Antianginal effects of intravenous nitroglycerin over 24 hours

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ABSTRACT To determine the constancy of hemodynamic and antianginal effects of the constant infusion of intravenous nitroglycerin (NTG) and their relationship to infusion rate and plasma NTG concentration, we administered maximal tolerated doses of intravenous NTG (range 10 to 120 μg/min, mean = 52 ± 33 μg/min) and placebo to 10 patients with chronic stable angina for 25 hr each in a randomized, double-blind fashion. Sublingual NTG (0.4 mg) was given at 24.5 hr of infusion as a positive control. Bicycle exercise time (NIH protocol), blood pressure, heart rate, exercise ST response, and venous plasma NTG were determined before and at 1, 4, 8, 24, and 24.5 hr. Plasma NTG was linearly related to infusion rate, reached a steady state within 15 min and was unchanged over 24 hr (mean = 5.5 ± 1.2 ng/ml). Mean plasma NTG clearance was 9.3 liters/min. However, during dose titration, patients demonstrated different relationships between plasma NTG and hemodynamic effects, with widely varying slopes and intercepts. Intravenous NTG produced a sustained reduction in blood pressure and a rise in heart rate at rest, and a reduction in blood pressure during submaximal exercise at as late as 24 hr, associated with reduced submaximal ST segment abnormality. In contrast, exercise tolerance to onset of angina showed a marked initial increase on intravenous NTG but fell progressively and did not differ from that with placebo at 24 hr. Increased exercise tolerance was associated with an increase in maximal heart rate and double product (heart rate × blood pressure), suggesting that direct coronary vasodilation and/or reduced left ventricular volume were the principal determinants of increased exercise tolerance. The rates of fall in exercise tolerance over time varied widely among patients. Sublingual NTG produced a marked increase in exercise tolerance after a 24.5 hr placebo infusion, but not after intravenous NTG, despite similar exercise tolerance on intravenous NTG and placebo at 24 hr. The plasma NTG concentrations achieved with intravenous NTG were at least twice those reported for the peak sublingual NTG effect and up to 50 times those reported for 5 mg/24 hr release NTG patches. Thus, constant NTG infusion can result in constant high plasma NTG, but the initial marked increase in exercise tolerance diminishes progressively over 24 hr, as previously observed with NTG patches, consistent with development of tolerance. After prolonged high plasma NTG concentrations, the effect of sublingual NTG on exercise tolerance can be abolished. We conclude that rapid attenuation of antianginal effects during exercise is an inherent result of the continuous administration of NTG. It remains uncertain whether similar tolerance limits the efficacy of intravenous NTG in patients with cardiac ischemia at rest.


TRANSDERMAL nitroglycerin patches can provide constant nitroglycerin (NTG) release over 24 hr.1–5 Early studies reported sustained antianginal activity of NTG patches.6 However, a number of recent studies have shown marked attenuation of NTG patch effect over 24 hr, and little or no effect during long-term administration.7–10 It has been suggested that this attenuation is due to nitrate tolerance.6,11 However, it is also possible that conventional NTG patch doses provide inadequate NTG delivery since reported plasma concentrations of NTG are quite low, averaging 0.1 to 0.15 ng/ml for a device that releases 5 mg NTG over 24 hr.1–5 In contrast, peak plasma concentrations after sublingual NTG can exceed 3 ng/ml.12 Thus, it remains uncertain whether assured, constant, high-dose NTG can provide continuous 24 hr benefit in patients with exertional angina due to coronary disease. Given the limitations of transdermal, oral, and sublingual NTG

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Supported in part by Public Health Services Research grant RR00040 from the Division of Research Resources, NIH, a Commonwealth of Pennsylvania Health Services Contract, and by grants from Ciba-Geigy, Key Pharmaceuticals, and Searle.

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Received July 14, 1987; revision accepted March 10, 1988.
delivery, this question might be best answered by intravenous NTG. Furthermore, intravenous NTG itself is an important therapeutic agent, but data with respect to the relationship of infusion rate, plasma concentration, circulatory response, and antianginal effects are limited. Therefore, we performed a double-blind placebo-controlled crossover study of the effects of 24 hr of high-dose intravenous NTG in patients with chronic stable exertional angina. Effects on exercise tolerance were correlated with NTG plasma levels along with resting, submaximal, and maximal hemodynamic effects and ST segment responses to exercise. In addition, responses to sublingual NTG before and after a 24 hr infusion of intravenous NTG and placebo were evaluated.

**Methods**

Ten men from 47 to 65 years old (mean = 56), with typical exertional angina historically relieved by sublingual NTG, were studied. Each had exercise-induced angina and objective evidence of ischemia on formal testing, as indicated by a prior unambiguously positive electrocardiographic response to diagnostic stress testing (n = 9) and/or reversible thallium perfusion defects (n = 7). Each patient showed a 60 sec or more increase in exercise tolerance (bicycle ergometry) to onset of chest pain immediately after administration of sublingual NTG, as evidence of initial NTG responsiveness, while receiving any concomitant medications that were continued during the study. Coronary angiography documented one or more fixed stenoses greater than 70% in all nine patients who had undergone catheterization. Two had undergone coronary bypass surgery.

Long-acting nitrates were discontinued at least 72 hr before study. Eight patients were receiving β-blocking drugs and five received calcium-channel blockers, which were continued during the study. We have repeatedly shown that the sensitivity of our protocol to antianginal effects of NTG is unaffected by concomitant constant treatment with other agents over test periods lasting up to 24 hr. Similarly, in the present study, subjects receiving concomitant β-blockers and/or calcium channel blockers did not differ from those on no antianginal therapy with respect to their baseline exercise performance or responsiveness to sublingual and intravenous NTG. Exercise testing was performed on a Godart bicycle ergometer by a well-characterized protocol. The initial workload was individualized and then increased by 20 W every 3 min so that angina was reproducibly elicited at between 3 and 6 min of exercise in the absence of nitrate effect. Exercise was stopped at the onset of angina. Heart rate and blood pressure were measured and a 12-lead electrocardiogram was obtained before and at 1 min intervals during and for 5 min after exercise. ST segment depression and the product of heart rate and systolic pressure (double product), an indirect index of myocardial oxygen consumption, were determined at 3 min of exercise and at onset of angina.

**Outpatient phase.** Four preliminary exercise tests, each separated by 24 hr, were performed to obtain and document exercise tolerance reproducibility, defined as variability of exercise duration to onset of angina of less than 1 min on two successive tests. No subjects were excluded for lack of reproducibility. One exercise test 3 min after administration of sublingual nitroglycerin was performed to verify NTG responsiveness, defined as an increase in exercise tolerance of more than 1 min above the highest baseline value obtained on the four preliminary tests.

Sublingual NTG dosage was 0.4 mg, and was kept constant throughout the protocol.

The maximum tolerated dose of intravenous NTG was then determined in each patient by titration to a systolic blood pressure less than 100 mm Hg, or to one infusion level below that producing symptomatic orthostasis or other intolerable side effects. Glass bottles and polyethylene tubing preequilibrated with NTG solution for 60 min were used for all NTG infusions. Infusion of NTG in a solution of 200 μg NTG/ml in 5% dextrose in water was begun at 10 μg/min and increased by 10 μg/min every 10 min to a maximum dose of 60 μg/min. If the desired hemodynamic end point was not reached, a 1 hr washout period ensued. Thereafter, a second titration with 400 μg NTG/ml was begun at 40 μg/min, with increments of 20 μg/min every 10 min until the desired end point was reached. NTG plasma levels were determined at the end of each titration level. After a washout period of at least 10 hr, the safety and hemodynamic effect of the maximal tolerated NTG dose was verified during a 1 hr constant infusion, with plasma levels at 5, 15, 30, and 60 min. The dose was decreased in one patient from 60 to 50 μg/min due to symptomatic hypotension during the 1 hr infusion.

**Inpatient phase.** Subjects were admitted to the Clinical Research Center of the Hospital of the University of Pennsylvania and randomly assigned to double-blind, 25 hr administration of either the previously identified maximal tolerated dose of intravenous nitroglycerin or placebo on day 1, with exercise testing at baseline, 1, 4, 8, and 24 hr after onset of infusion. An additional exercise test was performed 3 min after administration of sublingual NTG at the twenty-fifth hour of each infusion. The sublingual dose chosen (0.4 mg) had produced exercise enhancement during the intake phase of the study in each patient. After a 23 hr washout period, identical data were obtained on day 3 with the alternate blinded agent. Plasma nitroglycerin concentration was determined 15 min before each exercise test. Infusate samples for NTG concentrations were obtained immediately before and after completion of each 25 hr infusion. Patients were weighed daily under identical conditions.

**Plasma NTG assay.** Blood samples for plasma nitroglycerin assay were drawn via peripheral vein, from the upper extremity not used for NTG infusion, into prechilled heparinized glass tubes and quickly centrifuged at 2000 rpm at 4°C for 3 min. Plasma was then placed into prechilled silanized glass tubes containing 50 μl AgNO3 and immediately frozen at −20°C. NTG concentration was determined by an accepted gas-liquid chromatographic method.

**Statistical methods.** Correlations between continuous variables were evaluated by least squares linear regression. Comparisons of exercise performance and hemodynamic and ST segment changes at each time interval on active NTG and placebo days were made by paired Student’s t test. Comparison of variables over time on each test day were performed by one-way analysis of variance. Results are reported as the mean ± 1 SD, while figures show the mean ± 1 SE. The plasma NTG clearance over 24 hr was calculated in each subject who received a constant infusion as the mean infusion rate/mean plasma concentration.

**Results**

**Infusate NTG concentrations.** Measured infusate NTG was significantly less than calculated infusate NTG (243 ± 92 μg/ml measured, 280 ± 103 μg/ml calculated, p < .0025), despite use of glass and polyethylene infusion sets preincubated with NTG. The measured concentration was 175 ± 24 μg/ml at a calculated concentration of 200 μg/ml, or 88% of pre-
predicted, and 345 ± 35 μg/ml, or 86% of predicted at a
calculated concentration of 400 μg/ml. There was an
excellent correlation between infusion rates derived
from measured and calculated concentrations (y =
0.94x - 3.16, r = .97). Therefore, calculated infusion
rates are presented in the description of results.
Measured infusate NTG concentrations were virtually
identical at the onset and termination of the 25 hr
infusion periods.

Plasma NTG concentrations. During outpatient
titration, calculated maximal NTG infusion rate
ranged from 20 to 140 μg/min (mean = 67 ± 39
μg/min or 0.71 ± 0.46 μg/kg/min). Mean plasma
NTG levels increased in a highly linear fashion in
response to incremental doses of NTG (figure 1, r =
.99). Similar linearity was demonstrated when subsets
of patients receiving identical infusions during titration
were compared (r = .95 to .98) over infusion rate
ranges of 0–30 to 0–100 μg/min.

During the 1 hr constant infusion of the maximal
tolerated NTG dose, infusion rates ranged from 10 to
120 μg/min, (mean = 66 ± 39 μg/min or 0.67 ±
0.42 μg/kg/min. A mean plasma level of 7.7 ng/ml
was achieved within 15 min and was maintained with-
out significant variation for the entire 1 hr infusion
period. Analysis of variance indicated no significant
variation in individual plasma concentrations after 15
min.

During the first 45 min of the 25 hr inpatient infu-
sion, three additional patients required dose reduction
for hypotension. Thus, the mean dose from 1 to 25
hours was 60 ± 34 μg/min, or 0.61 ± 0.38 μg/kg/
min. A mean plasma level of 5.5 ng/ml was reached at
1 hr and it rose slightly over 24 hr (figure 2). However,
analysis of variance showed no significant change over
time. Nine subjects received identical maximal infusion
rates for 10 min on titration and for 15 min on
verification days. Mean plasma NTG was 7.9 ± 9.6
ng/ml on titration and 7.2 ± 7 ng/ml on verification
days (NS). Seven patients tolerated the same infusion
rate for 1 hr of dose verification and 25 hr on the
blinded active day without dose reduction. In these
subjects, 1 hr plasma NTG on verification days (mean
= 7.3 ± 6.2 ng/ml) and 25 hr plasma NTG on blinded
active days (mean = 5.8 ± 2.3 ng/ml) did not differ
significantly by paired t test. In seven patients with
constant infusion rates over 24 hr, the mean calculated
plasma NTG clearance was 9.3 ± 3.5 liters/min.

Hemodynamic effects at rest. During the titration
phase, the increase in resting heart rate and decrease in
blood pressure correlated weakly with NTG plasma
level in the group as a whole (r = .47, r = .25).
Analysis including NTG infusion rate showed similar
weak relationships. Stronger relationships were found
in individual subjects (figure 3). However, the slopes
and intercepts of these relationships varied markedly
between patients.

On the active test day, the blinded infusion of NTG
resulted in a decrease in resting systolic blood pressure
at 1 hr compared with placebo (127 vs 99 mm Hg, p
= .0001). A reduction in resting systolic pressure was
sustained throughout the 24 hr infusion (figure 4). An
increase in resting heart rate was seen at 1 hr (62 vs 71
beats/min, p = .03), and also persisted for 24 hr (fig-
ure 5).

Exercise tolerance. Mean exercise duration to onset of
angina during placebo and active 24 hr infusion are
shown in figure 6. Exercise duration during placebo

![FIGURE 1. Relationship between intravenous NTG infusion rate (μg/
min, horizontal axis) and mean plasma NTG concentration (ng/ml,
vertical axis) during stepwise titration in 10 patients. Crossbars repre-
sent the SEM.](image-url)
FIGURE 3. Top, Individual patient regression lines for the relationship between increase in heart rate (vertical axis, beats/min) and plasma NTG concentration (horizontal axis, ng/ml) during dose titration. The correlation coefficient for each patient is shown and the lines have been extended beyond the range of actual data values for purposes of illustration. Bottom, Individual regression lines for the relationship between fall in blood pressure (mm Hg, vertical axis) and plasma NTG concentration (ng/ml, horizontal axis), with correlation coefficients.
infusion showed no significant change over 24 hr. Baseline exercise duration was also identical before active and placebo infusions (mean = 278 vs 262 sec). After 1 hr of active infusion, exercise duration was markedly prolonged compared with that with placebo (479 vs 275 sec, p = .0004). Increased exercise duration was demonstrable but somewhat diminished at 4 hr (444 vs 251 sec, p = .0002) and 8 hr (398 vs 249 sec, p = .0002). In contrast, at 24 hr exercise tolerance during NTG infusion was no longer significantly greater than that with placebo (335 vs 287 sec, NS). However, considerable individual variation in the temporal pattern of exercise tolerance was observed, with five patients showing at least a 60 sec residual increase in exercise tolerance at 24 hr on the active NTG day.

Blood pressure at identical submaximal exercise levels, evaluated at 3 min of exercise, was consistently reduced during active NTG infusion compared with during administration of placebo (table 1). As a consequence, submaximal rate-pressure product was significantly reduced at 1, 4, and 24 hr. By contrast, heart rate at submaximal exercise was relatively unaffected by intravenous NTG, with a significant but modest increase only at 8 hr. This rate increase accounted for the lack of reduction in rate-pressure product at 8 hr.

ST segment depression at 3 min of submaximal exercise was also blunted during intravenous NTG as compared with control, but the difference was statistically significant only at 1 and 24 hr.

In contrast, at peak exercise (table 2) there was little alteration of maximal systolic pressure by intravenous NTG, but maximal heart rate was significantly elevated at 1, 4, and 8 hr in association with increased exercise tolerance. As a result, maximal rate-pressure product showed an increase at 1, 4, and 8 hr that fell to a level that did not differ from control at 24 hr. Thus, maximal rate-pressure product was elevated as long as exercise tolerance was significantly prolonged, and became similar to placebo values when exercise tolerance was no longer improved. Maximal ST segment depression was significantly reduced only at 1 and 8 hr.

Figure 7 shows exercise data in response to sublingual NTG at the twenty-fifth hour on active and placebo days. Sublingual NTG given at the twenty-fifth hour of placebo infusion resulted in marked prolongation of exercise duration compared with that at the 24th hour (442 vs 287 sec, p < .003). This change was
TABLE 1
Effect of intravenous NTG on heart rate, blood pressure, rate-pressure product and ST segment depression during each exercise test at submaximal exercise (mean ± SD)

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Rate-pressure product</th>
<th>ST segment depression (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Active p value</td>
<td>Placebo Active p value</td>
<td>Placebo Active p value</td>
</tr>
<tr>
<td>Control</td>
<td>90±10 87±13 NS</td>
<td>152±17 155±18 NS</td>
<td>13,754±2,754 13,606±3,253 NS</td>
</tr>
<tr>
<td>1 hr</td>
<td>85±13 85±11 NS</td>
<td>154±16 133±15 .02</td>
<td>13,188±2,795 11,285±1,954 .01</td>
</tr>
<tr>
<td>4 hr</td>
<td>89±12 90±14 NS</td>
<td>163±15 145±18 .002</td>
<td>13,908±2,552 12,147±2,699 .005</td>
</tr>
<tr>
<td>8 hr</td>
<td>90±13 95±12 .02</td>
<td>165±21 156±18 .04</td>
<td>14,971±3,286 14,886±3,151 NS</td>
</tr>
<tr>
<td>24 hr</td>
<td>88±12 90±11 NS</td>
<td>154±15 146±17 .006</td>
<td>13,648±2,828 12,933±2,767 .02</td>
</tr>
</tbody>
</table>

comparable to that produced by an active intravenous NTG infusion at the first hour. In marked contrast, at the twenty-fifth hour of active infusion there was no significant improvement in exercise duration in response to sublingual NTG (366 vs 335 sec, at 24 hr placebo, NS). Total exercise time in response to sublingual NTG during active infusion was also significantly less than that achieved in response to sublingual NTG during placebo infusion (366 vs 442 sec, p = .004).

Weight responses to NTG and placebo. At the onset of the placebo infusion, mean patient weight was 88.1 ± 10.8 kg, which did not differ significantly from that at the onset of NTG infusion (87.8 ± 11.0 kg). During the 24 hr placebo infusion, weight fell to 87.8 ± 10.6 kg, but the change was not significant. In contrast, during the 24 hr NTG infusion, weight rose significantly to 88.7 ± 10.6 kg (p < .0025).

Discussion

Our results demonstrate a linear and reproducible relationship between NTG infusion rate and plasma concentration in man, with a steady state achieved in 15 min or less. Remarkably high plasma concentrations are developed and tolerated well by ambulatory patients. However, maximal tolerated doses range widely, from 10 to 120 µg/min, and the dose-effect relationships for heart rate and blood pressure vary dramatically between individuals.

We also sought to determine whether constant, high-dose NTG delivery over 24 hr results in constant improvement in exercise time in patients with chronic stable angina. Improvement was marked at 1 hr and equivalent to the response to sublingual NTG, but it gradually declined so that exercise duration was similar to the preinfusion control and to placebo at 24 hr. The intravenous NTG doses used resulted in continuous, high mean NTG plasma levels that were two to three times those previously reported after sublingual NTG,12 up to 50 times those reported with single 5 mg release NTG patches,1-5 and eight to 10 times the predicted plasma concentrations for studies of multiple NTG patch “high dose” regimens in our laboratory.7 Plasma NTG levels achieved were also at least twice those predicted for the 105 mg release/24 hr NTG patch doses tested by Parker et al.8 in a few subjects. Nonetheless, attenuation of exercise response was similar to that noted with NTG patches7-8 and compatible with long-term results with oral isosorbide dinitrate.17 Thus, attenuation of nitrate effects on exercise tolerance during continuous nitrate administration apparently occurs over a wide range of plasma concentrations and cannot be overcome by administration of high nitrate doses per se. Considerable individual vari-

TABLE 2
Effect of intravenous NTG on heart rate, blood pressure, rate-pressure product and ST segment depression during each exercise test at maximal exercise (mean ± SD)

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Rate-pressure product</th>
<th>ST segment depression (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Active p value</td>
<td>Placebo Active p value</td>
<td>Placebo Active p value</td>
</tr>
<tr>
<td>Control</td>
<td>93±10 92±12 NS</td>
<td>160±16 166±19 NS</td>
<td>14,670±2,473 15,124±3,108 NS</td>
</tr>
<tr>
<td>1 hr</td>
<td>91±11 104±17 .001</td>
<td>164±17 173±22 NS</td>
<td>14,860±2,558 17,942±4,234 .01</td>
</tr>
<tr>
<td>4 hr</td>
<td>95±12 105±13 .0003</td>
<td>169±16 174±14 .02</td>
<td>16,041±3,106 18,485±3,269 .00003</td>
</tr>
<tr>
<td>8 hr</td>
<td>97±15 107±15 .006</td>
<td>173±15 180±21 NS</td>
<td>16,427±3,957 19,407±4,745 .005</td>
</tr>
<tr>
<td>24 hr</td>
<td>92±11 97±11 NS</td>
<td>164±15 163±20 NS</td>
<td>15,022±2,518 15,789±3,206 NS</td>
</tr>
</tbody>
</table>
ability was observed among the 10 patients studied with respect to the severity of attenuation of antian- giinal effects, with some individuals showing reduced but persistent effects at 24 hr. Studies of larger popula-
tions are needed to further define the extent and signifi-
cance of this variability.

The blunted response to conventional doses of sub-
lingual NTG (which had previously produced exercise
prolongation) that we found at the twenty-fifth hour of
constant infusion further extends the concept of NTG
tolerance. There was no improvement in exercise tole-
rance in response to sublingual NTG at the end of the
twenty-fifth hour of intravenous NTG infusion and
total exercise duration after sublingual NTG during
intravenous NTG infusion was significantly less than
that after sublingual NTG with intravenous placebo.
Abolition of beneficial effects of sublingual NTG
by prior NTG administration has not been de-
scribed and may be a function of the extremely
high plasma concentrations of NTG achieved.

Our data allow limited insight into the circulatory
mechanisms responsible for the development and at-
tenuation of improved exercise performance during
constant administration of high-dose NTG. NTG ef-
ects on resting blood pressure and resting heart rate
were maintained at 24 hr. Similarly, significantly re-
duced submaximal systolic blood pressure, usually
associated with a reduced rate-pressure product, and ST
segment depression persisted over 24 hr. These find-
ings are consistent with reduced myocardial oxygen
consumption (MVO₂) and a corresponding decrease in
asymptomatic ischemia at constant submaximal work-
loads. However, at 24 hr, these submaximal effects
were not associated with an increase in maximal exer-
cise tolerance. Thus, tolerance to antiangiinal effects
can be present despite persistent NTG effects on the
periphery and the heart itself during asymptomatic ac-
tivity. At peak exercise, in contrast, NTG infusion
resulted in a clear increase in peak heart rate and rate-
pressure product that paralleled improvement in exer-
cise tolerance at 1, 4, and 8 hr. At 24 hr, increased
peak heart rate, rate-pressure product and enhanced
exercise tolerance were absent.

The association of increased maximal heart rate and
rate-pressure product with prolonged exercise time to
angina strongly suggests that increased exercise toler-
ance was not attributable to an NTG-mediated de-
crease in MVO₂ resulting from altered heart rate and
blood pressure. Increased exercise tolerance may have
been due to an NTG-induced reduction in an MVO₂
determinant not reflected by rate-pressure product,
such as left ventricular volume during exercise. Re-
duced left ventricular filling pressure at rest, an early
and sensitive marker of NTG effect, results in reduced
ventricular volume and decreased wall stress at a con-
stant systolic pressure by the La Place effect. Since
the systolic integral of stress, or “shortening load,” is
a close correlate of MVO₂, reduced left ventricular
volume can reduce MVO₂, despite a constant heart rate
and arterial pressure. Thus, reduced left ventricular
volume could permit a higher maximal heart rate and
rate-pressure product without any intrinsic change in
the coronary circulation. Alternatively, increased
maximal rate-pressure product could reflect an actual
increase in myocardial oxygen supply, perhaps due to
dilatation of coronary stenoses. The temporal disso-
ciation we observed between NTG effects at maximal
and submaximal exercise has not been previously not-
ed, but data on submaximal and maximal rate-pressure
product over 24 hr are limited and relevant studies
have been conducted at lower NTG dose levels.

Whatever the mechanism, it appears that exercise
enhancement can be abolished at a time when resting and submaximal exercise effects of NTG on hemodynamics and myocardial ischemia persist. One potential explanation for this phenomenon would by sympathetic nervous system override of NTG vascular effects at maximal exercise.

This study does not address the basic mechanisms responsible for the pattern of responses observed. Nitrate tolerance has been demonstrated in vitro at the cellular level, associated with depletion of reduced sulphydryl groups necessary for nitrate activation of guanylate cyclase.\textsuperscript{21, 22} Observations in human subjects have shown reversal of attenuation of hemodynamic and coronary effects of NTG by administration of N-acetylcyesteine, or enhanced nitrate responsiveness during coadministration of N-acetylcyesteine.\textsuperscript{23-25} However, reversal of antianginal attenuation by N-acetylcyesteine has not been demonstrated.\textsuperscript{26} In addition, attenuation of antianginal effect may be related, at least in part, to counterregulatory hormonal and neural mechanisms, offsetting the direct vascular effects of NTG. The weight gain observed in our patients on the active NTG infusion day suggests that fluid retention does occur during long-term NTG infusion, and could result in a gradual increase in left ventricular volume over 24 hr. However, we have no other relevant data on this question and further study is necessary to eluciate the relative contributions of neurohumoral and cellular mechanisms.

Our data do provide new information on the pharmacokinetics and pharmacodynamics of intravenous NTG. The lack of time- and dose-dependency in NTG kinetics is in contrast to the findings of Noonan et al.,\textsuperscript{27} who observed NTG clearance to decrease with dose and time. However, the latter study used a smaller number of subjects (six), a smaller range of infusion rates (10 to 40 $\mu$g/min), and a shorter infusion period (40 min). In our study, the clearance of NTG from venous plasma was high, exceeding cardiac output. Similar observations have been made in animal preparations and are consistent with vascular uptake as a major mechanism of NTG clearance.\textsuperscript{28}

In contrast to infusion rate-plasma concentration relationships, dose-effect relationships varied markedly between patients and appreciably on repeated testing in the same patient, with four of 10 subjects requiring dose reduction on repeated challenge. This variability between and within patients underscores the importance of titration procedures in selecting appropriate nitrate doses.

Since intravenous NTG is an extremely important therapeutic agent in patients with acute infarction or unstable angina, the results of the present study are of great concern. However, we examined the effect of NTG on exercise tolerance in patients with fixed obstructive coronary disease and chronic stable exertional angina. Extrapolation of our results to other clinical situations may not be warranted since mechanisms of ischemia and ischemic pain in our patients were certainly different from those operant in patients with infarction and unstable angina.

Silent ischemia is another important manifestation of coronary disease to which the problem of nitrate tolerance is relevant. ST segment depression at 3 min of submaximal exercise improved on intravenous NTG and this improvement in "silent ischemia" did not parallel the time course of alterations in exercise tolerance, but persisted at 24 hr. However, studies using Holter ST monitoring methods in larger populations will be needed to evaluate the constancy of nitrate effects over time on silent ischemia.

The inclusion of patients on $\beta$-blockers and/or calcium-channel blockers in studies evaluating NTG effects remains controversial. However, such a population faithfully reflects current use of multiagent antianginal regimens. Studying only subjects willing and able to tolerate discontinuation of concomitant medications would raise additional safety concerns, impede patient recruitment, and create a major selection bias toward patients with mild exertional angina. Furthermore, our protocol design carefully standardizes exercise duration and documents comparable NTG responsiveness in all patients, irrespective of other therapy. Finally, in this study, as in others we have reported using similar methods and populations, NTG responses and their time course were quite comparable for patients receiving concomitant therapy and those receiving NTG alone.\textsuperscript{7, 12, 18} It is also possible that study of a larger population of subjects would have resulted in a small but statistically significant residual increment in exercise tolerance at 24 hr. Nonetheless, our data demonstrate dramatic attenuation of the effect of NTG on exercise tolerance in patients with stable exertional angina over 24 hr despite constant high plasma concentrations. Thus, this response pattern, previously observed for NTG patches, appears to be an inherent property of continuous NTG administration that cannot be overcome by use of higher doses. Furthermore, continuous high-dose regimens can actually abolish the beneficial effects of conventional doses of sublingual NTG. Thus, our study strengthens the rationale for further evaluation of intermittent patterns of NTG administration, which appear not to induce nitrate tolerance.\textsuperscript{29}
We are indebted to Janine Carter, Lucille Kuc, and Mary Johnson for their invaluable assistance in manuscript preparation; to the Clinical Research Center nursing staff for their assistance in performance of this study; and to the medical house staff and clinical faculty of the Hospital of the University of Pennsylvania for their generous assistance in patient recruitment.

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D Zimrin, N Reichek, K T Bogin, G Aurigemma, P Douglas, B Berko and H L Fung

Circulation. 1988;77:1376-1384
doi: 10.1161/01.CIR.77.6.1376

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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