Effects of Nitroglycerin on “Maximal” Oxygen Intake and Exercise Electrocardiogram in Coronary Heart Disease

By JEAN-MARIE R. DETRY, M.D., AND ROBERT A. BRUCE, M.D.

SUMMARY

Oxygen intake ($\dot{V}_{\text{O}_2}$) was measured during the last few minutes of a multistage treadmill test of maximal exercise in 12 healthy middle-aged persons, 32 patients with angina, and 23 survivors of myocardial infarction free of angina. Repetition of the same test, after each individual rested 30 min and took 0.4 mg nitroglycerin sublingually, increased $\dot{V}_{\text{O}_2}$ max in patients with angina (by 14.5%, $P < 0.001$) and in patients with prior infarction (by 6%, $P < 0.005$) but not in healthy persons. Angina at $\dot{V}_{\text{O}_2}$ max was prevented in 12 patients. Maximal heart rate was increased by 11% in the angina group and by 4% in the myocardial infarction group; the maximal blood pressure-heart rate product was increased ($P < 0.005$) only in patients with angina. S-T voltages from 50 to 69 msec after the nadir of S wave (S-T₁) were quantified by computer averaging of 100 beat samples at several intervals during and after exercise. The amount of S-T₁ depression during and after exercise was significantly reduced after administration of nitroglycerin in all three groups.

We conclude that nitroglycerin: (1) increases maximal circulatory conductance of $\text{O}_2$ in patients with coronary heart disease, whether or not limited by angina, mainly by increased maximal heart rate, and (2) lessens evidence of electrocardiographic myocardial ischemia and lowers frequency if angina pectoris despite the same or a higher pressure-rate index. These effects suggest a reduction in peripheral vascular tone and left ventricular end-diastolic pressure and volume with nitroglycerin.

Additional Indexing Words:
Maximal oxygen consumption
Postexercise electrocardiogram
Pressure-rate product

Nitroglycerin often allows patients with angina pectoris to perform more work than that ordinarily associated with chest pain. A decrease in myocardial oxygen requirements caused by diminished heart volume, secondary to arterial and venous dilatation by nitroglycerin, could explain this effect. The prevention of angina pectoris is accompanied by a decrease in left ventricular end-diastolic pressure and an improvement of left ventricular performance.

During moderate exercise nitroglycerin also improves left ventricular function in patients with coronary heart disease but free of angina, and lowers the left ventricular end-diastolic pressure of normal subjects.

The magnitude of postexercise S-T segment depression in patients with angina pectoris is diminished by sublingual nitroglycerin or isorbide dinitrate.

In this study the effects of nitroglycerin on maximal oxygen intake, heart rate, blood pressure, and electrocardiographic S-T re-
Table 1

Mean Changes in Circulatory and Oxygen Intake Responses to Exercise

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
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<th>Angina pectoris patients</th>
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Abbreviations: HR = heart rate (beats/min); SBP = systolic blood pressure (mm Hg); \(\frac{HR \times SBP}{100}\) = systolic pressure-heart rate product; \(\dot{V}_o_2\) max = maximal oxygen intake (ml O\(_2\)/min/kg body weight); \(P\) = probability based upon paired t-test.
sponse, in patients with coronary heart disease with or without angina are compared with normal responses.

**Methods**

Ambulatory patients with coronary heart disease included 23 patients (mean age 50.3 years) with healed myocardial infarction but no angina, and 32 (mean age 51.4 years) with typical angina pectoris induced by exercise. They were compared with 12 healthy, asymptomatic, middle-aged men (mean age 46.2 years).

Subjects with systemic hypertension (BP > 160/95), clinically manifest heart failure, or those taking drugs such as digitalis or beta-blocking agents were excluded. Subjects in the normal group had a normal physical examination and resting electrocardiogram, no prior history of coronary heart disease, and no postexercise S-T segment depression exceeding -0.1 mv.

After physical examination and recording of 12 lead resting electrocardiogram, each person performed a multistage treadmill test of maximal exertion as previously described. Briefly, speed and grade of the treadmill were increased every 3 min until a self-determined limit of maximally tolerated fatigue, dyspnea, or chest pain was reached. A bipolar precordial CB5 electrocardiogram was continuously monitored and none of the subjects had a significant arrhythmia. A continuous recording of a bipolar and Frank X, Y, and Z electrocardiogram on magnetic tape was obtained during 3 min of resting in the sitting position before the test, the entire exercise, and the first 6 min of recovery in the sitting position. Direct paper ECG records were also obtained at approximately 1-min intervals for monitoring. Blood pressure was measured by sphygmomanometer before the test, after 2½ min of exercise (end of stage 1), and during the first seconds of recovery.

One-minute samples of expiratory gases were collected through a low resistance open circuit into evacuated neoprene balloons during the last 3 or 4 min of exercise. O2 tension of dried air before and after CO2 absorption was measured with a Beckman O2 analyzer, and expiratory volume was measured (STPD) with a calibrated gasometer (American Meter Co.). Oxygen intake was calculated from the following equation:

\[
\dot{V}_O_2 = \dot{V}_E \left( kx_2 - [k + 1] \frac{x_1x_2}{x_1} \right)
\]

where \(\dot{V}_E\) = minute volume of expired air (STPD)

**Results**

**Effects on Maximal Oxygen Intake (\(\dot{V}_{O_2}\) max)**

Repeating the same multistage test of maximal exercise within 1 hr and with 0.4 mg nitroglycerin sublingually at the start of exercise, produced no significant change in

\[
k = 0.2647 \text{ (or ratio of } \frac{F_{1O_2}}{F_{1N_2}} \text{ or } 0.2093 \text{ or } 0.7906)\]

\[
x_1 = F_{E02} \text{ without } CO_2 \]

\[
x_2 = F_{E02} \text{ with } CO_2 \text{ (prior to } CO_2 \text{ absorption).}
\]

Exercise S-T responses were measured by computer averaging of hundred-beat samples with the P-R interval as zero reference voltage. These samples were obtained at rest, at the end of each exercise stage, at maximal exercise, at initial recovery, and at each minute of recovery. S-Tv designates voltage of the S-T segment from 50 to 69 msec after the nadir of S wave, with 32 voltage measurements for each heart beat. Thus, each S-Tv voltage is the mean of 3,200 voltage measurements.

After the first test, the subjects were allowed to rest sitting in a chair for half an hour after which resting ECG and blood pressure were again recorded. The same exercise was then resumed after the patient had received 0.4 mg nitroglycerin sublingually.

Significances of changes were tested by Student's paired t-test.

**Figure 1**

Acute effects of nitroglycerin (NG) on maximal oxygen intake.
maximal oxygen intake in normal subjects (table 1 and fig. 1).

Patients with healed myocardial infarction showed a 6% increase in maximal oxygen intake \((P < 0.005)\), even though they experienced no chest pain on either test. Patients who were previously limited by angina pectoris, and who had lower \(V_{O_2}\) max than infarct patients, showed a 14.5% increase in \(V_{O_2}\) max \((P < 0.001)\). On the nitroglycerin test, 12 patients were symptomatically limited by dyspnea and fatigue rather than by chest pain. Increments in \(V_{O_2}\) max were mainly caused by increase in heart rate with nitroglycerin, since maximal oxygen pulse* increased by only 2% in patients with infarct and 3.5% in patients with angina.

**Effects on Heart Rate and Blood Pressure**

Resting heart rate prior to treatment with nitroglycerin was significantly higher \((P < 0.001)\) in all three groups (table 1). Heart rate during exercise and recovery was higher on retesting with nitroglycerin (table 1 and fig. 2); maximal heart rate was increased 4\% \((P < 0.02)\) in normal subjects, 4\% \((P < 0.001)\) in patients with infarct, and 11\% \((P < 0.001)\) in patients with angina.

Systolic blood pressure at submaximal exercise (stage 1) was significantly lower in all three groups with nitroglycerin; at maximal exercise only patients with infarct showed a significant decrease in systolic pressure \((P < 0.05)\).

The pressure-rate product (product of systolic blood pressure and heart rate) was significantly higher before second exercise in all three groups (table 1 and fig. 3). At submaximal exercise, pressure-rate product was unchanged by nitroglycerin; at maximal exercise, however, pressure-rate product was significantly \(P < 0.005\) increased in patients with angina.

**Effects on S-T Segment Depression**

On the initial control test, S-T\(_B\) voltages at maximal exercise were \(-0.152\), \(-0.213\), and \(-0.328\) mv for normal subjects, patients with angina, and patients with infarct, respectively. It is important to note that the relationship of S-T segment depression as defined by S-T\(_B\) measurements, to heart rate varied significantly in these three groups (fig. 2). Normal subjects characteristically showed counterclockwise hysteresis loops in this relationship in recovery after exercise. This was caused by the marked reduction in S-T force, with relatively little slowing of heart rate during the first 20 sec after maximal exercise. As heart rate diminished over the next 4 to 5 min, the S-T voltage appeared to "overshoot" and then return toward the initial exercise relationship. Patients with angina showed lower maximal heart rate, excessive S-T depression, and clockwise hysteresis loop of S-T-heart rate relationship in recovery (fig. 2). Thus the ECG evidence of myocardial ischemia persisted longer than the tachycardia. Patients with healed myocardial infarction showed somewhat higher maximal heart rate, and even more marked S-T depression consistent with a greater maximal oxygen intake of this group. The hysteresis pattern of the S-T-heart rate relationship also tended to be intermediate between those of the normal and angina groups.

Nitroglycerin altered the S-T responses of all three groups since S-T\(_B\) depression was significantly less marked at submaximal and maximal exertion (fig. 4). S-T depression was also less important during the recovery, but the difference was significant only for patients with angina in early recovery. The relationship of S-T segment depression to heart rate was also modified by nitroglycerin (fig. 2); the loops were displaced to the right and superiorly in all three groups.

**Discussion**

There are three topics that warrant discussion in this study; the different ways coronary heart disease limits exercise performance, the significance of maximal oxygen intake in coronary patients, and the implications of

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changes induced by nitroglycerin treatment. Comment about the limitations of the experimental design is also indicated.

The half-hour resting period between the two maximal tests of the present study was too short to allow a complete recovery, since resting heart rate was still significantly higher than control before nitroglycerin was taken and exercise was repeated; this finding was in agreement with previous reports on the hemodynamic effects of repeated exercise, and could be the result of insufficient cooling of body temperatures when resting periods between workloads were too short. Repeat maximal treadmill testing after half an hour of rest in a different group of 13 normal subjects (mean age 33 years) induced a significantly higher heart rate (by 11 beats/min, \(P < 0.001\)) at submaximal exercise (end of stage I), but not at maximal exercise (+2 beats/min, \(P > 0.05\)). Thus, part of the cardioacceleration observed during submaximal stages of the second exercise test with nitroglycerin represents a residual effect of previous exercise testing.

Exercise heart rate after nitroglycerin treatment has been previously found to be increased or unchanged. Repeating the maximal exercise test after a half-hour resting period did not modify the close relationship between exercise heart rate and magnitude of S-T segment depression nor that between angina threshold and pressure-time index. Consequently, higher heart rate should be

Figure 2

Effects of nitroglycerin on relationship of S-T segment depression to heart rate. S-T\(_{50-69}\) designates voltage of S-T segment from 50 to 69 msec after the nadir of S wave, with the P-R interval as zero reference voltage. Exercise samples were obtained at the end of stage I and of stage II, and at maximal exercise. The arrows in each panel represent the percentage changes observed at maximal exercise, and probabilities of such changes occurring by chance alone.

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Acute effects of nitroglycerin on systolic pressure-heart rate product (product of heart rate and systolic blood pressure) during multistage treadmill test. Vertical dotted lines indicate values at rest and at the end of stage I. An index of myocardial reserve is represented by the difference in this product at maximal exercise and at rest.

attended by more important S-T segment depression and earlier onset of anginal pain. In this study the higher heart rate after nitroglycerin was associated with less S-T segment depression and later onset of anginal pain. Therefore, the influence of experimental protocol, if any, would enhance the significance of changes observed.

Maximal exercise capacity is decreased in coronary heart disease, whether or not performance is limited by angina. In the present study, maximal oxygen intake in normal subjects was within the range predicted for age, but it was only 81% of normal in patients with infarct and 61% in patients with angina.

This low exercise capacity was attended by a lower pressure-rate product at maximal exercise, not only in patients with angina but also in patients with infarct not limited by angina. Whereas limitation of capacity in coronary patients is most evident at maximal exercise, altered performance is also apparent at submaximal levels. For example, the pressure-rate product at stage I was 168 in normal subjects, 183 in patients with infarct, and 198 in patients with angina. This suggests greater acceleration of heart rate, or more peripheral vasoconstriction, to compensate for lower cardiac output in patients with coronary heart disease. Left ventricular end-diastolic pressure is elevated in these patients at submaximal exercise. Thus, angina pectoris is neither the first nor only manifestation of abnormal exercise performance.

The threshold at which angina is experienced is individually constant when expressed in terms of tension-time index or its derivatives. This threshold does not seem to be identical for angina induced by exertion and that induced by atrial pacing, left ventricular end-diastolic pressure is not elevated during the latter stress. Major factors limiting maximal performance in patients with coronary heart disease without angina are not entirely defined; elevation of left ventricular end-diastolic pressure should be more marked
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at maximal than submaximal exercise\textsuperscript{4} and could be a major factor.

After nitroglycerin is taken, the maximal oxygen intake remains unchanged in the normal group, despite a slightly higher heart rate. The increased maximal oxygen intake in patients with prior infarct (+6\%) and in patients with angina (+14.5\%) was mainly the result of a higher maximal heart rate (+4\% and 11.5\%, respectively). The pressure-rate product at maximal exercise was unchanged in normal subjects and in patients with infarction, because of a minor fall in pressure at maximal exercise. This product significantly increased in patients with angina because of an even greater increment in heart rate with associated increments in $V_{O_2} \text{ max}$ and probably in cardiac output also; simultaneously anginal pain was prevented in 12 of them. The pressure-rate product used in this study is not identical with the tension-time index,\textsuperscript{26} since central and peripheral arterial systolic pressures are different, particularly during exercise.\textsuperscript{27} Increase in maximal systolic pressure-heart rate product, however, suggests that the relation between the tension-time index and angina threshold probably was modified by nitroglycerin. An increased angina threshold after nitroglycerin absorption is not surprising, since a major mechanism of action of the drug seems to be a reduction in heart volume secondary to a transient decrease in venous return as a consequence of dilatation of both the arteriolar and venous beds.\textsuperscript{1, 2, 28} Reduced heart volume diminishes myocardial oxygen requirements for a given tension-time index, which may permit the higher maximal systolic pressure-heart rate product that is observed in angina patients after treatment with nitroglycerin. This higher angina threshold, accompanied by an improvement in left ventricular function during exercise,\textsuperscript{3} would allow the patients to reach a higher exercise level and a higher maximal oxygen intake. A discrepancy with findings of Robinson\textsuperscript{16} probably results from a different protocol because maximal exercise probably was not attained in his study after treatment with nitroglycerin.

It is postulated that improved left ventricular function with diminished heart volume during upright exercise\textsuperscript{4} explains the increased maximal heart rate and oxygen consumption after treatment with nitroglycerin in patients with prior infarction.

The magnitude of $S-T$ segment depression during exercise in patients with coronary heart disease is closely related to the myocardial oxygen needs expressed by the pressure-time index and by heart rate alone.\textsuperscript{15} $S-T$ segment depression during and after exercise was less marked after nitroglycerin was taken in normal subjects as well as in patients with coronary heart disease (figs. 2 and 4), despite higher maximal heart rate, and a higher maximal pressure-rate product in patients with angina. This lowering of $S-T$ segment depression at submaximal and maximal exercise levels is also attributed to a decreased heart volume and lower myocardial oxygen requirements despite a similar or even higher pressure-rate product. That the same effect is discernable also in normal middle-aged subjects, suggests that exercise $S-T$ segment depression in this group is also related to hemodynamic determinants of myocardial metabolism, and not simply to tachycardia.\textsuperscript{29}

The significant increase in maximal oxygen intake and maximal heart rate after nitroglycerin was taken in angina patients has practical implications. Firstly, it documents the clinical value of recommendation of the prophylactic use of nitroglycerin just before anticipated stress. Secondly, it sufficiently raises the threshold for exertion at which angina occurs in severely limited patients for them to participate in physical training programs. This may permit attainment of higher heart rates above the level needed for them to achieve a cardiac effect of physical training.\textsuperscript{30} Thirdly, decreased myocardial ischemia during exercise often diminishes the frequency of ventricular premature beats and even possibly the risk of fatal arrhythmias in patients with coronary heart disease.\textsuperscript{7}

In conclusion, nitroglycerin increases maximal oxygen intake and heart rate, lessens electrocardiographic signs of myocardial ischemia, and alters the relationship between
threshold for angina and the systolic pressure-heart rate product. Much of the exercise effect may be a consequence of an acute reduction in heart volume and, secondarily, improvement of left ventricular function when partial redistribution of blood volume away from the thorax to the peripheral vasculature occurs.

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