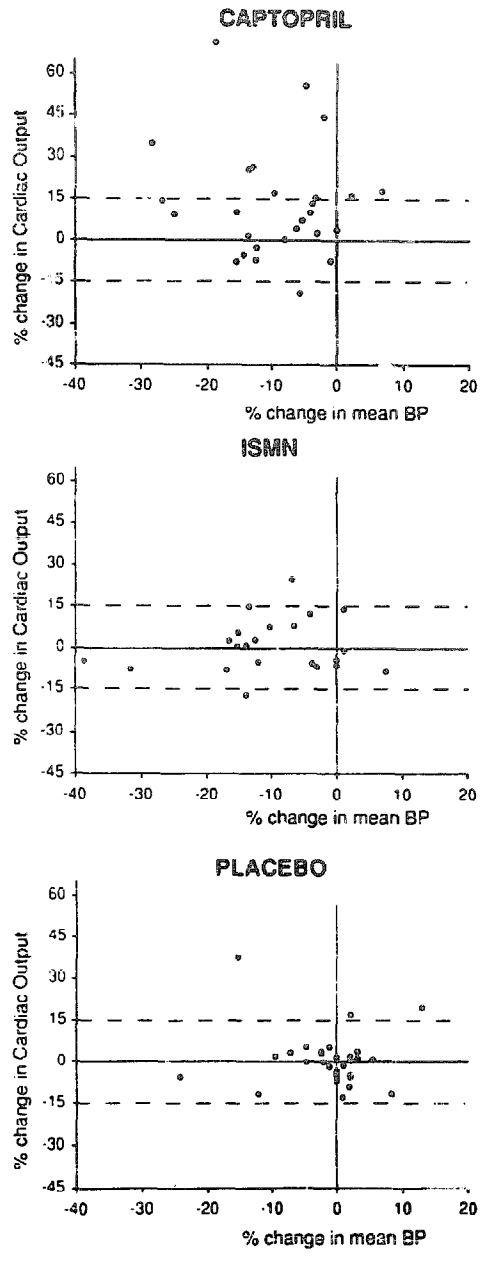

Figure 2. Correlation between percent changes in cardiac output and the percent changes in mean blood pressure (BP) 1 h after the first dose in the captopril, isosorbide mononitrate (ISMN) and placebo groups.

Discussion

Rationale for early use of vasodilators in acute myocardial infarction. There is growing evidence that nitrates (16) and converting enzyme inhibitors (7–9,22,23) may limit infarct expansion and attenuate ventricular dilation after myocardial infarction. Typically, the renin-angiotensin system is maximally activated within 72 h of acute myocardial infarction (33), with infarct expansion (2,22) and ventricular dilation (8) also starting during these first few days. Therefore, it is possible that afterload reduction during the very early phase of myocardial infarction could produce greater benefit than that of treatment started later during the recovery phase. However, the ventricular dilation and hypertrophy of noninfarcted myocardium that occur after myocardial infarction in response to increased wall stress may help to maintain cardiac output (34); therefore, blocking these compensatory mechanisms early after infarction could in theory be disadvantageous. Moreover, reducing blood pressure in the acute phase of infarction with these agents might have some adverse effects that could outweigh any benefits of earlier treatment.

However, indirect comparison of outcome in clinical studies of captopril started 24 to 48 h (8) and 8 to 9 days (7) after Q wave infarction suggests that starting treatment earlier may preserve ventricular shape and function more effectively. For, although ventricular dilation between the end of the 1st week after infarction and after 3 months was prevented to a similar extent by captopril at both times, dilation during the 1st week after infarction was greater than in the subsequent months, and early dilation was prevented by captopril therapy started at 24 to 48 h.

About one third to one half of all deaths during the 1st month after admission to the hospital with suspected acute myocardial infarction, occur on the day of admission or on the next day (35,36). A large proportion of these deaths, particularly those after thrombolytic therapy (37,38), have been attributed to causes such as cardiogenic shock and cardiac rupture (37) that are related to early infarct expansion and ventricular dilation (5). Consequently, delaying treatment even by 24 to 48 h may cause death that might otherwise have been prevented. Concerns have been ex-

pressed that reductions in blood pressure and coronary perfusion pressure during the acute phase of infarction might critically reduce myocardial perfusion, leading to infarct extension and, early after fibrinolysis, might increase the risk of reocclusion of recanalized coronary arteries (39). Indeed, for this reason, patients who had received fibrinolytic therapy were excluded from one study of captopril started in the acute phase of infarction (22). However, nitrates have been used widely in acute myocardial infarction, are well tolerated even during fibrinolysis and appear to produce beneficial effects not just on ventricular remodeling (16) but also on mortality (17).

Hemodynamic effects in the present study. In the present study, although both isosorbide mononitrate and captopril reduced blood pressure rapidly, stroke volume and cardiac output were maintained or, with captopril, increased in the acute phase. This may help to explain the clinical observation that patients who receive vasodilators tolerate the early reduction in blood pressure well whether (23,24) or not (22) fibrinolytic therapy has been given. Both the isosorbide mononitrate and the captopril regimens used in this study produced moderate early blood pressure reductions compared with values in the control group that did not persist beyond the first few days (24). Other than producing a transient reduction in systemic vascular resistance at 1 h, isosorbide mononitrate did not appear to have any effects on the hemodynamic variables measured. In contrast, captopril increased cardiac output and stroke volume and decreased peripheral vascular resistance throughout the 1-month scheduled treatment period, with the increase in cardiac output persisting even after treatment had been stopped. Captopril produced reductions in afterload and preload, both of which are thought to be important in the remodeling process (6,13). This may explain the differences in effects between captopril and nitrates because the latter predominantly affect preload with less influence on afterload. Another explanation for the apparent lack of effect of the isosorbide mononitrate regimen studied may be the development of tolerance to the three-times daily dosing schedule. This possibility is supported by the improvements in ventricular function observed in previous studies of other nitrate regimens (16). Also, about one third of the patients in this study received nitrates intravenously, which may have made it more difficult to detect any effects of oral nitrates on cardiac function.

Study limitations. Doppler echocardiography has been well validated for the assessment of cardiac output (31) and is a particularly useful noninvasive method for investigating hemodynamic changes after vasodilator therapy (40). The changes in cardiac output and other hemodynamic variables were estimated indirectly from the percent changes in stroke volume, assuming that the aortic cross-sectional area remained constant. Aortic diameter is difficult to measure accurately and reproducibly, and small differences can introduce large variations in flow calculations. However, changes in aortic area during a short time period, as in this study, have been shown to be small even with large flow changes (29,30), so that any errors in the assessment of hemodynamic variables are not likely to be significant. Individually stroke volume, cardiac output and ejection fraction are insensitive measures of left ventricular function because, for example, a dilated ventricle can often maintain a near-normal stroke volume despite a larger diastolic volume (41,42). However, although the present study only provides information about stroke volume, the results are in agreement with those of Sharpe et al. (8), who found that stroke volume index was increased and ventricular dilation prevented by captopril therapy started at 24 to 48 h. Treatment was given for just 4 weeks in the present study, and follow-up was continued for another 2 weeks after the end of treatment. This may appear relatively short, but the first few months after infarction constitute a particularly important period in the remodeling process. Consequently, vasodilator treatment during this early period may quickly produce a large part of any beneficial effects that might be observed with longer treatment.

Clinical implications. This study shows that both captopril and isosorbide mononitrate are well tolerated hemodynamically in the acute phase of infarction and their effects on cardiac function (particularly those of captopril but perhaps also those of the nitrate with a regimen that avoids tolerance) appear beneficial. Current large trials of these agents involving several tens of thousands of patients with acute myocardial infarction, such as Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS)-II [25], ISIS-4 (43), Gruppo Italiano per lo Studio della Sopravivenza Nell'Infarto Miocardio (GISSI)-3 [44] and the Chinese captopril study [45]), will help to determine directly whether these promising hemodynamic effects translate into any survival advantage or provide reliable information about safety.

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