Incidence of early tolerance to hemodynamic effects of continuous infusion of nitroglycerin in patients with coronary artery disease and heart failure

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ABSTRACT  Sustained therapy with nitroglycerin (NTG) has been reported to provoke the development of early tolerance. Because continuous intravenous NTG infusion is commonly used in patients with coronary artery disease and heart failure, we evaluated the incidence of early tolerance developed within the first 24 hr of therapy in 31 responders to NTG. After documentation of response to NTG, defined as a 10 mm Hg or greater or a 30% or greater reduction in mean pulmonary arterial wedge pressure (PAWP), 16 patients were blindly, randomly assigned to receive placebo and 15 patients were continued on same-dose NTG. Both groups showed an identical fall in PAWP at peak NTG titration (11 ± 4 mm Hg). Discontinuation of NTG in the placebo group resulted in a rapid increase in PAWP to levels not significantly different from baseline (19 ± 5 mm Hg at 2 hr vs 23 ± 6 mm Hg at baseline; p = NS). In the NTG group, PAWP fell from 27 ± 9 to 14 ± 7 mm Hg, was 16 ± 9 mm Hg at 2 hr (p < .05 vs baseline), and continued to be significantly lower than baseline for 8 hr; however, due to attenuation of effect, PAWP values at 12, 20, and 24 hr were not significantly different from placebo or baseline values. Analysis of individual data showed there were eight patients (group A) who had a persistent effect and seven patients (group B) who developed tolerance, which was defined as an increase in PAWP to values within 10% of baseline or a greater than 34% increase (2 × coefficient of variation of PAWP in the placebo group 2 to 24 hr after discontinuation of NTG) from values measured at the end of NTG titration. These two groups differed only in their baseline systemic vascular resistance (2195 ± 765 vs 1517 ± 355 dyne-sec-cm⁻⁵; p < .05). No difference was found in any other baseline hemodynamic or hormonal variables or in the magnitude of hemodynamic change during peak NTG titration and hormonal changes during the study. This study therefore provides further evidence for the development of early tolerance to the hemodynamic effects of continuous NTG administration. Tolerance is developed in approximately half of patients with coronary artery disease and heart failure. The development of tolerance cannot be predicted by baseline hemodynamic and hormonal values or their changes during NTG therapy.


SINCE THEIR INTRODUCTION over a century ago, organic nitrates have played an important role in the treatment of ischemic heart disease. Recent data demonstrating beneficial hemodynamic effect as well as improvement in exercise capacity and survival have also resulted in a widespread use of these drugs in the treatment of acute and chronic congestive heart failure. Since organic nitrates are easily absorbed from various body organs, many formulations have been developed for sublingual, buccal, oral, and topical administration. Intravenous nitrate preparations have also become available in the last several years. This therapeutic modality allows rapid onset of effect, easy titration, and a continuous and constant effect and has therefore been used frequently for in-hospital treatment of ischemic myocardial disease and heart failure. Recent experience with transdermal nitroglycerin (NTG), however, has demonstrated the development of early and substantial attenuation of the cardiocirculatory effects, raising the possibility that sustained plasma concentrations of NTG may lead to early development of tolerance to the hemodynamic effects of the drug. Such tolerance to NTG, if present with contin-
uous infusion of the drug, would impose an important limitation to its intravenous administration.

The objectives of the present study were therefore to evaluate the incidence and magnitude of tolerance to continuous intravenous infusion of NTG and to attempt to determine potential hemodynamic or hormonal characteristics that could predict the development of this phenomenon. Since patients with coronary artery disease (CAD) and elevated left ventricular filling pressure are usually treated with NTG, we performed our evaluation in such patients.

Methods

Patient selection. The study was designed to include patients at least 21 years of age with clinical or angiographic evidence of CAD and mean pulmonary arterial wedge pressure (PAWP) of 15 mm Hg or higher as a result of left ventricular systolic and/or diastolic failure. Angiographic evidence of CAD was defined as 70% or greater obstruction of a major epicardial coronary artery, whereas clinical evidence of CAD was defined as a history of myocardial infarction documented by characteristic electrocardiographic and enzymatic changes.

Patients with the following conditions were not allowed in the study: (1) angiographic evidence of left main CAD, (2) unstable angina, (3) hypertension, (4) primary valvular disease, (5) pulmonary edema, (6) thyrotoxicosis, or (7) recent acute myocardial infarction within 30 days before the initiation study.

Forty patients were enrolled into the study, including 29 men and 11 women, aged 45 to 77 years (mean ± SD 59 ± 8). The diagnosis of CAD was based on angiographic findings in 38 patients and on history of myocardial infarction documented by typical changes in the electrocardiogram and serum myocardial enzymes in two patients. Left ventricular ejection fraction was measured in 36 patients and ranged from 0.10 to 0.68 (mean 0.30 ± 0.14). All patients had symptoms of heart failure for a period of at least 1 month.

Hemodynamic measurements and computations. Right heart catheterization was performed with a balloon-tipped, triple-lumen, Swan-Ganz catheter, which allowed the measurements or right atrial and pulmonary arterial pressure as well as PAWP. The reference point for the procedure was at the mid-chest level with the patient in a supine position. All pressures were recorded on Electronics for Medicine AR 6 or VR 12 recorders, and mean pressures were measured with the use of electronic integration. Heart rate was determined by electrocardiographic recording and systemic blood pressure was measured by the standard cuff method. Cardiac output was determined by the thermodilution technique, as previously described. Measurements were performed in triplicate with ice-cold 5% dextrose in water as the indicator. Mean arterial blood pressure, cardiac index, stroke volume index, left ventricular stroke work index, systemic vascular resistance, and pulmonary vascular resistance were calculated by standard formulas. The determination of plasma levels of epinephrine and norepinephrine was performed with an isotope radioenzymatic technique. Plasma renin activity was measured by radioimmunoassay. Plasma levels of nitroglycerin were assayed by a method similar to that described by Settlage et al. using gas chromatography/negative ion mass spectrometry with on-column injection (Cal Lab East, Richmond, VA). The coefficient of variation was 4.08% for intra-assay and 13.1% for interassay precision.

Study protocol. All patients were studied in a stable clinical condition. Usual doses of digitalis, diuretic agents, and antiarrhythmic drugs were continued throughout the study. All long-acting vasodilators were withheld for at least 24 hr before the initiation of the study. Because of reported spontaneous hemodynamic changes after insertion of the pulmonary arterial catheter, baseline hemodynamic values were measured at least 24 hr after the performance of this procedure. Hemodynamic stability (less than 10% variation) was ensured by two consecutive readings performed at approximately 30 min intervals; values obtained at the last measurement were used as baseline values. After baseline measurements, an intravenous infusion of open-label NTG was started at a rate of 20 μg/min through special NTG polyethylene tubing. The infusion was regulated by an infusion pump (IVAC 530) and the rate was increased approximately every 5 min in increments of 30 to 60 μg/min to achieve a 30% or greater or a 10 mm Hg or greater reduction in mean PAWP or until a maximum dose of 560 μg/min was reached. After achieving the desired hemodynamic response, a constant infusion rate of NTG was maintained, and stability of PAWP (<10% variability) was ensured for at least 30 min. At that point the patients were assigned at random, according to a computer-generated schedule, to receive an infusion of either the same dose of NTG or an identical-appearing placebo infusion of NTG vehicle labeled to maintain the blinding. The infusion was then maintained at a constant rate for 24 hr. Hemodynamic measurements were repeated 2, 4, 8, 12, 20, and 24 hr later. At that point the infusion of the study drug was discontinued and hemodynamic measurements were repeated 15, 30, and 60 min after discontinuation.

Measurements of plasma hormones. Blood samples for catecholamines and renin were drawn at baseline, at the end of NTG titration, at 24 hr of constant drug infusion, and 30 min after discontinuation of the drugs.

Measurements of plasma NTG level. Plasma NTG levels were measured at the end of NTG titration and at 24 hr of constant NTG infusion in a sample of five consecutive patients who were found at the end of the study to have received NTG.

Statistical analysis. One-way repeated measures analysis of variance (ANOVA) and the Newman–Keuls test used to evaluate the temporal hemodynamic effects of the study drugs in each group, and single comparisons were performed with Student’s t test. Coefficient of variation was calculated as standard deviation of the mean/mean × 100. Analyses were performed with the use of the CLINFO system and the SAS statistical package on the IBM 370 system at the University of Southern California. All values are expressed as mean ± SD. A p value of less than .05 was considered statistically significant.

Results

Nineteen of 40 patients were initially assigned to be treated with NTG, and the other 21 patients were assigned to receive placebo. No significant differences were found between these two groups in age, duration of symptoms of heart failure, left ventricular ejection fraction, and measured or calculated baseline hemodynamic values (table 1).

Five of the patients were excluded from the study because of failure to achieve the desired PAWP response to open-label NTG titrated to its maximum dose of 560 μg/min. Three of these patients were assigned to receive NTG therapy and two were assigned to receive placebo. One patient who was assigned to receive placebo was excluded because the baseline
TABLE 1
Comparison between patients receiving NTG and placebo

<table>
<thead>
<tr>
<th></th>
<th>NTG (n = 19)</th>
<th>Placebo (n = 21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59 ± 8</td>
<td>58 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular ejection fraction *</td>
<td>0.27 ± 0.11</td>
<td>0.32 ± 0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of CHF (mo)</td>
<td>29 ± 38</td>
<td>15 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>88 ± 11</td>
<td>87 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>98 ± 13</td>
<td>96 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.2 ± 0.6</td>
<td>2.4 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>25 ± 7</td>
<td>29 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>11 ± 6</td>
<td>8 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>38 ± 9</td>
<td>35 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Mean PAWP (mm Hg)</td>
<td>26 ± 8</td>
<td>24 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes-sec-cm⁻²)</td>
<td>1808 ± 648</td>
<td>1758 ± 612</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dynes-sec-cm⁻²)</td>
<td>240 ± 118</td>
<td>224 ± 130</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular stroke work index (g-m/m²)</td>
<td>25 ± 11</td>
<td>28 ± 11</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Measured in 17 patients assigned to receive NTG and in 18 patients assigned to receive placebo.

PAWP had declined to less than 15 mm Hg 24 hr after the insertion of the pulmonary catheter. Two patients receiving placebo dropped out of the study because of worsening symptoms and one patient receiving NTG was excluded because of inability to obtain adequate pressure tracings due to malfunction of the pulmonary arterial catheter. Thirty-one patients therefore responded to NTG, were blindly, randomly assigned to receive the study drug, and completed the study. Sixteen of these patients received placebo and 15 received NTG.

**Hemodynamic changes over time**

*Placebo group.* Titration of open-labeled NTG resulted in no statistically significant effects on heart rate, mean blood pressure, cardiac index, mean right atrial pressure, and systemic and pulmonary vascular resistance. NTG significantly reduced mean pulmonary arterial pressure and PAWP. These pressures decreased during infusion of NTG from 34 ± 8 to 21 ± 5 mm Hg and from 23 ± 6 to 12 ± 4 mm Hg, respectively, (p < .05). Both variables showed rapid increase after substitution of NTG with placebo, and values at 2 hr were 29 ± 6 and 19 ± 5 mm Hg, respectively; both were not significantly different from control. No further significant changes were noted in both variables during the study. The values of PAWP measured during the study are shown in figure 1. Coefficient of variation of PAWP was measured in each patient between 2 and 24 hr after discontinuation of NTG; the mean value for the entire group was 17%.

**NTG group.** As in the placebo group, NTG titration resulted in a significant fall in mean pulmonary arterial pressure and PAWP without a statistically significant change in other measured or calculated hemodynamic values. Mean pulmonary arterial pressure fell from 39 ± 10 to 24 ± 8 mm Hg (p < .05) and remained significantly lower than baseline values for 12 hr. Values measured at 20 and 24 hr of therapy were not statistically different from baseline. Mean PAWP demonstrated a similar change and fell from 27 ± 9 to 14 ± 7 mm Hg at peak NTG titration. Although values remained lower than baseline for the entire study duration, a gradual increase in PAWP was found and the decrease in PAWP at 12 hr was no longer statistically significant (figure 1).

**Comparison of changes in PAWP between the two treatment groups.** Figure 2 demonstrates the change in PAWP from control in the 16 patients receiving placebo and in the 15 patients receiving NTG. Both groups showed an identical fall in PAWP at peak NTG titration (11 ± 4 mm Hg). However, discontinuation of NTG
in the placebo group resulted in rapid increase in PAWP resulting in a significant difference between the two groups at 2 to 12 hr with a probability of <.001 to <.01. At 20 hr, the change in PAWP from control was comparable in the two groups, and the values at 24 hr were 2 ± 4 mm Hg for the placebo group and 7 ± 6 mm Hg for the NTG group. This difference was again statistically significant but at a higher probability value (p < .05).

Individual analysis of tolerance. We defined tolerance as an increase in PAWP to values comparable to baseline values (<10% difference) or a percent increase exceeding twice the coefficient of variation of PAWP recorded between 2 to 24 hr after discontinuation of NTG in the placebo group (34%).

Eight patients demonstrated persistent response to NTG (group A), and the other seven patients developed tolerance to the effect of the drug (group B). Figure 3 graphically depicts changes in PAWP from baseline values in the two NTG groups (A and B) and in 16 patients treated with placebo. Changes in PAWP from baseline showed significant difference between group A and the control group starting a 2 hr and persisting for the entire study duration. In contrast, the changes from baseline in group B were different from changes in the control group only during the early part of the study, and values at 12 hr (−2 ± 6 mm Hg in the control group and −7 ± 7 mm Hg in group B) were already not statistically different.

Comparison between groups A and B. A comparison between baseline hemodynamic values in group A and B showed no significant differences in heart rate (86 ± 8 vs 87 ± 10 beats/min), mean blood pressure (102 ± 13 vs 97 ± 16 mm Hg), cardiac index (1.9 ± 0.5 vs 2.5 ± 0.7 liter/min/m²), mean right atrial pressure (11 ± 4 vs 9 ± 9 mm Hg), mean pulmonary arterial pressure (40 ± 10 vs 37 ± 11 mm Hg), mean PAWP (29 ± 10 vs 25 ± 8 mm Hg), and pulmonary vascular resistance (259 ± 122 vs 230 ± 133 dyne-sec-cm⁻⁵). The ejection fraction was 0.27 ± 0.10 in group A and 0.28 ± 0.14 in group B; this difference was also not statistically significant. In contrast, the two groups differed in their baseline values of systemic vascular resistance (figure 4); values were higher in patients who did not develop tolerance to NTG (2195 ± 765 vs 1517 ± 355 dyne-sec-cm⁻⁵). A comparison of baseline plasma levels of catecholamines and plasma renin activity demonstrated comparable levels of epinephrine (83 ± 126 vs 83 ± 101 pg/ml), norepinephrine (737 ± 519 vs 595 ± 506 pg/ml), and renin activity (4.3 ± 8.9 vs 1.6 ± 2.1 ng/ml/hr) between the two groups. A comparison of changes in all measured hemodynamic variables between the two groups demonstrated no significant difference.

FIGURE 2. Difference in mean PAWP from baseline (BL) in patients receiving placebo and NTG.

FIGURE 3. A comparison of the difference in mean PAWP from baseline (BL) in eight patients without tolerance (group A) and seven patients who developed tolerance to NTG (group B). *p < .05 vs BL; **p < .01 vs BL.
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at 24 hr (27 ± 9 mm Hg) than at peak NTG titration (22 ± 9 mm Hg).

**Discussion**

These results clearly demonstrate the development of tolerance to the hemodynamic effects of intravenous infusion of NTG occurring within the first 12 hr of therapy in approximately half of our patients. The findings of persistent NTG blood levels at the end of the study showed that the attenuation of the effects of NTG was not caused by a reduction in drug concentration in the blood. These findings bear important clinical implications and reemphasize the potential therapeutic limitations of NTG when given in a continuous, uninterrupted fashion in patients with CAD and heart failure. The relationship between continuity of exposure to organic nitrates and the development of tolerance to their vasodilatory effect was first demonstrated in animal experiments. Recent investigations of the effects of continuous NTG administration via transdermal systems have also demonstrated a development of early tolerance to the hemodynamic and anti-ischemic effects in patients with angina pectoris and heart failure.

Individual analysis of our data shows that not all patients develop tolerance to the effects of NTG; approximately half of the patients maintained their initial response to the drug. This conclusion may be limited by the fact that the duration of the study was restricted to 24 hr and tolerance to NTG may occur later in some patients. Although this possibility cannot be excluded by our results, the findings in this study and others suggest that tolerance to NTG when administered continuously is an early phenomenon that occurs within several hours of therapy.

An ability to predict the development of tolerance in patients treated with intravenous NTG would be of obvious clinical importance. In this study, patients who developed tolerance demonstrated a lower baseline systemic vascular resistance. The explanation for this finding in not readily apparent, especially since other differences between the groups that may suggest milder hemodynamic impairment in patients with tolerance were not statistically significant and no difference was found in baseline left ventricular function and levels of circulating catecholamines and renin. In addition, individual date showed overlap between the two groups, demonstrating that baseline values of systemic vascular resistance are a poor predictor of the effects in an individual patient.

Previous reports suggested that tolerance to the effect of vasodilator drugs may result from activation of vaso-

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**FIGURE 4.** Individual and group values of systemic vascular resistance in patients with persistent effect of NTG on left ventricular filling pressure (group A) and patients who developed tolerance to NTG (group B).

The change in plasma hormonal levels is demonstrated in figure 5 for the two groups. A tendency for elevation in plasma renin activity was seen at peak NTG titration and at 24 hr in group A. The changes, however, were not significant when compared with baseline values. Similarly, no significant changes were seen in the levels of both epinephrine and norepinephrine during the infusion of NTG or after its discontinuation in the two groups of patients treated with this drug.

**Plasma NTG levels.** The measurements of plasma NTG levels were performed in a sample of five consecutive patients treated with NTG during peak drug titration and at 24 hr of NTG infusion (figure 6). Mean NTG plasma level was 21,200 ± 6768 pg/ml at peak NTG titration and 20,299 ± 7986 pg/ml at 24 hr of NTG titration. These two values were not significantly different. In spite of persistence of NTG in plasma, in these patients PAWP was significantly higher (p < .05)
constrictor forces such as sympathetic nervous system and the renin angiotensin system, which are mediated by a fall in systemic blood pressure and may counteract the initial vasodilatory effect.\textsuperscript{23, 24} Our results cannot support such a mechanism, since no difference was found in the magnitude of hemodynamic changes with initiation of NTG therapy and in the levels of catecholamines and renin during NTG administration between patients who did and did not develop tolerance. However, more frequent assessment of hormonal plasma levels or a direct functional assessment of the autonomous nervous systems during nitrate therapy may provide further understanding of the role of sympathetic nerve activity in the attenuation of vasodilatory effect of NTG.\textsuperscript{25}

Five of our patients failed to demonstrate a reduction of PAWP in spite of titration of NTG to very large doses. A similar finding is seen when NTG is given intravenously to patients with heart failure caused by acute myocardial infarction\textsuperscript{26} or orally to patients with

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Values of plasma renin activity, epinephrine, and norepinephrine as measured at baseline (BL), at peak NTG (PE), and at 24 hr of continuous NTG infusion, in eight patients who showed persistent effect (group A) and seven patients who developed tolerance to NTG (group B). The difference between the two groups was not statistically significant.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Values of NTG plasma levels and mean PAWP at peak drug titration (open bars) and at 24 hr of NTG infusion (shaded bars) in five patients receiving NTG.}
\end{figure}
chronic heart failure.\textsuperscript{27} Although failure to respond to high doses of NTG may be caused by resistance of the vascular system to the drug, early development of tolerance shortly after exposure to NTG due to nitrate-mediated oxidation of critical sulfhydryl groups in the nitrate receptors cannot be excluded. The depletion of intracellular stores of sulfhydryl groups within vascular tissue has been suggested by Needleman and Johnson\textsuperscript{28} as the mechanism of tolerance to organic nitrates. These sulfhydryl groups are needed for conversion of organic nitrates to s-nitrosothiols in the smooth muscle cell, which are believed to activate the enzyme guanylate cyclase. This enzyme leads to increased levels of intracellular cyclic guanosine monophosphate, which causes vasodilatation.\textsuperscript{29} Recent studies seemed to support this assumption by demonstrating that NTG-induced peripheral and coronary dilatory effect could be potentiated by N-acetylcysteine, a source of sulfhydryl groups.\textsuperscript{30, 31} A recent preliminary report by Packer et al.\textsuperscript{32} has also shown reversal of tolerance to NTGs hemodynamic effects in a group of patients with heart failure after the administration of N-acetylcysteine.\textsuperscript{32} More clinical data, however, are needed for further definition of the potential role of sulfhydryl donors in the prevention of tolerance to organic nitrates.

Recent experimental data have demonstrated that, similar to NTG nitroprusside also appears to promote muscle relaxation by increasing tissue levels of cyclic guanosine monophosphate.\textsuperscript{33} In an experiment in vitro by Axelsson et al.\textsuperscript{34} vascular smooth muscle made tolerant to NTG demonstrated some cross-tolerance to nitroprusside with respect to its relaxant effect and the response of cyclic guanosine monophosphate. Other investigators, however, failed to find cross-tolerance and postulated that the initial site of action in the vascular smooth muscle may be different for NTG and nitroprusside. Because of the obvious clinical importance, further clinical investigation will be needed to establish the presence or absence of cross-tolerance between these two drugs.

The loss of NTG-mediated hemodynamic effect within several hours after initiation of therapy in patients with CAD demonstrated in our study emphasizes the need for continuous monitoring of the hemodynamic effect of the drug. Although hemodynamic monitoring has been traditionally performed by invasive methods, echocardiographic and Doppler techniques\textsuperscript{35, 36} may allow a noninvasive evaluation of volumetric and hemodynamic effects of nitrate therapy and assurance of their persistence.

Recent clinical investigations have demonstrated that nitrate tolerance can be reversed or even prevented by the use of intermittent dosing rather than continuous nitrate therapy.\textsuperscript{37–39} Although the intravenous route for NTG administration is advantageous for the initial therapy of unstable ischemic disease or heart failure, an intermittent regimen seems to be preferred for prolonged treatment with organic nitrates. Further studies are needed, however, to determine the duration of the nitrate-free periods required to prevent or reverse tolerance to the effect of nitrate therapy in patients with CAD and heart failure.

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