Increased left ventricular emptying at maximal exercise after reduction in afterload

Kai Andersen, M.D., and Harald Vik-Mo, M.D.

ABSTRACT Twelve healthy men were studied by M mode echocardiography during exercise to investigate the effect of afterload reduction on left ventricular function at maximal exertion. They performed two maximal exercise bicycle tests 4 hr apart while in the semisupine position and were given 20 mg nifedipine sublingually 30 min before the second test. During the first test end-systolic dimension decreased (p < .01) and fractional shortening increased from rest to peak exercise (p < .01), while end-diastolic dimension did not change significantly. At maximal exercise systolic blood pressure was lower after nifedipine than in the preceding control test (202 ± 10 [mean ± SD] vs 212 ± 14 mm Hg; p < .01), while heart rate was not significantly changed (168 ± 15 vs 162 ± 13 beats/min). End-systolic dimension was lower (25.6 ± 3.3 vs 28.8 ± 4.2 mm; p < .01) and fractional shortening higher (50.7 ± 6.0% vs 45.3 ± 7.0%; p < .01) while end-diastolic dimension was unchanged (52.3 ± 1.9 vs 52.4 ± 2.6 mm). Our data indicate increased left ventricular emptying at maximal exercise after nifedipine, most probably due to reduction in afterload.


IT IS NOT CLEAR whether the demonstrated inverse relationship between left ventricular afterload and performance1–3 is also operative at maximal exercise, when the ability of ventricular ejection would be expected to be completely utilized. If so, a decrease in afterload might disclose a potential of systolic emptying even beyond that at maximal exertion. In a recent echocardiographic study in normal men, we found changes in left ventricular dimensions that indicated ventricular dilatation at maximal exercise after atenolol along with concomitant increase in systolic myocardial shortening.4 This suggested disclosure of a diastolic reserve through the Frank-Starling mechanism. Since the response of blood pressure to exercise has been shown to be reduced by atenolol,5,6 we speculated that decreased afterload might have contributed to the increased myocardial shortening. The purpose of our study was therefore to investigate the effect of reduction of afterload on left ventricular function at maximal exercise in normal man.

Subjects and methods

Twelve men who were 28 to 39 years old (mean 34) were studied. Six others were excluded from the study due to unsatisfactory quality of echocardiograms obtained during exercise. None had evidence of cardiopulmonary disease as determined by history, physical examination, blood pressure, and electrocardiographic (ECG) or M mode echocardiographic examination. All were physically fit, but none participated in competitive athletics. Informed consent was obtained from all subjects before the study.

Bicycle exercise. Exercise was performed on an electrically braked bicycle ergometer by subjects in the semisupine position with the trunk elevated to about 20 degrees after 30 min of rest in the same position. The initial workload was 50 W, with subsequent increases of 50 W every 3 min until exhaustion.

Measurements and calculations. Systolic and diastolic blood pressures were measured by cuff sphygmomanometry as the pressures at Korotkoff phases I and V, respectively. Mean blood pressure was calculated as one-third of the difference between systolic and diastolic pressure added to the diastolic pressure.

M mode echocardiograms were obtained with an Ekoline 20A Echocardiograph (Smith-Kline Instruments) with a hand-held 2.25 MHz transducer in the standard intercostal space at the left sternal border.7 The echocardiograms, a single-lead ECG, and the respiratory phases traced by a nasal thermistor were recorded simultaneously with a Honeywell strip-chart recorder at a paper speed of 100 mm/sec. Heart rate was measured from the ECG. Left ventricular dimensions were measured at the level of the chordae tendineae between the leading edges of echoes from the left border of the interventricular septum and the posterior wall endocardium. End-diastolic dimension (EDD) was measured at the onset of the QRS complex on the ECG and end-systolic dimension (ESD) was measured on the vertical axis at the nadir of the septum8 (figure 1). The measurements were made at end-expiration and represent the average of at least three cardiac cycles. Fractional shortening was calculated as: (EDD − ESD)/EDD × 100%.

Study design. Blood pressure measurements and echocardiographic recordings were made in each subject while at rest with
the feet on the ergometer pedals, during the last 30 sec of each exercise level, and at 1, 3, 5, and 10 min after termination of exercise, with the subject’s feet still on the pedals.

All subjects performed two exercise tests 4 hr apart. The longest duration of exercise common to both tests was defined as the maximal exercise level for each subject. For afterload reduction, 20 mg nifedipine was administered sublingually 30 min before the second test.

**Statistical analysis.** Each subject served as his own control. Differences in variables between rest and peak exercise in each test were evaluated by Wilcoxon’s test (two-tailed) for comparison of paired data. A two-way analysis of variance with repeated measures was performed for evaluation of differences before and after nifedipine administration. If this demonstrated significant results, Wilcoxon’s test for comparison of paired data was performed on data from each stage of the protocol. Differences were regarded significant when p < .05.

**Results**

The duration of exercise was 14.1 ± 1.7 (mean ± SD) min before and 13.3 ± 1.5 min after nifedipine (p < .05).

Heart rate, blood pressure, left ventricular dimensions, and fractional shortening at rest and maximal exercise before and after nifedipine are listed in table 1. During the control test, systolic and mean blood pressures increased markedly during exercise. Diastol-

![FIGURE 1. Echocardiograms from one subject at semisupine rest (A) and maximal exercise (B) showing measurements of EDD and ESD. Resp = tracing of respiration.](image)

**TABLE 1**

<table>
<thead>
<tr>
<th>HR (beats/min)</th>
<th>Blood pressure (mm Hg)</th>
<th>EDD (mm)</th>
<th>ESD (mm)</th>
<th>FS (%)</th>
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<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Mean</td>
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<tr>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Rest</td>
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<td>84</td>
<td>99</td>
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<td>±7</td>
<td>±13</td>
<td>±6</td>
<td>±6</td>
<td>±2.8</td>
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<tr>
<td>Exercise</td>
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<td>212</td>
<td>94</td>
<td>133</td>
</tr>
<tr>
<td>±13</td>
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<td>±8</td>
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<tr>
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<td>&lt;.001</td>
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<td></td>
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</tbody>
</table>

Values are mean ± SD.

HR = heart rate; FS = fractional shortening.
ANDERSEN and VIK-MO

Blood Pressure

Values are mean ± SD.

FIGURE 2. Systolic and diastolic blood pressures during maximal semisupine exercise before (closed circles) and after (open circles) nifedipine. Values are mean ± SD.

ic blood pressure also increased significantly. ESD decreased and fractional shortening increased while EDD did not change significantly.

After nifedipine administration, the directional change from rest to peak exercise was similar to that in the control test for all variables (table 1). Except for a nonsignificant change in systolic blood pressure at the fifth minute of recovery (figure 2), systolic and diastolic blood pressures were significantly lower throughout the exercise test after nifedipine. Heart rate was significantly higher at all stages of the test except at maximal exercise and the first minute of recovery (figure 3). EDD after nifedipine did not differ from that in the control test (figure 4). At the highest exercise levels ESD was significantly lower (figure 4) and fractional shortening greater after nifedipine than before drug (figure 5).

Discussion

The experimental design of our study has been shown to allow comparison of left ventricular dimen-
sions assessed by echocardiography during maximal exercise before and after a drug intervention. During the control test ESD decreased from rest to peak exercise while EDD did not change significantly. This is in accordance with our previous findings, which indicated increased stroke volume during exercise due to augmented emptying without ventricular dilatation. It is also in agreement with radionuclide angiographic and other echocardiographic studies, although the exercise levels in the echocardiographic studies were less than in ours. However, conflicting results of left ventricular dilatation during exercise have been reported by both techniques.

In our study ESD was not affected by nifedipine at rest or the lower exercise levels. During severe exertion, however, ESD was lower and fractional shortening greater after drug intervention than before while EDD remained unchanged. Thus, our findings indicate further emptying of the normal left ventricle at maximal exercise after nifedipine by a more pronounced decrease in end-systolic volume.

Systolic, diastolic, and mean blood pressures were reduced by nifedipine throughout the test. This might be attributed to the demonstrated decrease in systemic vascular resistance after administration of the drug. Accordingly, nifedipine seems to reduce left ventricular afterload also at maximal exercise. Thus, the echo-
Cardiographic findings might be explained by reduced impedance to systolic emptying, thereby suggesting that the inverse relationship between left ventricular afterload and performance is operative also at maximal exertion. It is unlikely that the evidence of increased myocardial shortening was due to increased preload since EDD at rest and during exercise did not differ between the two tests. The lack of change in preload after nifedipine is in agreement with previous findings in subjects at rest without impaired ventricular function.\(^2\) \(^9\) \(^2\)\(^0\)

Nifedipine has a negative inotropic effect, as demonstrated after intracoronary administration,\(^2\)\(^1\) \(^2\)\(^2\) which has been shown to be offset by a reflex-mediated increase in contractility when the drug is administered systemically.\(^2\)\(^2\) In our study this negative inotropic effect might have contributed to the lack of increase in stroke volume at rest and at lower exercise levels. However, the high level of circulating catecholamines at maximal exertion\(^2\)\(^3\) might have further counteracted the negative inotropic effect of nifedipine, allowing increased emptying of the left ventricle at peak exercise through the reduction in afterload.

It is unlikely that the increase in heart rate can explain the present finding of increased ventricular emptying. Increase in heart rate has been shown to be associated with a decrease in both EDD and ESD\(^2\)\(^4\) and has been demonstrated to augment the velocity but not the extent of myocardial shortening.\(^2\)\(^4\) \(^2\)\(^5\) This is in contrast to our study in which EDD remained unchanged and fractional shortening increased. In addition, the evidence of increased emptying appeared when the difference in heart rate was less pronounced.

Cardiac output has been demonstrated to increase after nifedipine and this has been shown to be associated with a decrease in systemic vascular resistance.\(^1\)\(^8\) \(^2\)\(^0\) Our study suggests that the increase in cardiac output in subjects at rest is primarily due to increased heart rate. This is in agreement with findings in normal subjects\(^2\)\(^0\) and in patients with suspected or manifest coronary artery disease.\(^1\)\(^9\) The increase in heart rate after nifedipine administration has been shown to be due to a baroreceptor-mediated reflex increase in \(\beta\)-adrenergic tone secondary to systemic vasodilatation.\(^2\)\(^6\) \(^2\)\(^8\) In contrast to the increase at rest and during mild and moderate exercise, we did not find significant increase in heart rate at maximal exercise after nifedipine. This might reflect the conspicuous increase in circulating catecholamines at maximal exertion compared with that at rest and submaximal exercise.\(^2\)\(^3\) Accordingly, in our study the sympathetic stimulation might also have been complete at peak exercise in the test before drug intervention. This might explain the lack of significant increase in heart rate at maximal exercise after nifedipine despite the reduction in blood pressure. Thus, our results suggest that increased stroke volume might have contributed to augmentation of cardiac output at severe exertion after nifedipine when heart rate no longer appeared to be consistently increased by the drug.

In a recent study in normal subjects, stroke volume during exercise did not change in association with the blood pressure reduction after inhibition of the angiotensin-converting enzyme.\(^2\)\(^9\) However, it has been shown in dogs that the increase in blood pressure after
angiotensin infusion is partly due to an increase in preload subsequent to redistribution of blood, mainly from the splanchnic region. If this mechanism is operative in humans, a decrease in preload might explain the lack of increase in stroke volume after afterload reduction by inhibition of angiotensin-converting enzyme.

In summary, our data indicate increased left ventricular emptying at maximal exercise after nifedipine, most probably due to reduction in afterload.

References

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