Comparative Effects of Nitroglycerin, Nifedipine and Metoprolol on Regional Left Ventricular Function in Patients with One-vessel Coronary Disease

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SUMMARY To compare acute effects of nitroglycerin (0.8 mg sublingually), nifedipine (5 ng/kg/min i.v.) and metoprolol (0.15 mg/kg i.v.) on normal, ischemic and scarred myocardial segments in man, we performed simultaneous hemodynamic and radionuclide measurements of left ventricular function. Sixteen patients with isolated left anterior descending (LAD) disease were studied at rest and during exercise. Nine patients had angina and exercise-induced ischemia (LAD stenosis) and seven patients had previous transmural myocardial infarction and no ischemic changes during thallium imaging (LAD occlusion). The effects of the drugs on regional ejection fraction of the involved anteroseptal region and the normal posterolateral area were compared.

Global ejection fraction at rest did not change after nitroglycerin, increased after nifedipine and decreased after metoprolol. In patients with ischemia, the exercise ejection fraction improved after all drugs due to increased regional fraction in ischemic segments; i.e., a regional antiischemic effect evidenced by improved regional function could be demonstrated with all three agents. Regional ejection fraction increased from 35.8 ± 19.5% to 66.2 ± 15.2% (± SD) after nitroglycerin (p < 0.001), to 61.7 ± 8.7% after nifedipine (p < 0.001), and to 48.4 ± 7.0% after metoprolol (p < 0.01). In regions of myocardial scar, regional ejection fraction was not changed after any drug. In normal areas, regional ejection fraction remained unchanged after nitroglycerin and nifedipine, but decreased after metoprolol. Despite similar antiischemic effects of all three drugs, underlying hemodynamic mechanisms were quite different and may provide a rationale for combined forms of treatment. These results may help to select optimal drug combinations to improve myocardial performance in patients with chronic ischemic heart disease.

MEDICAL treatment of ischemic heart disease is mainly based on three groups of drugs — nitrates, β-adrenoceptor blockers and slow-channel inhibitors (calcium antagonists) — whose clinical efficacy has been clearly demonstrated. An important effect of such drug interventions during acute ischemia is the reduction of myocardial oxygen consumption, achieved by nitrates primarily through a reduction in preload and afterload, by calcium antagonists through similar mechanisms and coronary artery dilatation, and by β-adrenoceptor blockers mainly through decreases in heart rate and contractility. In addition, all of these drugs are thought to induce a redistribution of coronary blood flow between normal and ischemic myocardium, and some may also have direct protective effects on the myocardium.

Because the ischemia in patients with coronary artery disease is regional, major interest has been directed to the study of regional differences in myocardial perfusion and function. Investigations in conscious experimental animals with chronic coronary arterial stenosis indicated that exercise causes severe regional myocardial dysfunction and hemodynamic abnormalities. Drug-induced changes in regional left ventricular function have also been studied in experimental animal models and reduction of exercise-induced regional dysfunction in dogs by nitroglycerin, propranolol and verapamil has been demonstrated. Although a few reports have investigated such drugs in man using catheterization techniques, little information is available on comparative effects of these agents on regional left ventricular function in man. With the introduction of noninvasive radionuclide ventriculography and quantitative analysis of regional left ventricular function, differences of drug effects on normal, ischemic and scar myocardial segments can be studied in man.

In this study, we compared the acute effects of nitroglycerin, nifedipine and metoprolol on normal, ischemic and scar myocardial segments at rest and during exercise in patients with well-defined one-vessel coronary artery disease and related these noninvasive findings to simultaneous hemodynamic measurements.

Materials and Methods

Patients
Sixteen patients, 14 men and two women, ages 23–68 years (mean 45.2 ± 10.7 years), were studied. Only patients with significant one-vessel left anterior descending (LAD) disease and angina pectoris or previous transmural myocardial infarction were included into the study. Patients with additional coronary artery lesions, valvular heart disease or lung disease were excluded. Accordingly, only patients with thallium defects in the anteroapical or septal left ventricular wall without deficits in other areas were included. Since the study design called for withdrawal of all antianginal drugs before the study, patients with angina at rest or unstable chest pain could not be included. Three patients with a history of myocardial infarction were re-
ceiving chronic digitalis and diuretic therapy, which was not changed during the study period. No patient had clinical or ventriculographic signs of mitral regurgitation at rest or during exercise. All patients had normal lung function measurements at rest.

According to history, coronary angiography and noninvasive exercise testing, two groups were formed. Group A consisted of nine patients with angina, proximal LAD stenosis greater than 75% and evidence of ischemia on exercise ECG (four patients) or thallium-201 scintigraphy (nine patients). Group B consisted of seven patients with documented transmural anteroseptal myocardial infarction (more than 2 months earlier), subtotal (two patients) or total (five patients) LAD occlusion and no ischemic changes on exercise ECG or thallium-201 scintigraphy (only diagnostic loss of R waves in precordial leads or persistent scar myocardial defects).

For comparison of control values, nine normal men, ages 31–53 years (mean 43.7 ± 8.0 years) were studied but received no drugs. Eight of them were referred for evaluation of atypical chest pain and one for evaluation of an episode of paroxysmal atrial fibrillation. All had normal clinical findings. Exercise ECG, exercise thallium-201 scintigraphy, global ejection fraction response to exercise as well as hemodynamics at right-heart catheterization were normal at rest and during exercise. All patients studied by left-heart catheterization for evaluation of chest pain had normal coronary arteries (eight patients) and a negative ergonovine test (five patients).

The two groups of patients and the control group did not differ with respect to age, sex, weight or height. All patients gave informed consent. The study protocol has been approved by the ethics committee of the Department of Internal Medicine, University of Basel, Switzerland.

Study Protocol

Antianginal drugs were withdrawn 5 days and nitrates 24 hours before the study. All patients then underwent a symptom-limited, graded exercise test for ECG and thallium-201 scintigraphy as well as left-heart catheterization. In nine patients (seven in group A and two in group B) and in all control subjects, biplane contrast ventriculography was performed not only at rest, but also during exercise. The results of these tests determined whether patients were included in the study.

Standard hemodynamic variables and radionuclide ejection fraction were measured simultaneously. First, control measurements were obtained at rest and during the last 2 minutes of a 5-minute exercise study at a work level known to produce exercise limiting symptoms (angina in group A and fatigue in group B). The average work load reached was 86.1 ± 30.9 W for group A, 64.3 ± 13.4 W for group B and 91.7 ± 18.9 W for the control group. After a recovery period of 45 minutes, the intervention study was started.

All patients received nitroglycerin, nifedipine and metoprolol in a predefined, randomized sequence* and were studied after each drug both at rest and during exercise at the same work level as for control measurements. The dosages of each drug, the time delay of the measurements after administration of the drugs and the recovery period allowed before application of the next drug are shown in table 1. Nitroglycerin was given sublingually, nifedipine in two infusions over 5 minutes at rest and at the beginning of exercise, and metoprolol as an i.v. injection.

Radionuclide Ventriculography

Equilibrium radionuclide data were accumulated at rest and continuously during exercise for left ventricular ejection fraction calculations, as previously described. Multiple-gated equilibrium radionuclide ventriculograms were performed by in vivo labeling of red blood cells with 20 mCi of technetium-99m 20–30 minutes after cold pyrophosphate had been injected. After metoprolol, which required a recovery period of 24 hours, a second dose of technetium-99m was administered before the next drug was studied such that during a 2-minute acquisition period an average of $8 \pm 3.2 \times 10^4$ counts could be accumulated after background subtraction within the left ventricular region of interest in the end-diastolic frame. Imaging was then performed with an Anger single-crystal scintillation camera equipped with a high-sensitivity collimator in a 40–50° left anterior oblique projection with 5–10° of caudal tilt, which best separated the left ventricle from the other heart chambers. Data were acquired with a nuclear medicine computer system (Medtronic/MDS-A2). The cardiac cycles of a 2-minute acquisition period at rest or peak exercise were assembled at corresponding times to generate composite images throughout the heart cycle. A rectangular region of interest was arbitrarily placed around the left ventricle at end-diastole to calculate ejection fraction. A computer algorithm (MUGE) automatically determined the edge of the left ventricle at end-diastole using the second derivative of the count profile. Each subsequent frame was processed at the same threshold level to determine the changing count rate within the left ventricle (variable region of interest). A computer-assigned background region of interest outside the left lower quadrant of the left ventricle was used to correct for noncardiac activity. Ejection fraction (EF) was then calculated from the time-activity curve according to the formula:

$$((C_{ED} - C_{ES})/C_{ED}) \times 100,$$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Measurement begin after</th>
<th>Recovery time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>—</td>
<td>45 min</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>0.8 mg sublingually</td>
<td>1 min</td>
<td>75 min</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>5 mg/kg/min iv. (10 min)</td>
<td>Immed</td>
<td>75 min</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>0.15 mg/kg i.v.</td>
<td>5 min</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

TABLE 1. Study Protocol and Drug Therapy
where \( C_{ED} \) = left ventricular counts at end-diastole and \( C_{ES} \) = left ventricular counts at end-systole, each corrected for background. In two group B patients, radionuclide data could not be analyzed after metoprolol in one patient and after nifedipine in one patient because of gating problems.

Ejection fractions calculated by this technique correlate well with those determined by biplane cineangiography \( (r = 0.90 \) in our laboratory). The reproducibility of ejection fraction measurements by this technique is excellent. \(^{38}\)

**Regional Analysis**

For regional analysis, we used a previously reported method. \(^{39}\) The computer determined a center of gravity of the left ventricular activity at end-diastole (MDS algorithm). From this center, eight radial sectors of \( 45^\circ \) were defined. Because of overlap with aorta or left atrium, three of these eight sectors were excluded from further analysis (fig. 1). The remaining five sectors were assigned to the three main coronary arteries: the two anteroseptal sectors to the LAD, the two posterolateral sectors to the left circumflex coronary artery (LCx), and one inferoapical sector in the left anterior oblique view to the right coronary artery (RCA), which is normally perfused by this vessel but could also be perfused by the LAD or LCx. We analyzed and compared only the involved anteroseptal and the normal posterolateral area. The change in counts from end-diastole to end-systole in each sector was used to calculate regional ejection fraction similar to the calculation of global ejection fraction. The same background value determined independently by computer for global LV ejection fraction measurements was used for the two individual sectors. Mainly because of the method used, regional ejection fraction values were lower in anteroseptal than in other regions. We validated this method in 12 normal subjects and 26 patients with one-vessel coronary artery disease and showed that it is reproducible at rest and during exercise \( (r \) for regional EF at least 0.92). \(^{38}\) Because of variability of serial measurements despite unchanged camera positioning, a change in regional EF had to be at least 10% (2 standard deviations) in an individual patient to be considered significant.

**Hemodynamic Measurements**

For hemodynamic measurements and determinations of mixed venous oxygen content, a flow-guided, flexible-tip catheter without balloon was placed in the pulmonary artery. Because no patient had active pulmonary artery hypertension, pulmonary artery diastolic pressure was used as measure of left ventricular filling pressure. \(^{39}\) Oxygen consumption for calculation of cardiac output (Fick’s principle) was determined by a Hellige oximeter. Because all patients had normal arterial oxygen saturation at left-heart catheterization, this measurement was assumed to remain unchanged for all further calculations. \(^{40}\) Peripheral arterial pressure was measured with an inflatable cuff; mean pressure was assumed to be diastolic pressure + \( \frac{1}{3} \) (systolic – diastolic) pressure. Stroke volume (SV), pulmonary and total peripheral vascular resistance as well as the heart rate–systolic blood pressure product and end-diastolic volumes (SV/EF) were calculated. Changes in volumes were therefore derived from changes in radionuclide ejection fraction and changes in hemodynamic stroke volume.

**Exercise Studies**

All patients and normal subjects underwent supine bicycle exercise on an electronically braked Elema-Schönander ergometer (type EM 350), which kept a constant work load for each patient during the entire exercise period over a pedal range of 45–70 rpm. The same exercise level predetermined to produce exercise-limiting symptoms was used for the first and each successive test in each patient. Hemodynamic and radionuclide data were accumulated at rest and during the last 2 minutes of exercise. The exercise ECG was not analyzed, for only one lead was recorded for arrhythmia monitoring and to serve as trigger signal for the gated radionuclide studies. We previously showed that a similar protocol provided reproducible results for global ejection fraction. \(^{38}\)
Statistical Methods

The original study design comprised three categories of patients and three treatments to be applied to each patient. To control for both categories of patients and order effect of treatments, a balanced set of Latin squares was chosen.\textsuperscript{36} Three groups of patients were planned: patients with LAD occlusion and scar, patients with high-grade LAD stenosis and exercise-induced ischemia and patients with nonsignificant (20–50%) LAD lesions. The design was disturbed by the fact that during the study period, the group with nonsignificant coronary artery lesions had to be dropped because only two patients could be included and one of them evidenced latent cardiomyopathy by increased left ventricular filling pressures at rest. To test the validity of this study protocol and to rule out period effects between any two drugs consecutively tested, analysis of variance was carried out according to a crossover design and confirmed that only separate drug effects were studied. To provide normal reference values, control subjects without heart disease were studied in the same manner without drugs.

All results are presented as mean ± sd, except in some figures, in which for graphic reasons the mean ± sem are shown. Interference testing was carried out by analysis of variance (sources of variation: between categories, between treatments). If applicable, Duncan’s multiple-range test was applied at a level of significance of \( \alpha = 0.05 \). To compare rest-exercise measurements under control and treatment conditions, the \( t \) test for paired comparisons was used. Because of repeated use of the control-value the level of significance was adopted to \( \alpha = 0.02 \) according to the Bonferroni method (\( \alpha = 0.05/\text{number of comparisons} \)).

Results

Control Values Without Therapy

During control measurements, resting hemodynamic variables showed no significant group differences except for LV filling pressure, which was elevated in patients with previous infarction (13.4 ± 2.5 mm Hg vs 10.3 ± 2.2 mm Hg in control patients, \( p < 0.05 \)) (table 2). During exercise, LV filling pressure increased the most in patients with angina (to 26.3 ± 5.9 mm Hg), less in group B patients (to 20.4 ± 3.9 mm Hg) and remained normal in control subjects (13.9 ± 2.4 mm Hg; \( p < 0.001 \) between groups). Before therapy, there were no other significant group differences in hemodynamic variables.

Figure 2 shows the results of global and regional ejection fraction at rest and during exercise in the two patient groups and the control subjects. Without therapy, global ejection fraction increased during exercise in all normal subjects, from 56.8 ± 3.8% to 65.5 ± 3.4% (\( p < 0.01 \)). In contrast, ejection fraction decreased in group A patients with angina from a normal resting level of 64.7 ± 6.6% to 56.7 ± 12.2% (\( p < 0.05 \)) during exercise, but it remained depressed in group B patients with previous infarction (41.9 ± 12.7% at rest vs 42.7 ± 17.8% during exercise). Regional analysis of left ventricular function demonstrated significant group differences in the involved anteroseptal region (fig. 2). During exercise, patients with ischemia showed a highly significant decrease in regional ejection fraction, whereas patients with a history of transmural anteroseptal myocardial infarction already had a depressed regional ejection fraction at rest and no significant change during exercise. In contrast, all patients showed an increase in regional ejection fraction in the normally perfused posterolateral area similar to that of normal subjects. According to these results, the anteroseptal area could be considered an ischemic region in group A patients and an area of scar in group B patients; the posterolateral segments behaved normally in all patients.

Single Drug Effects

The changes in hemodynamic values and global left ventricular function induced by acute administration of the three antianginal drugs are summarized in table 3 and in figure 3. These results are presented for all 16 patients together because there were no statistically different drug-induced changes in global hemodynamic variables during exercise between both patient groups except for heart rate, which increased after nitroglycerin in group A patients only.

Nitroglycerin significantly reduced left ventricular filling pressure, end-diastolic volume and diastolic blood pressure (during exercise), which induced an increase in heart rate (in group A patients only) compared with control measurements. Cardiac index, systolic blood pressure and total peripheral resistance were not changed significantly. Global left ventricular ejection fraction remained unchanged at rest, but improved significantly during exercise, mainly in patients with exercise-induced ischemia due to a highly significant improvement in regional function in ischemic segments (fig. 4, table 3). There were no important changes after nitroglycerin in normal or scar myocardial segments.

Nifedipine induced a strong vasodilatation reflected by significant reductions in total peripheral resistance, blood pressure and left ventricular filling pressure (during exercise). This was associated with an increase in heart rate (presumably reflex), cardiac index and ejection fraction, but end-diastolic volumes remained unchanged. Regional analysis (fig. 5, table 3) revealed a significant improvement in function in ischemic segments, but also a tendency to increased regional ejection fraction in normal and scar myocardial segments.

Metoprolol mainly reduced heart rate, cardiac index and systolic blood pressure (during exercise), but did not change diastolic blood pressure, end-diastolic volume and global ejection fraction significantly. (Resting ejection fraction decreased significantly only in group A patients.) Acute \( \beta \) blockade also induced an increase in total peripheral resistance and left ventricular filling pressure (during exercise). Although regional ejection fraction was reduced in patients with exercise-induced ischemia at rest, it improved significantly in ischemic segments during exercise (fig. 6, table 3). In addition, there was a negative effect of acute \( \beta \)
blockade on normal segments during exercise; no significant changes could be found in scar segments.

**Comparison of Antianginal Drug Effects**

To compare the different antianginal drug effects and to assess which hemodynamic variable was influenced most favorably by which treatment, we compared drug-induced changes between treatment periods as well as with control and normal measurements. Because the most marked effects were observed during exercise when group A patients developed ischemia, only results during exercise are compared (table 4).

**Global Left Ventricular Function**

Significant differences between all three drugs were found in their effects on heart rate, diastolic blood pressure, cardiac index and total vascular resistance. Nitroglycerin and nifedipine improved left ventricular ejection fraction and filling pressure similarly and differed also in this respect from metoprolol. Nitro-
increase in left ventricular filling pressure (and to a lesser extent in diastolic blood pressure), which were ameliorated best by nitroglycerin and nifedipine. Whereas nitroglycerin also reduced end-diastolic volume, nifedipine lowered total peripheral resistance and systolic blood pressure. Metoprolol, on the other hand, reduced heart rate and the double product as well as cardiac index. Therefore, hemodynamic mechanisms of the three antianginal drugs differed importantly.

**Regional Left Ventricular Function**

In patients with ischemia during exercise (group A), regional ejection fraction in the involved anteroseptal area was significantly improved after all drugs. This antiischemic effect was not significantly different in the three drugs tested. After nitroglycerin and nifedipine, regional ejection fraction in ischemic segments returned to normal and to a slightly subnormal level after metoprolol. In patients with areas of scar, the anteroseptal regional ejection fraction remained unchanged after all drugs at rest as well as during exercise. The same was true at rest for the normal posterolateral area, but here, regional ejection fraction decreased during exercise after metoprolol.

**Discussion**

The present study was designed to study and compare the effects of nitrates, calcium antagonists and β-adrenoceptor blocking drugs on normal, ischemic and scar myocardial segments in man and to assess the different hemodynamic effects in view of combined medical treatment. Changes in regional left ventricular function after antianginal medication have mainly been studied in animals. 17–27 Studies in man have been performed during left-heart catheterization, 11, 15, 16, 28–30 and, more recently, with echocardiography, 41, 42 but

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**TABLE 3. Drug-induced Changes in Global and Regional Left Ventricular Function During Exercise**

<table>
<thead>
<tr>
<th></th>
<th>Nitroglycerin</th>
<th>Nifedipine</th>
<th>Metoprolol</th>
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<tbody>
<tr>
<td></td>
<td>p vs C</td>
<td>p vs C</td>
<td>p vs C</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>119.2 ± 11.7</td>
<td>125.6 ± 15.6</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>190.6 ± 20.9</td>
<td>186.9 ± 21.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mm Hg)</strong></td>
<td>99.4 ± 12.0</td>
<td>92.8 ± 12.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Cardiac index (l/min/m²)</strong></td>
<td>6.8 ± 2.2</td>
<td>6.9 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Stroke index (ml/m²)</strong></td>
<td>57.0 ± 15.8</td>
<td>54.9 ± 12.8</td>
<td>NS</td>
</tr>
<tr>
<td><strong>LV filling pressure (mm Hg)</strong></td>
<td>23.8 ± 5.8</td>
<td>17.3 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>End-diastolic volume index (ml/m²)</strong></td>
<td>115.7 ± 44.8</td>
<td>98.3 ± 37.4</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Total vascular resistance (dyn-sec-cm⁻²)</strong></td>
<td>867.1 ± 294.3</td>
<td>799.4 ± 234.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Ejection fraction (%)</strong></td>
<td>50.6 ± 16.1</td>
<td>58.2 ± 16.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Regional EF ischemic segment (%)</strong></td>
<td>35.8 ± 19.5</td>
<td>66.2 ± 15.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Regional EF scar segment (%)</strong></td>
<td>26.7 ± 23.4</td>
<td>31.3 ± 32.6</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Regional EF normal segment (%)</strong></td>
<td>73.8 ± 15.5</td>
<td>75.4 ± 14.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± sd.
Abbreviations: LV = left ventricular; EF = ejection fraction; C = control.
these techniques are limited by the number of repetitive studies possible, by the difficulty of performing exercise measurements and by the restricted view of myocardial segments. With the introduction of gated equilibrium radionuclide ventriculography and the possibility of quantitating regional ejection fraction, a new, noninvasive tool was established to study global and regional left ventricular function repeatedly over several hours. We validated a method for quantitative regional ejection fraction analysis in pa-

Figure 3. Acute drug effects on standard hemodynamic variables: heart rate (HR), cardiac index (CI), ejection fraction (EF), end-diastolic volume index (EDVI), left ventricular filling pressure (pulmonary artery diastolic pressure [PAPD]), systolic and diastolic blood pressure (SBP and DBP) and total vascular resistance (TVR). Percent changes vs control values at rest and peak exercise (ex) are shown. Significance levels shown were calculated based on absolute changes.

Figure 4. Effect of nitroglycerin (dotted line) on global and regional ejection fraction at rest and during exercise in all 16 patients. Control values are connected by solid lines. Presentation and abbreviations are as in figure 2.

Figure 5. Effect of nifedipine (dotted line) on global and regional ejection fraction at rest and during exercise in 15 patients (one group B patient without measurements after nifedipine for technical reasons). Control values are connected by solid lines. Presentation and abbreviations are as in figure 2.
patients with one-vessel coronary artery disease and showed that serial measurements at rest and during exercise provide reproducible results.\textsuperscript{35} In the present investigation, we applied this method to study and compare the effects of different antianginal drugs in a given patient population.

To separate the effects on normal, ischemic and scar myocardial segments, we selected only patients with well-defined one-vessel LAD disease. It remains to be shown whether the method used to quantitate regional left ventricular function will also be feasible in patients with multivessel disease. Patients either had angina and objective noninvasive evidence of ischemia (no history of myocardial infarction) or had a documented transmural myocardial infarction without angina or objective evidence of ischemia. In view of the left anterior oblique projection used to analyze regional left ventricular function from radionuclide ventriculography, this human model seems to be most suitable for the separate study of involved (ischemic or scarred) anteroseptal regions perfused by the LAD coronary artery and the noninvolved (normal) posterolateral area perfused by the circumflex coronary artery.

Repetitive exercise studies were performed to assess the effects of all three drugs on control measurements. The reproducibility of work performance during serial exercise in patients with angina pectoris has been demonstrated by Lassvik,\textsuperscript{43} but others have found that cardiac index and pulmonary artery pressures tended to decrease in repeat studies, especially at lower exercise levels and after short recovery periods (30 minutes vs 60 minutes).\textsuperscript{44, 45} In addition, the difference between serial exercise measurements decreased with increasing number of tests.\textsuperscript{45} In view of this experience and to avoid persistent drug effects at the time the second or third drug was administered, a recovery period of 75 minutes was allowed after nitroglycerin and nifedipine and 24 hours after metoprolol. Analysis of variance according to a crossover design confirmed that there was no significant carryover effects between any two drugs consecutively tested and that independent of therapy there were no statistically significant differences in results of the last compared with the first exercise study. Furthermore, the exercise level was predetermined to be symptom-limited and kept the same for all further investigations. Before the present investigation, all patients had at least two exercise tests (for thallium-201 scintigraphy and predetermination of the angina-inducing work level); we therefore compared in our study exercise tests 3 to 6, where differences should be negligible. Indirect proof for the validity of the study protocol is also provided by oxygen consumption measured during each exercise period: It showed no significant differences, indicating that energy expenditures remained unchanged for the first and the three successive tests.

Because acute drug effects were compared separately in the same patients, short-acting drug preparations have been used. Nitroglycerin was given sublingually, nifedipine in short infusions and metoprolol as an i.v. injection. Because of the lack of steady-state pharmacokinetics of i.v. nifedipine, measurements were obtained immediately after 5-minute infusions at rest and separately during exercise to assure “maximal” drug effects. In this manner, the study could be completed in all patients within 28 hours, including a maximum

![Figure 6](http://circ.ahajournals.org/content/67/2/298/F6)

**Figure 6.** Effect of metoprolol (dotted line) on global and regional ejection fraction at rest and during exercise in 15 patients (one group B patient without measurements after metoprolol for technical reasons). Control values are connected by solid lines. Presentation and abbreviations are as in figure 2.

<table>
<thead>
<tr>
<th>Table 4. Comparison of Drug Effects on Global and Regional Left Ventricular Function During Exercise (vs Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global LV function</strong></td>
</tr>
<tr>
<td>HR</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>Nifedipine</td>
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<tr>
<td>Metoprolol</td>
</tr>
</tbody>
</table>

Significant group differences are represented by different symbols: arrows indicate changes vs control; arrows in parentheses indicate changes that are significant by single comparison but not by multiple group comparison.

Abbreviations: LV = left ventricular; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; PAPD = pulmonary artery diastolic pressure; CI = cardiac index; TVR = total vascular resistance; EF = ejection fraction; EDVI = end-diastolic volume index; NL = normal segment; ISCH = ischemic segment; SCAR = scar segment; ↑ = increase; ↓ = decrease; — = no significant change vs control.
of two administrations of technetium-99m and an acceptable time duration for leaving the flow-guided pulmonary catheter in place. To limit the study protocol to four exercise tests (besides the two prestudy exercise tests) over 1 1/2 days, we did not include a placebo period. Instead, we studied a control group of normal subjects without therapy to obtain comparable normal values for this study frame. Although perhaps clinically more desirable, the study could not be carried out with chronic drug therapy over several days or weeks because of the hemodynamic and radionuclide measurements performed. Obviously, the extent of described changes is mainly dose-dependent and therefore of secondary importance for the present investigation.

Analysis of regional left ventricular function showed that all three groups of antianginal drugs have a significant antiischemic effect. During exercise, regional ejection fraction in the ischemic anteroseptal region of patients with high-grade LAD stenosis improved significantly after each drug. This effect was quantitatively most important after nitroglycerin, but the difference between the three drugs was not statistically significant. Improved perfusion in different groups of patients after these drugs has recently been described using the xenon washout technique during left-heart catheterization and pacing. The improvement in regional ejection fraction was only present in the ischemic region, whereas there were no such changes in normal or scar areas. In these latter regions, the effect of acute β blockade differed from that of nitroglycerin and nifedipine. After metoprolol, regional ejection fraction decreased significantly during exercise in normal segments. This finding may point to the negative inotropic effect of acute β-adrenergic blocking drugs on normal myocardium that has been described in animal experiments. Despite the similar antiischemic effect of all three drugs, the underlying hemodynamic mechanisms were quite different. After nitroglycerin, left ventricular filling pressure, end-diastolic volume and diastolic blood pressure decreased significantly, implying that a reduction in preload and afterload were the predominant effects. Afterload was reduced even more by the vasodilatory effect of nifedipine reflected in reductions of systemic vascular resistance, blood pressure and left ventricular filling pressure. The negative inotropic action of this drug described under experimental conditions or after intracoronary injection was not apparent in this investigation as in previous hemodynamic studies in man. We noted significant increases in ejection fraction, cardiac index and heart rate, probably due to reflex sympathetic activity observed after nifedipine. Metoprolol acted by decreasing heart rate and, at least during exercise, systolic blood pressure. In addition, a mild negative inotropic effect resulted in a reduction of resting left ventricular ejection fraction in patients with LAD stenosis and in a decrease of regional left ventricular function in normally perfused myocardial segments. Despite this effect, we, like others, observed an increased global ejection fraction during exercise after β blockade in patients with ischemia. The exercise data obtained with all these drugs were demonstrated at the same exercise level (same work performed) and with the same measured pulmonary oxygen consumption. Results might have been somewhat different at a comparable level of myocardial oxygen consumption as derived for instance from the rate-pressure product. Despite this fact, differences in the mode of action of the three antianginal drugs described earlier could be confirmed in this study. Other factors, such as redistribution of coronary blood flow between normal and ischemic regions and direct myocardial protective effects, could also have contributed.

Comparison of the different drug effects with control measurements and normal exercise performance revealed that ischemia-induced hemodynamic changes were best normalized by nitroglycerin. Nifedipine changed the hemodynamic pattern similarly, but a strong vasodilatation associated with reflex sympathetic activity implied that patients with increased vascular tone and those with bradycardia or maybe borderline heart failure might profit most from this drug. Metoprolol, on the other hand, acted differently, mainly reducing heart rate and systolic blood pressure, and thus the double product. Therefore, this drug seems to be especially useful in patients with hypertension or "hyperdynamic hearts," but less so in patients with borderline heart failure. Based on such considerations, certain patients might profit even more by combination of either two or even three drugs, but long-term studies are needed. Side effects not seen in our study will also influence the choice of treatment.

Thus, this study may have significant clinical implications for future drug therapy in patients with chronic ischemic heart disease. Improvement of regional left ventricular function in ischemic segments demonstrated after all antianginal drugs tested despite markedly differing hemodynamic mechanisms provides a rational basis for combined use of these antianginal drugs in selected patients. It may be assumed that the antiischemic action of such combinations should be additive. In addition, the different hemodynamic profiles shown in figure 3 and table 4 may help to select optimal drug combinations to improve myocardial performance in individual patients.

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