Effects of Nitroglycerin on Responses of the Systolic Time Intervals to Exercise

By Willard S. Harris, M.D., Neset Aydan, M.D., and Jean M. Pouget, M.D.

SUMMARY

The effects of 0.6 mg sublingual nitroglycerin on responses of the left ventricular (LV) systolic time intervals to a 4-min exercise step test were determined in 10 patients with angina and 10 normal controls. In normal subjects, the exercise test shortened total electromechanical systole corrected for heart rate (Q2, x) 22 msec but left the LV ejection time corrected for heart rate (LVET,) unchanged. By contrast, in the angina group, exercise failed to shorten the Q2, but prolonged the LVET, 25 msec. In both groups, nitroglycerin shortened the LVET, and Q2, after exercise. By decreasing LV afterload, preload, and hypoxia, and by improving LV function, nitroglycerin abolished the abnormal marked prolongation of LVET, after exercise in angina patients and converted the failure of their Q2, to shorten after exercise into a normal shortening of Q2,.

Nitroglycerin also had marked effects at rest, which contributed importantly to its effects on the systolic temporal responses to exercise. Suppression by nitroglycerin of LVET prolongation after exercise diminishes myocardial oxygen consumption and is antianginal. Most important, assessment of this action provides an objective, though noninvasive, means to evaluate the efficacy of nitrates in improving LV performance with exercise in angina patients.

Additional Indexing Words:
Pre-ejection period
Ischemic heart disease
Nitrates
Left ventricular ejection time
Angina
Noninvasive assessment of drug action

A NONINVASIVE method for assessing left ventricular performance with exercise was recently found to differentiate patients with angina pectoris from normal controls.1 The method was based on determinations of the left ventricular systolic time intervals before and 30 sec after a standard 4-min exercise step test. In normal subjects, total electromechanical systole corrected for heart rate (Q2,) shortened, while the left ventricular ejection time corrected for heart rate (LVET,) remained unchanged. In angina patients, owing to impaired left ventricular performance and increased afterload, the Q2, failed to change, while the LVET, lengthened markedly.

The aim of the present study was to determine whether nitroglycerin (glyceryl trinitrate), which can ward off angina, might prevent these abnormal responses of the systolic time intervals to the exercise test in angina patients. Were such preventive effects to occur, they might provide the basis for an objective, though noninvasive, means of assessing the therapeutic efficacy of nitrates, including "long-acting" ones. Moreover, the delineation of such effects might enhance understanding of angina, particularly its pathogenesis and its relief by nitroglycerin. Consequently, the effects of nitroglycerin on the left ventricular systolic temporal responses to exercise were investigated in angina patients and, for comparison, in normal subjects.

Methods

Ten male patients with angina pectoris, mean age ± sx 52.7 ± 1.6 (range 46–61) years, and 10 approximately age-matched normal controls, mean age ± sx 49.4 ± 2.5 (range 37–58 years), were studied. All patients had anginal pain brought on by exertion, cold, meals, or emotion and relieved by rest and nitroglycerin. One patient had a myocardial infarction 5 months before study, and three had a myocardial infarction 2 years or more before study. One patient had mild hypertension (arterial pressure 165/100 mmHg), which was asymptomatic and untreated. None had clinical evidence of congestive heart failure, but

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one, the hypertensive patient, had minimal cardiomegaly on chest X-ray. Five, including the four known to have had old myocardial infarctions, had electrocardiographic evidence of old myocardial infarction, anteroseptal in three and inferior wall in two. Of the remaining five patients, one had nonspecific ST-T-wave abnormalities and another had a mean frontal QRS axis of -90°. Normal controls were healthy, but sedentary, hospital employees with neither history nor physical signs of heart disease. Each had a normal 12-lead electrocardiogram, Master double two-step exercise test, and chest X-ray. All subjects gave written informed consent and were studied in the postabsorptive state without sedation.

A bipolar electrocardiographic lead was obtained across the anterior thorax, with the negative electrode in the second intercostal space at the right midclavicular line and the positive electrode in the fifth intercostal space at the left midaxillary line. A contact microphone was placed over the third intercostal space at the left sternal border and was strapped firmly to the chest. The indirect carotid pulse tracing was obtained with an Electronics for Medicine pulse-sound microphone PS-1b held manually over the common carotid artery in the neck. With the subject resting supine, the electrocardiogram, phonocardiogram, and indirect carotid pulse tracing were recorded simultaneously at 100 mm/sec paper speed with 20-msec time lines on an Electronics for Medicine multichannel photographic recorder, and arterial pressure was measured with a cuff sphygmomanometer on the arm.

After a 10-min rest period, three sets of measurements were obtained at 3-min intervals with the subjects supine. The average of these three is reported as the preexercise set of measurements. With the electrocardiographic lead and chest microphone kept in place, the subject then stood erect and, in time to a metronome, stepped up and down a 6-in platform for 4 min, making 24 complete trips (96 steps)/min. This exercise was previously found to increase average oxygen consumption fourfold in normal controls and patients with angina.1 Electrocardiographic recordings in the last 15 sec of exercise were used to measure heart rate during exercise. Immediately after exercise, the subjects lay down, and at 30 sec and 1, 2, 3, 4, 5, 7, 10, and 15 min after the end of exercise arterial pressure was measured and recordings were obtained for the phases of systole. This study, performed without nitroglycerin, is called the baseline exercise study. On another day, each subject repeated the study exactly the same way except that 1 min before beginning the exercise he received 0.6 mg nitroglycerin sublingually.

On a third day, the effects of nitroglycerin at rest were determined in three of the patients with angina. While they rested supine, their arterial pressures and systolic time intervals were determined at 6 and 3 min and immediately before and after 30 sec, 1, 2, 3, 4, 5, 7, 10, 15, 25, and 40 min after sublingual administration of 0.6 mg nitroglycerin. The average of the three sets of measurements before nitroglycerin is reported as the prenitroglycerin set of measurements.

Special care was taken to avoid loss of potency of the nitroglycerin, which is volatile. Tablets were obtained directly from the manufacturer, used only during the next 3 months, and kept in their original high-density polyethylene container, which was stored in a cool, but nonrefrigerated, light-free drawer. Except for 10-sec periods required for tablet dispensation, the metal screw cap of the container was kept tightly closed.

Total electromechanical systole, or the Q-S₂ interval, was measured from the onset of the Q wave of the electrocardiogram to the first high-frequency vibration of the aortic component of the second heart sound. The left ventricular ejection time (LVET) was measured from the onset of the rapid rise of the carotid pulse tracing to the trough of its incisura. The preejection period (PEP) was calculated by subtraction of the LVET from the Q-S₂ interval. All intervals were determined as the average of measurements on 10 consecutive beats, each read to the nearest 5 msec. Heart rate was derived by dividing the average R-R interval into 60.

The Q-S₂ interval and LVET vary inversely with heart rate. Using data from supine normal adults at rest, Weissler and associates² have derived linear regression equations that relate these time intervals to heart rate. With these equations, the Q-S₂ interval and LVET in the present study were corrected for heart rate as follows: 

Q₂₁ (msec) = Q-S₂ interval (msec) + 2.1 heart rate (beats/min); 

LVET₁ (msec) = LVET (msec) + 1.7 heart rate beats/min).

Because studies with right atrial pacing and atropine have shown that cardioacceleration by itself does not shorten the preejection period, ³ a correction for heart rate was not applied to the preejection period. Statistical analyses were performed by Student’s t test.⁴

**Results**

Average measurements before and 30 sec after exercise appear in tables 1 and 2. Before both exercise studies the normal and angina groups had similar resting levels of systolic and diastolic arterial pressure, Q₂₁, and LVET. At rest before the baseline exercise but not before the postnitroglycerin exercise, the angina group had a significantly longer preejection period (P < 0.01) and faster heart rate (P < 0.05) than did the normal group. Heart rate during the last 15 sec of exercise exceeded preexercise values, without nitroglycerin, by (mean ± se) 43 ± 2.2 beats/min in the normal group and 42 ± 3.5 beats/min in the angina group and, with nitroglycerin, by 55 ± 3.7 beats/min in the normal group and 48 ± 3.8 beats/min in the angina group. Two angina patients had chest pain, which began during the 4th min of exercise without nitroglycerin. None had chest pain after nitroglycerin.

Figures 1 and 2 show average changes from preexercise measurements 30 sec to 15 min after the end of exercise. Without nitroglycerin, the normal
and angina groups did not differ significantly from one another in their increases in heart rate and systolic and diastolic arterial pressures after exercise. Following nitroglycerin, they did not differ significantly from one another in their increases of systolic arterial pressure or changes in diastolic arterial pressure after exercise. In the angina group, but not the normal group, the increases in heart rate 1–10 min after exercise were significantly higher (P < 0.05 to < 0.001) with than without nitroglycerin. As a result, after nitroglycerin the increases in heart rate 4–10 min postexercise were significantly higher (P < 0.05 to < 0.02) in the angina group than in the normal group.

Thirty seconds after exercise without nitroglycerin the preejection period had fallen below its preexercise level by about 29 msec in both groups; it remained significantly shortened for 7 min after

### Table 1

**Systolic Time Intervals* in 10 Normal Subjects and 10 Angina Patients before and after Exercise without Nitroglycerin**

<table>
<thead>
<tr>
<th>Test state</th>
<th>Heart rate (beats/min)</th>
<th>Arterial pressure (mm Hg)</th>
<th>Q2* (msec)</th>
<th>LVET* (msec)</th>
<th>P*P (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting control:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>73 ± 2.4</td>
<td>119 ± 3.7</td>
<td>79 ± 2.7</td>
<td>551 ± 3.5</td>
<td>417 ± 4.4</td>
</tr>
<tr>
<td>Angina patients</td>
<td>85 ± 4.8</td>
<td>122 ± 6.0</td>
<td>83 ± 4.7</td>
<td>560 ± 3.4</td>
<td>407 ± 5.0</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>30 sec postexercise:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>90 ± 2.1</td>
<td>144 ± 5.9</td>
<td>81 ± 3.3</td>
<td>528 ± 3.2</td>
<td>417 ± 3.2</td>
</tr>
<tr>
<td>Angina patients</td>
<td>103 ± 6.4</td>
<td>147 ± 9.2</td>
<td>88 ± 3.9</td>
<td>562 ± 6.7</td>
<td>432 ± 7.3</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.005</td>
<td>NS</td>
</tr>
<tr>
<td>Changes from resting control 30 sec postexercise:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>17 ± 1.9</td>
<td>23 ± 3.7</td>
<td>2 ± 1.8</td>
<td>-22 ± 3.6</td>
<td>0 ± 3.2</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Angina patients</td>
<td>18 ± 4.7</td>
<td>22 ± 5.7</td>
<td>5 ± 1.4</td>
<td>2 ± 8.5</td>
<td>25 ± 5.9</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>P for difference between postexercise responses of normal and angina groups</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.025</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Mean = se.

Abbreviations: NS = not significant at 0.05 level; for others see text.

### Table 2

**Systolic Time Intervals* in 10 Normal Subjects and 10 Angina Patients before and after Exercise following Nitroglycerin**

<table>
<thead>
<tr>
<th>Test state</th>
<th>Heart rate (beats/min)</th>
<th>Arterial pressure (mm Hg)</th>
<th>Q2* (msec)</th>
<th>LVET* (msec)</th>
<th>P*P (msec)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
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<tr>
<td>Resting control:</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>71 ± 2.6</td>
<td>119 ± 4.4</td>
<td>80 ± 4.4</td>
<td>555 ± 4.0</td>
<td>418 ± 4.5</td>
</tr>
<tr>
<td>Angina patients</td>
<td>80 ± 4.0</td>
<td>120 ± 6.0</td>
<td>79 ± 3.7</td>
<td>557 ± 5.0</td>
<td>407 ± 4.4</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>30 sec postexercise, with nitroglycerin:</td>
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<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>93 ± 3.9</td>
<td>137 ± 7.5</td>
<td>80 ± 3.4</td>
<td>521 ± 3.6</td>
<td>406 ± 2.8</td>
</tr>
<tr>
<td>Angina patients</td>
<td>106 ± 6.2</td>
<td>140 ± 8.5</td>
<td>81 ± 3.9</td>
<td>539 ± 6.6</td>
<td>403 ± 5.0</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Changes from resting control 30 sec postexercise, with nitroglycerin:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>22 ± 3.3</td>
<td>17 ± 3.0</td>
<td>-1.5 ± 2.2</td>
<td>-35 ± 4.6</td>
<td>-12 ± 4.1</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Angina patients</td>
<td>26 ± 3.3</td>
<td>16 ± 2.8</td>
<td>1 ± 2.0</td>
<td>-18 ± 3.6</td>
<td>-4 ± 4.1</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>P for difference between postexercise responses of normal and angina groups</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.025</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Mean = se.

Abbreviations: NS = not significant at 0.05 level; for others see text.
exercise in the normal group (fig. 1) and 4 min after exercise in the angina group (fig. 2). In the normal group shortening of the preejection period after exercise was unaffected by nitroglycerin; the preejection period returned to its preexercise level at 7 min and remained there 7–15 min postexercise. In the angina group, by contrast, nitroglycerin seemed to diminish slightly the tendency of the preejection period to shorten after exercise; not only did shortening of the preejection period become insignificant after 2 min postexercise, but the preejection period lengthened 6 ± 2 msec (P < 0.025) beyond its preexercise levels at both 10 and 15 min postexercise.

Without nitroglycerin the two groups differed significantly from one another in responses of the Q2c, 30 sec to 3 min postexercise (P < 0.05 to < 0.005) and of the LVETc, 30 sec to 2 min postexercise (P < 0.01 to < 0.005). At 30 sec postexercise the Q2c was shortened 22 ± 3.6 msec (P < 0.001) in the normal subjects but was lengthened 2 ± 8.5 msec, a small and insignificant change, in the angina patients (fig. 3), while the LVETc was unchanged in the normal subjects but was lengthened 25 ± 5.9 msec (P < 0.005) in the angina patients (fig. 4). Prolongation of the LVETc in the angina patients remained significant for 7 min postexercise (fig. 2).

After nitroglycerin the two groups differed significantly from one another in responses of the Q2c, 30 sec (P < 0.025) and 1 min (P < 0.02) postexercise but not of the LVETc, 30 sec to 15 min postexercise (figs. 1, 2). At 30 sec postexercise the Q2c was shortened 35 ± 4.6 msec (P < 0.001) in the normal subjects and 18 ± 3.6 msec (P < 0.001) in the angina patients.
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Figure 2

Mean (±SE) changes (Δ) from preexercise levels 30 sec to 15 min after the end of exercise in 10 angina patients. The abnormal postexercise responses of failure of Q2c to shorten and marked prolongation of LVETc were converted to normal by nitroglycerin.

the angina patients (fig. 3), while the LVETc was shortened 12 ± 4.1 msec (P < 0.02) in the normal subjects and 4 ± 4.1 msec, an insignificant amount, in the angina patients (fig. 4). Thus, nitroglycerin converted the abnormal responses of the angina group, which were failure of Q2c to shorten and marked prolongation of LVETc, into the normal responses of shortening of Q2c and slight shortening or no change in LVETc. The effects of nitroglycerin on the Q2c responses to exercise 30 sec and 1 min after exercise were only slightly greater (by about 8 msec) in the angina group than in the normal group. In contrast, the effects of nitroglycerin on the LVETc responses to exercise were twice as great in the angina group, −29 ± 6.8 msec at 30 sec and −31 ± 6.4 msec at 1 min postexercise, than they were in the normal group, −14 ± 3.3 msec at 30 sec and −15 ± 4.0 msec at 1 min postexercise.

Figure 5 shows average effects of nitroglycerin, at rest and postexercise, in three angina patients, who received the drug once with and once without exercise. Thirty seconds after the three patients had finished exercising without nitroglycerin, their average LVETc exceeded its preexercise duration by 22 msec. In contrast, 30 sec after they had completed the same exercise following nitroglycerin, their LVETc was shorter than its preexercise duration by 6 msec. Thus, 30 sec postexercise, which was also 5% min after nitroglycerin administration, nitroglycerin shortened the LVETc by the sum of 22 and 6 msec, or 28 msec. When these three patients were restudied at rest without exercise, the LVETc was shortened only 12 msec by nitroglycerin 5 min after

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its administration. In these three angina patients, on the average, 12 msec, or about 43%, of the change superimposed by nitroglycerin on the LVET, responses 30 sec after exercise was attributable to effects of nitroglycerin at rest. The remaining 16 msec, or 57%, appeared to be specific for exercise. Likewise, in these three patients, 6 msec, or about 35%, of the 17 msec shortening superimposed by nitroglycerin on the Q2c responses 30 sec after exercise was attributable to effects of nitroglycerin at rest, with the remaining 11 msec, or 65%, specific for exercise. As figure 5 further shows, with the patients resting, abbreviation of the LVETc and Q2c persisted longer than 5½ min after nitroglycerin was given. Consequently, effects of the drug at rest also contributed to the shortening that nitroglycerin superimposed upon the LVETc and Q2c after the first 30 sec postexercise. Shortening of the preejection period 30 sec and 1 min after exercise was diminished 8 and 6 msec, respectively, by nitroglycerin.

**Figure 3**
Changes from resting levels in Q2c, 30 sec after exercise. P values refer to differences between the mean changes occurring after exercise without and with nitroglycerin. As the right-hand panel shows, in the angina patients nitroglycerin converted the abnormal failure of the Q2c to shorten after exercise into the normal response of shortening.

**Figure 4**
Changes from resting levels in LVETc, 30 sec after exercise. P values refer to differences between the mean changes occurring after exercise without and with nitroglycerin. In the angina patients, nitroglycerin abolished the abnormal prolongation of the LVETc after exercise.

**Figure 5**
Mean effects of 0.6 mg sublingual nitroglycerin on the LVETc and Q2c in a group of three angina patients. Effects of nitroglycerin after exercise (broken lines) were calculated by subtraction of the postexercise responses without nitroglycerin from the postexercise responses after nitroglycerin. Nitroglycerin shortened the LVETc and Q2c not only at rest without exercise (solid lines), but even more so following exercise.
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erin. When these three patients were restudied at rest without exercise, the preejection period 5 and 7 min after nitroglycerin administration was abbreviated only 1 msec. Consequently, the effects of nitroglycerin on the preejection period at rest are slight enough to be ignored.

Discussion

At rest before both exercise tests, the angina group had an average preejection period 9–16 msec longer and an average LVETc about 11 msec shorter than the normal group had. Although this tendency toward a long preejection period and short LVETc may reflect a mild impairment of ventricular function at rest in some angina patients,2 differences between the normal and angina groups at rest were relatively small and, except for those involving the preejection period on one day, were insignificant. In contrast, the two groups clearly differed from one another in responses of the LVETc and Q2c, 30 sec to 2 min after exercise without nitroglycerin. In the normal subjects, exercise shortened the Q2c but left the LVETc unchanged or slightly shortened. In the angina group, by contrast, exercise left the Q2c unchanged but greatly prolonged the LVETc.

These results with the LVETc and Q2c resemble those previously reported for this test.1 Contrary to the previous findings, however, the present normal and angina groups failed to differ significantly from one another in responses of their preejection period, heart rate, or systolic or diastolic arterial pressure 30 sec to 15 min postexercise. These discrepancies between the two studies probably reflect, in part, the higher proportion of hypertensive patients (five of 20) in the previous angina group and the fact that, although all 20 previous angina patients had chest pain with the test, only two of the present 10 angina patients did. The new findings clarify three aspects of the exercise test. First, responses of the Q2c and LVETc to the test are more sensitive and consistent than those of heart rate, arterial pressure, or preejection period in discriminating between normal and abnormal left ventricular performance with exercise. Second, the marked differences between the normal and angina groups in postexercise responses of total electromechanical systole (Q-S, interval) and left ventricular ejection time cannot be attributed to differences in heart rate or systolic arterial pressure, which rose equally in both groups. Third, the finding that the LVETc prolonged markedly after exercise in the eight angina patients who experienced no chest pain during the test adds to previous evidence1 that this prolongation is not due to pain. More likely, by increasing myocardial oxygen requirements, the prolongation of ejection relative to heart rate, which exercise induces in the ischemic left ventricle, contributes to the development of anginal pain.5

Determinants of the systolic temporal responses to exercise in normal subjects and angina patients, discussed in detail elsewhere,1 may be summarized as follows. By increasing venous return, exercise evoke the Starling mechanism;6,7 by inducing a discharge of catecholamines,8 exercise augments myocardial contractility.7,9 Both in normal subjects and angina patients, these myocardial responses to exercise accelerate the isovolumic rise of left ventricular pressure,10 leading to an earlier opening of the aortic valve and a shorter preejection period.8 In angina patients, elevation of left ventricular end-diastolic pressure by exercise11,12 probably also contributes to shortening of the preejection period.

Left ventricular ejection time relative to heart rate varies directly with venous return, stroke volume or cardiac output, and with afterload, but inversely with myocardial inotropy.13–15 While the enhancement of venous return and cardiac output by exercise tends to lengthen the LVETc, the positive inotropic effects of exercise tend to shorten it. In normal subjects, because of a balance between these two opposite effects of exercise, the LVETc remains unchanged after the present exercise test. In angina patients, however, owing to an imbalance caused primarily by impairment in performance of the ischemic left ventricle, the LVETc prolongs abnormally after the same exercise test.1 In addition, by reason of its larger than normal volume during exercise, the ischemic left ventricle incurs, through the Laplace relation, an abnormally great afterload,11,18 which probably also contributes to this LVETc prolongation.18

The positive inotropic effects of rhythmic exercise7 shorten the Q2c, or total electromechanical systole relative to heart rate,15,18 in normal subjects but not in angina patients. Unable to translate the inotropic stimuli of exercise into a normal enhancement of ejection rate,1,21,22 the ischemic left ventricle must, instead, prolong its ejection in order to meet, in part, the need for increased cardiac output during exercise. In patients with angina, this abnormal lengthening of the ejection phase appears to nullify the shortening effects of rhythmic exercise on total electromechanical systole.

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When given to angina patients 1 min before the 4-min exercise test, nitroglycerin caused, relative to the postexercise responses without nitroglycerin, a significant rise in heart rate, fall in systolic arterial pressure, and marked shortening of the LVET, and \(Q_2\), but minimal changes in the preexercise period, for several minutes after the end of exercise (Fig. 2). Most important, nitroglycerin prevented the abnormal prolongation of LVET, after this exercise test in angina patients and converted the abnormal failure of their \(Q_2\) to shorten after exercise into a normal shortening of \(Q_2\). This ability of nitroglycerin to normalize responses of the left ventricular systolic time intervals to mild or moderate exercise in angina patients can be explained by its known or postulated actions. By reducing peripheral arteriolar and venous tone, nitroglycerin diminishes systolic arterial pressure and venous return to the heart.\(^{20}\) The resulting decrease in left ventricular end-diastolic volume\(^{24}\) tends to cause a fall in cardiac output.\(^{24-26}\) The lessening in aortic impedance, combined with the reduction in left ventricular systolic volume,\(^{24}\) diminishes left ventricular systolic wall stress, or afterload. The tendency of the reductions in peripheral arteriolar tone and in cardiac output to lower systemic arterial pressure evokes reflex cardiac stimulation through baroreceptor mechanisms, leading to increases not only in heart rate but also, to an unknown degree, in sympathetically mediated positive inotropic effects on the myocardium.\(^{27,28}\)

By lessening the excess of myocardial oxygen needs relative to blood supply, nitroglycerin diminishes myocardial hypoxia. In addition, there is experimental evidence that nitroglycerin may increase blood flow to an ischemic area of myocardium by causing redistribution of coronary blood flow.\(^{29,30}\) Several investigators have suggested that nitroglycerin may indirectly cause a redistribution of blood flow in ischemic myocardium by decreasing the left ventricular size, end-diastolic pressure, afterload, and intramyocardial tissue pressure gradient.\(^{31,32}\) Reduction of myocardial hypoxia, perhaps combined with sympathetically mediated positive inotropic effects, would improve left ventricular function.

Thus, by diminishing left ventricular afterload and output and, perhaps, by reducing myocardial hypoxia and ischemia and improving left ventricular function, nitroglycerin prevents the abnormal exercise-induced prolongation of left ventricular ejection relative to heart rate that is characteristic of patients with angina. Since these actions of nitroglycerin keep the ejection phase of left ventricular systole from lengthening abnormally in angina patients, the shortening effects of rhythmic exercise on total electromechanical systole are no longer offset in these patients and consequently the \(Q_2\) shortens normally.

The same cardiovascular actions of nitroglycerin, with the omission of its effects on myocardial hypoxia and ischemia, account also for its shortening the LVET, and \(Q_2\), after exercise in the normal subjects. Nitroglycerin may have a greater than normal influence on the systolic time intervals in angina patients, for it affected the LVET, responses 30 sec and 1 min after exercise twice as much in the angina group as in the normal group. Verification of this interesting possibility requires further studies.

Nitroglycerin has pronounced effects on the systolic time intervals at rest, which contribute importantly to its effects on the systolic temporal responses to exercise. Thus, in the three angina patients who received 0.6 mg nitroglycerin with and without exercise, approximately one third to one half of the changes superimposed by nitroglycerin on the LVET, and \(Q_2\), responses to exercise could be ascribed to effects of nitroglycerin at rest, while the remaining half to two thirds of the changes appear to be specific for effects of the drug with exercise.

A change in LVET or \(Q_2\) equals a change in the observed LVET or Q-S2 interval relative to the normal mean regression line for the systolic time interval against heart rate. Relative to its normal mean regression line at rest, the LVET is markedly lengthened by exercise in angina patients before but not after they have received nitroglycerin. Relative to its normal mean regression line at rest, the Q-S2 interval fails to be shortened normally by exercise in angina patients who have not received nitroglycerin but is shortened normally by exercise after they have taken nitroglycerin. Considered from another viewpoint, in the present range of heart rates, exercise raises the LVET regression line for heart rate in angina patients but not in normal subjects and lowers the Q-S2 interval regression line for heart rate in normal subjects but not in angina patients. Nitroglycerin lowers the LVET and Q-S2 interval regression lines for heart rate at rest and after exercise both in normal subjects and angina patients. Thus, nitroglycerin induces responses of total electromechanical systole
and the duration of left ventricular ejection, relative to heart rate, that counteract the abnormal responses of these intervals to the exercise test in angina patients. These systolic temporal responses to nitroglycerin reflect its effects on left ventricular filling, afterload, contractility, and, perhaps, synchrony of contraction.

Suppression by nitroglycerin of LVETe prolongation after exercise would, itself, diminish myocardial oxygen consumption and, therefore, be antianginal. The efficacy and the duration of action of "long-acting" nitrates have been difficult to demonstrate objectively in man.33 Suppression of abnormal LVETe prolongation after exercise, detectable noninvasively, provides the basis for a new method of evaluating objectively the efficacy of nitrates in patients with angina pectoris.

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