The Effect of Nifedipine on Cardiopulmonary Responses during Exercise in Normal Subjects*

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We investigated the effects of a single dose of nifedipine (10 mg orally) on exercise performance during progressive incremental cycle ergometry in nine sedentary normal subjects in a double-blind, placebo-controlled crossover study. Maximum work load after nifedipine (213 ± 42 watts; mean ± SD) was less than after placebo (222 ± 41 watts; p<0.05). Maximum oxygen consumption was unchanged. In addition, the drug decreased lactate threshold from 19.7 ± 4.9 ml O₂/min/kg to 15.5 ± 5.5 ml O₂/min/kg (p<0.02); gas exchange anaerobic threshold was unaffected. There were higher plasma lactate concentrations at low and intermediate exercise intensities after nifedipine compared with placebo (p<0.05). Systolic blood pressure was lower at high work loads (p<0.05) and heart rate was higher at low work loads (p<0.05) after nifedipine. We conclude that the short-term administration of nifedipine limits peak performance and increases plasma concentration of lactic acid in normal subjects. One or more of the following mechanisms may account for these observations: (1) nifedipine decreases blood flow to skeletal muscle by diverting blood to nonexercising tissues; (2) nifedipine increases catecholamine levels, thereby augmenting lactic acid production; and (3) nifedipine decreases skeletal muscular contractility by selectively impairing fatigue-resistant fibers.

Nifedipine, a calcium-channel blocking agent, is a potent arterial vasodilator and is useful in treating a variety of cardiovascular and noncardiovascular disorders. In many of these disorders, such as hypertension and ischemic heart disease, exercise training is used as an adjunct to such therapy. It is therefore important to understand the effect of nifedipine on exercise performance and the training response.

It has been demonstrated that long-term administration of nifedipine to healthy volunteers blunted the conditioning response and attenuated maximal performance. The latter effect was confirmed by others, however, no study has measured the effects of short-term administration of nifedipine on gas-exchange variables, anaerobic threshold, and plasma concentration of lactate. We have investigated the effect of a single dose of nifedipine on these variables using progressive incremental cycle ergometry in normal untrained subjects. The design of the study was double-blind, comparing oral administration of 10 mg of nifedipine and placebo. Measurements of gas-exchange anaerobic threshold, lactate threshold, maximum oxygen consumption (V̇O₂max), power output (watts), heart rate, and blood pressure were made.

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Materials and Methods

Two exercise studies were carried out within ten days on nine adults (seven men and two women) aged 26 to 39 years (mean, 33 years). They were untrained, apart from taking part in occasional weekend sporting activities.Expired concentrations of carbon dioxide and oxygen, as well as minute ventilation (Ve) were measured every 15 seconds; and from them, oxygen consumption (V̇O₂), carbon dioxide production (V̇CO₂), the respiratory exchange ratio, the ventilatory equivalent for oxygen, and heart rate (determined electrocardiographically by averaging of R-R intervals) were calculated by an on-line minicomputer (DEC 11/23) and the results printed out for each 15-second period. Systolic and diastolic blood pressures were measured by sphygmomanometer during the last 15 seconds of each minute. Expired flow was measured with a pneumotachograph, integrated, and summed electronically to give expired volume. The pneumotachograph is of the screen type which has standard resistance of 0.036 cm H₂O/L/sec (Erich Jaeger, Inc.). The linearity of the pneumotachograph was verified by supplying a constant volume with a 3-L accurately calibrated syringe at frequencies from 6/min to 86/min. Twenty-four values for Ve were selected in the range of 18 L/min to 248.7 L/min. The volume supplied and the volume measured after the correction factors were correlated.

Least-squares linear regression analysis showed the best fit to the line to be y = 1.0194 and x = -0.982 (r = 0.99; p<0.0001). These data indicate linearity of the pneumotachograph (Erich Jaeger 36/70) over the range that the measurements were made. Before each exercise test, the pneumotachograph was calibrated with the 3-L syringe and Ve calculated using factors to correct to body temperature and pressure, saturated. The gas analyzers were calibrated with a mixture of oxygen and carbon dioxide in nitrogen accurate to 0.003 percent. Both the gas analyzers and pneumotachograph were calibrated before and after each exercise. Testing was performed approximately 90 minutes after administration of the drug. Identical-appearing nifedipine and placebo were administered in a double-blind single-crossover design. Seven of the nine subjects received active drug first. An intravenous cannula was inserted into an antecubital vein to collect blood to determine lactate and nifedipine levels. Exercise was performed on an electrically braked cycle ergometer (Erich Jaeger, Inc). The subjects rested for ten minutes on...
the ergometer to determine basal levels; and during this time, \( V_E \), continuous expired oxygen concentration, and \( V_CO_2 \), (collected in a mixing bag) were monitored. Basal readings for \( V_E \), \( V_O_2 \), \( V_CO_2 \), and heart rate were determined; and a sample of blood was drawn to determine levels of lactic acid and nifedipine. Exercise was begun with a three-minute warm-up period of unloaded cycling at 40 to 60 revolutions per minute. The pedaling rate was kept constant during the exercise, and the load was increased by \( 20 \) W each minute for men and \( 15 \) W for women to the point of exhaustion. Blood was drawn for lactic acid determinations at the end of each minute. Maximum oxygen consumption was defined as a plateau (an increase equal to or less than \( 0.2 \) L/min) in the \( V_O_2 \) with increasing work loads for the last two 15-second collection periods of two consecutive minutes. Such a plateau was reached in 11 of the 18 tests performed. In the absence of such a plateau, \( V_O_2 \) max was taken as the \( V_O_2 \) at the point of volitional fatigue. The anaerobic threshold was estimated by the following two techniques: (1) indirectly, by measuring the points where \( V_E \) and the ventilatory equivalent for oxygen departed from linearity (or increased systematically) when graphed against work load\(^a\) (this will be referred to as the gas-exchange anaerobic threshold); and (2) directly, by measuring the inflection point of the lactic acid level when graphed against work load (this will be referred to as the lactate threshold). The gas-exchange anaerobic threshold and the lactate threshold are expressed as the \( V_O_2 \)/kg corresponding to the work loads at which the inflections occurred. Coded graphs of the \( V_E \) and the ventilatory equivalent for oxygen vs work load were read by two observers independently. There was no difference between the interpretation of the gas-exchange anaerobic threshold by these two observers. The data were pooled and mean values taken.

**Blood Levels of Nifedipine and Lactic Acid**

Samples of blood to determine nifedipine levels were drawn immediately before testing (90 minutes after nifedipine administration). Serum was separated and frozen within 15 minutes and stored. Levels of nifedipine were measured after completion of the study; analysis was performed only on the active drug samples by a gas chromatographic technique (Biodecision Laboratory).

For determining lactic acid levels, blood was collected during the last 15 seconds of each minute into 5-ml Vacutainer tubes (Becton Dickinson A3200X518) which contained 10 mg of potassium oxalate and 12.5 mg of sodium fluoride. The samples were immediately cooled and the plasma separated by centrifugation within 15 minutes of collection. Plasma concentrations of lactate were determined with an analyzer (DuPont Automatic Clinical Analyzer ACA II) using the manufacturer's method for the lactic acid test.\(^b\)\(^c\) A serum-based control with a mean value of 2.0 mM/L had a day-to-day reproducibility of 0.1 mM/L (± SD), and a serum-based control with a mean value of 13.7 mM/L had a day-to-day reproducibility of 0.2 mM/L (± SD) during this study.

**Statistics**

All values are expressed as the mean ± standard deviation. Student's \( t \)-test for paired data was used to compare the placebo and nifedipine. A value of \( p<0.05 \) was taken as the level of significance. Correlations were made using the method of least-squares linear regression.

**RESULTS**

**Gas-Exchange Variables and Work Loads**

Compared with administration of placebo, nifedipine was associated with no significant changes in \( V_E \), \( V_O_2 \), ventilatory equivalent for oxygen, or respiratory exchange ratio at any level of exercise. The \( V_O_2 \)max after nifedipine was \( 39.0 ± 8.5 \) ml/min/kg vs \( 40.3 ± 5.6 \) ml/min/kg for placebo (not significant); however, nifedipine decreased the maximum work load from \( 222 ± 41 \) W after placebo to \( 213 ± 42 \) W after nifedipine (\( p<0.05 \)).

**Plasma-lactate Levels**

Administration of nifedipine was associated with increased mean plasma concentrations of lactate at all levels of exercise (Fig 1), but only the values of 0-W work load and 50 and 75 percent of maximum work load were significantly different (\( p<0.05 \)). Lactate levels were higher after nifedipine than placebo in eight of the nine subjects at 50 and 75 percent of maximum work load. In seven of nine subjects, nifedipine was associated with lactate levels greater than those after placebo at all work loads.

**Gas-Exchange Anaerobic Threshold and Lactate Threshold**

Gas-exchange anaerobic threshold was not affected by nifedipine; the threshold occurred at a \( V_O_2 \) of

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**Figure 1.** Plasma concentrations of lactic acid during exercise after nifedipine (N) and placebo (P). Single asterisk indicates \( p<0.05 \) vs placebo; double asterisk indicates \( p<0.01 \) vs placebo.
FIGURE 2. Systolic and diastolic blood pressures during exercise after nifedipine (N) and placebo (P). Asterisk indicates p<0.05 vs placebo.

20.1 ± 5.0 ml/min/kg and 20.5 ± 5.0 ml/min/kg (not significant) after nifedipine and placebo, respectively. Despite the higher resting concentrations of lactate after nifedipine, a clear inflection could be identified as exercise progressed and indicated the lactate threshold. There was a significant decrease in lactate threshold from 19.7 ± 4.9 ml/min/kg after placebo to 15.5 ± 5.5 ml/min/kg after the drug (p<0.02). The gas-exchange anaerobic threshold and lactate threshold after placebo did not differ significantly from each other and were positively correlated (r = 0.75; p<0.02).

Hemodynamic Variables

Nifedipine decreased systolic blood pressure at all work loads, but only the 75 and 100 percent values were statistically significant (p<0.05 for both values) (Fig 2). Diastolic blood pressure was not significantly different at any exercise level (Fig 2). Heart rate (Fig 3) was greater after nifedipine than after placebo at zero work load (p<0.05) and at 25 percent (p<0.01) and 50 percent (p<0.05) of maximum work levels. Double-product (systolic blood pressure times heart rate) was significantly less with nifedipine at high work loads, compared to placebo (p<0.05) (Fig 4).

Serum Nifedipine Levels

The mean serum levels of nifedipine were 85.0 ± 38.3 ng/ml. There were no significant correlations between nifedipine levels and any hemodynamic or gas-exchange variables. There was a trend for plasma lactate levels at 50 percent maximum work load to be higher in those individuals with higher nifedipine levels, but this correlation did not reach statistical significance (r = 0.65; p = 0.06).

DISCUSSION

The calcium-channel blockers were originally developed to treat patients with angina pectoris; in these patients, calcium-channel blockers have been shown to increase the duration of exercise before the onset of angina. The uses of these drugs have expanded to include other cardiovascular diseases such as hypertension, hypertrophic cardiomyopathy, pulmonary hypertension, and congestive heart failure. In addition, the drugs are being used for other conditions, such as asthma, migraine headache, Raynaud's disease, and depression, in which no significant cardiovascular impairment exists. This study is relevant to this group of patients in whom exercise for rehabilitation or recreation is frequently an important activity.
We investigated the effect of a single dose of nifedipine on exercise performance in subjects with normal cardiovascular systems. It should be emphasized that these data need to be confirmed in patients with various cardiovascular diseases.

Previous studies have shown the following circulatory effects of nifedipine during exercise in normal subjects: decreased left ventricular afterload; decreased systemic vascular resistance; decreased end-systolic volume (due to increased left ventricular fractional shortening); increased heart rate; decreased double-product; and unchanged end-diastolic volume.6 The effects on exercise performance are decreased exercise time and impaired training effect.5,6 The \( \text{VO}_2\) max is not affected.5

In our study, administration of nifedipine was associated with a significant decrease in lactate threshold, increased lactate concentrations in the plasma at intermediate exercise intensities, and reduced maximum work load. The 4 percent reduction in maximum work load, although statistically significant, is of questionable physiologic significance. These effects were observed with a low dose of nifedipine. Although it is not possible to state the mechanism of these effects, we propose that one or a combination of four actions of nifedipine might account for our findings.

First, nifedipine-induced vasodilatation in nonexercising tissues may result in relative underperfusion of exercising muscle and a relative overperfusion of nonexercising tissues. Nifedipine increases blood flow to the limbs in exercise in proportion to the increase in cardiac output in patients with congestive heart failure.11 Caution should be exercised in extending these results to normal subjects, since congestive heart failure is associated with increased sympathetic tone and increased systemic vascular resistance at rest.12,13 In subjects with angina pectoris, nifedipine does not alter the distribution of cardiac output to the legs at rest;14 however, during exercise, nifedipine results in decreased femoral venous oxygen content, suggesting that the drug alters the redistribution of cardiac output to the legs during exercise by shunting blood output away from exercising muscle.14 These measurements have not been made in normal subjects.

Secondly, the nifedipine-induced increase in lactate levels may be attributable to augmentation of exercise hyperemia and accelerated lactate efflux from muscle, coupled with a relative diversion of the increase in blood flow from sites of lactate removal, particularly the liver and kidneys. Flaim et al10 have demonstrated that diltiazem, also a calcium-channel blocker, increases blood flow to skeletal muscle and renal and hepatic beds in exercising rats, but the proportional increase in blood flow to muscle was much greater than to the liver and kidneys. Therefore, at a given submaximal exercise load, nifedipine may increase the rate of lactate efflux relative to production and removal. Augmented efflux of lactate should have delayed the onset of muscular exhaustion, which is due, in part, to accumulation of lactic acid in muscle cells to a level that interferes with excitation-contraction coupling.15-18 Since maximum work loads achieved were reduced by nifedipine, enhanced efflux of lactate probably did not occur.

Thirdly, the elevated concentrations of lactate after nifedipine might be due to stimulation of catecholamine release. This effect has been demonstrated after short-term administration at rest.19,20 The addition of epinephrine or norepinephrine (or both) to the perfuse of isolated canine skeletal muscle has been shown to increase lactate concentration compared with control.14 Raffestin et al22 have demonstrated that nifedipine (20 mg sublingually) results in increased lactate and catecholamine levels during sustained submaximal exercise in normal subjects. These observations raise the possibility that the lactate levels were increased by the effect of the catecholamines on glycolysis, which enhances the production of lactate by

![Figure 4. Double-product (systolic blood pressure times heart rate times 10^-7) during exercise after nifedipine (N) and placebo (P). Asterisk indicates p<0.05 vs placebo.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21523/...)}
stimulating the conversion of phosphorylase “b” to
phosphorylase “a.” Contrary to our study, there was no
impairment of maximum exercise performance.38

Fourthly, nifedipine might increase lactate produc-
tion and decrease performance by impairing skeletal
muscle contractility. Although extracellular calcium is
not thought to be critical in skeletal muscle contrac-
tion, verapamil has been shown to decrease twitch
tension in vitro.39 Although nifedipine does not possess
the local anesthetic properties of verapamil,40 we
consider that a contributing factor to the increased
lactate levels with exercise and the impaired work
performance may be an effect on muscular contractile
properties.

The anaerobic threshold is used to assess the impact
of various interventions on oxygen transport during
submaximal exercise.35-36 Although the lactate thresh-
old decreased after nifedipine, the gas-exchange anaer-
obic threshold was unchanged. The reason for this
disparity is unclear, but it does suggest that these two
measurements are not causally related. There was a
significant correlation between the gas-exchange anaer-
obic threshold and the lactate threshold with placebo
(r = 0.78; p < 0.02), but after nifedipine the lactate threshold occurred at a lower work load,
whereas the gas-exchange anaerobic threshold was
unchanged. Although lactate and ventilatory or gas
exchange thresholds have been shown to correlate,8
the significance of this correlation has been ques-
tioned.35

Dissociation of the gas-exchange anaerobic thresh-
old and the lactate threshold has been observed in
other conditions. In McArdle’s syndrome, which is
characterized by the lack of phosphorylase (the enzy-
me essential for the production of lactic acid during
exercise), the gas-exchange anaerobic threshold oc-
curred in the absence of significant lactate produc-
tion.35 Hughes et al40 have shown that in normal
subjects, glycogen depletion increased the lactate
threshold but decreased the ventilatory threshold. In
addition, ventilatory anaerobic threshold was lower
than lactate threshold at a pedaling frequency of 50
cycles per minute but not at 90 cycles per minute.35 It
is not surprising that ventilatory and lactate kinetics
during progressive exercise are not correlated, since
ventilation is influenced by the interaction of neural,
humoral, mechanical, and metabolic factors.

Although nifedipine has a negative inotropic effect in
vitro, cardiac output is usually increased at rest after
nifedipine, due to an increase in sympathetic stimula-
tion and decreased afterload.31 Therefore, it is highly
unlikely that any negative inotropic effect decreased
exercise performance. In our study, nifedipine in-
creased heart rate during low to intermediate levels of
exercise but not at higher levels of exercise. Heavy
levels of exercise are probably associated with max-
imum sympathetic stimulation, which would obscure
any chronotropic effects of nifedipine. In addition,
systolic blood pressure and the double-product were
lowered only with high levels of exercise. Increased
left ventricular emptying has been demonstrated in
normal subjects after nifedipine, probably due to
afterload reduction;4 however, this improvement is
counteracted by other peripheral effects which limit
exercise performance.

Since exercise training is frequently employed in
patients with and without cardiovascular disease, reha-
bitation and exercise training during administration
of nifedipine may be impaired by the reduced lactate
threshold. Additional long-term studies need to be
performed to confirm these findings. Duffey et al8
showed that during 5.5 weeks of training, nifedipine
(compared with placebo) decreased exercise endur-
ance time. After stopping the drug, VO₂max
significantly increased beyond the level reached dur-
ing treatment with nifedipine. These observations
suggest that nifedipine blunts the training effect and
impairs maximum performance. The mechanisms
causing this remain to be elucidated, but future studies
should focus on perfusion of exercising muscles, mus-
cle lactate kinetics, and catecholamine measure-
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Pulmonary Immunotoxicology
A meeting of the Immunotoxicology Discussion Group, on the subject of pulmonary immunotoxicology/immunobiology, will be held at the F. E. Herbert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, June 23-24. Information on the meeting can be obtained from Dr. L. D. Loose, Pfizer, Inc., Eastern Point Road, Groton, CT 06340 (203:441-4692). Registration information may be obtained from Ms. I. Mahabir, Smith, Kline and French Laboratories, 1500 Spring Garden Street, Philadelphia 19101 (215:270-7289).