Dose requirements and hemodynamic effects of transdermal nitroglycerin compared with placebo in patients with congestive heart failure

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ABSTRACT The dose requirements and duration of effect of transdermal nitroglycerin in patients with heart failure are not clearly established. In a first series of eight patients with chronic heart failure we gave transdermal nitroglycerin in incremental doses until pulmonary capillary wedge pressure fell at least 30% within 4 hr in three consecutive patients. Thus we found that a single dose of 60 mg/24 hr (120 cm²) was the minimal effective dose. Transdermal nitroglycerin or placebo was then given as a single application of 60 mg/24 hr in random double-blind fashion to 15 additional patients with heart failure (eight received transdermal nitroglycerin and seven received placebo), and hemodynamics were monitored for up to 24 hr. After administration of transdermal nitroglycerin, the control pulmonary capillary wedge pressure of 22 ± 7 mm Hg fell by 6 ± 6 mm Hg at 2 hr (p < .05) and reached maximal reduction of 8 ± 6 mm Hg (p < .01) at 4 hr. The reduction in wedge pressure remained significant through 12 hr but was no longer statistically significant by 18 hr after administration of the drug. Transdermal nitroglycerin also significantly reduced pulmonary arterial and right atrial pressures as well as pulmonary vascular resistance from 4 through 12 hr but did not affect systemic hemodynamics. No significant hemodynamic changes occurred after administration of placebo. Thus transdermal nitroglycerin is an effective vasodilator in patients with heart failure, but a dose of at least 60 mg/24 hr is needed. Even with this dose, hemodynamic effects do not last beyond 18 hr, suggesting altered absorption or development of tolerance. Circulation 71, No. 5, 980–986, 1985.

VASODILATORS are commonly used for the treatment of acute and chronic congestive heart failure. Among the presently available vasodilator agents, only nitrates and angiotensin-converting enzyme inhibitors have produced sustained hemodynamic improvement along with increased exercise tolerance in placebo-controlled trials in patients with chronic heart failure.1–6 Both captopril and nitrates require frequent dosing, so that practical problems related to drug delivery and patient compliance still exist. The duration of action of sublingually administered nitroglycerin is far too short to be of practical value for long-term therapy. Orally administered isosorbide dinitrate and topically applied nitroglycerin ointment produce significant hemodynamic effects for as long as 4 to 8 hr, but still require multiple daily dosing.7, 8 The recent introduction of transdermal delivery systems for nitroglycerin has raised the possibility of once-daily dosing.9, 10 However, the dose requirements and duration of effect of these preparations are not clearly established.9–12 Early claims of a prolonged duration of action were based on uncontrolled studies that did not account for spontaneous changes in hemodynamics.13 Recent studies have suggested a duration of action of transdermal nitrate delivery systems of less than 24 hr and have raised the possibility of early tolerance or altered absorption.11, 12, 14 This study was designed to assess the dose responsiveness and pharmacodynamics of a single transdermal dose of nitroglycerin compared with placebo in patients with chronic congestive heart failure.

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CIRCULATION
Methods

Patient selection. The study population consisted of 23 patients with a history of severe congestive heart failure (NYHA class III to IV) of at least 3 months' duration. Clinical symptoms and signs of congestive heart failure as well as one of the following obtained within the previous 2 weeks were required for inclusion in the study: cardiac thoracic ratio on a standard chest x-ray of greater than 50%, left ventricular ejection fraction by radionuclide angiocardiography of less than 45%, or left ventricular end-diastolic dimension by echocardiogram greater than 55 mm. Heart failure was due to ischemic heart disease as diagnosed by a history of previously documented myocardial infarction or coronary arteriographic results or was due to idiopathic congestive cardiomyopathy, which was diagnosed if no other cause of congestive heart failure was apparent. Patients with primary pulmonary or valvular heart disease were excluded. No patient had angina pectoris requiring prophylactic antianginal medications. All patients were receiving previous digitalis or diuretic therapy. Diuretics and any vasodilator drugs were withheld at least 24 hr before study. Written informed consent was obtained from each patient, and the study protocol was approved by the local human studies committees.

Procedures. In qualifying consenting patients, right heart catheterization was performed percutaneously with a Swan-Ganz thermodilution catheter. Heart rate was monitored by electrocardiogram. Systemic blood pressure was measured by the standard cuff technique and cardiac output was measured by thermodilution. At least three baseline measurements of pressures and cardiac output were repeated at 20 min intervals until they varied by less than 15%. Pulmonary capillary wedge pressure was taken as occluded pulmonary arterial pressure or pulmonary arterial diastolic pressure. Pulmonary arterial diastolic pressure was used only if at least one pulmonary arterial occluded pressure was obtained and differed from pulmonary arterial diastolic pressure by less than 4 mm Hg. Pulmonary arterial occluded and diastolic pressures were not interchanged in any patient. Derived hemodynamic values were calculated as follows: mean arterial pressure was taken as diastolic blood pressure plus one-third of the pulse pressure, cardiac index as cardiac output divided by body surface area, systemic vascular resistance as mean arterial pressure minus right atrial pressure divided by cardiac output and expressed in units, and total pulmonary vascular resistance as mean pulmonary arterial pressure divided by cardiac output and expressed in units.

Study protocol. The study was conducted in two parts. In part I we sought to determine the consistently effective single dose of transdermal nitroglycerin. An effective dose was defined as that dose needed to produce a reduction in pulmonary capillary wedge pressure of at least 30% within 4 hr of administration in three consecutive patients. The initial dose of transdermal nitroglycerin was a patch releasing 5 mg/24 hr (Transderm-Nitro, CIBA Pharmaceutical Co.). The dose was subsequently doubled to 40 mg/24 hr then increased in 20 mg/24 hr increments until three consecutive patients met the criteria described. Transdermal nitroglycerin was applied to an area of the upper abdomen that had been cleansed and shaved. Pressures were monitored for at least 4 hr if no response was seen or until peak hemodynamic effect, defined as the lowest wedge pressure observed that did not drop further over two successive determinations at 1 hr intervals. Eight patients participated in this first portion of the study and each received only one test dose. In patients who did not respond within 4 hr, the transdermal nitroglycerin patch was removed and 1 hr later sublingual nitroglycerin (0.4 mg) was administered and followed by hemodynamic measurements after 5 and 10 min.

Part II of the study consisted of a randomized, double-blind, placebo-controlled trial in 15 patients using the dose determined from part I. Patients were randomly assigned to receive transdermal nitroglycerin (eight patients) or identical placebo-containing patches (seven patients) applied in the same manner as in part I. Hemodynamic measurements were the same as in part I; however, they were monitored for 24 hr after drug application. In three patients who received placebo and one who received transdermal nitroglycerin, the position of the Swan-Ganz catheter in the pulmonary artery could not be maintained for the full 24 hr.

Data analysis. Data were analyzed by Student's t test for paired data to compare intragroup differences and for unpaired data to compare placebo- and nitroglycerin-treated patients. All data were analyzed first by a two-way analysis of variance for repeat observations, and t tests were performed only if the f statistic was significant. A difference was not considered statistically significant unless it was different from control within the same group and also different between groups at the same point in time. Differences were considered statistically significant at p < .05.

Results

Part I. Baseline characteristics of patients participating in this dose-finding phase are shown in table 1. A total of eight patients were required to establish the effective dose of transdermal nitroglycerin. These patients were all men who had significant hemodynamic abnormality and left ventricular dysfunction consistent with heart failure. They had elevated pulmonary capillary wedge pressure and reduced cardiac index along with decreased left ventricular ejection fraction and increased cardiac dimensions. All patients were taking maintenance doses of digoxin and diuretics, and two patients (Nos. 7 and 8) were also taking isosorbide dinitrate, which was discontinued at least 24 hr before study.

The effects of transdermal nitroglycerin on pulmonary capillary wedge pressure in each patient are shown in figure 1. It was observed that six patches releasing 10 mg/24 hr each, or a total application of nitroglycerin equivalent to 60 mg released over 24 hr, was required to produce at least a 30% reduction of pulmonary capillary wedge pressure in three consecutive patients. This dose covered an area of 120 cm². There was significant variability among patients; the greatest response of any patient was seen in the first patient given a 10 mg/24 hr dose, whereas the second patient receiving that same dose had very little response. In patients who did not respond to transdermal nitroglycerin, sublingual nitroglycerin was still effective. In these patients pulmonary capillary wedge pressure at baseline was similar to that of responders (21 ± 8 [SD] vs 19 ± 7 mm Hg). Within 10 min of administration of sublingual nitroglycerin to these nonresponders, pulmonary capillary wedge pressure fell by an average of 6 ± 1 mm Hg (equal to −25%). Thus lack of response to transdermal nitroglycerin in these
TABLE 1
Baseline characteristics of patients with heart failure given different doses of transdermal nitroglycerin

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Cause of CHF</th>
<th>CTR (%)</th>
<th>LVDD (mm)</th>
<th>LVEF (%)</th>
<th>HR (bpm)</th>
<th>MAP (mm Hg)</th>
<th>PCW (mm Hg)</th>
<th>CI (l/min/m²)</th>
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<tbody>
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<td>55</td>
<td>CAD</td>
<td>50</td>
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<td>116</td>
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<td>2</td>
<td>55</td>
<td>ICC</td>
<td>63</td>
<td>77</td>
<td>—</td>
<td>99</td>
<td>116</td>
<td>26</td>
<td>2.10</td>
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<td>3</td>
<td>63</td>
<td>ICC</td>
<td>57</td>
<td>—</td>
<td>—</td>
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<td>88</td>
<td>18</td>
<td>2.90</td>
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<td>62</td>
<td>CAD</td>
<td>60</td>
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<td>63</td>
<td>ICC</td>
<td>62</td>
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<td>24</td>
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<td>94</td>
<td>31</td>
<td>2.17</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
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<td>51</td>
<td>—</td>
<td>27</td>
<td>71</td>
<td>133</td>
<td>21</td>
<td>2.10</td>
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<td>CAD</td>
<td>51</td>
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<td>44</td>
<td>69</td>
<td>103</td>
<td>20</td>
<td>2.54</td>
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<td>8</td>
<td>56</td>
<td>CAD</td>
<td>—</td>
<td>—</td>
<td>15</td>
<td>77</td>
<td>90</td>
<td>10</td>
<td>3.13</td>
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<td>Mean</td>
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<td>—</td>
<td>56.3</td>
<td>63.5</td>
<td>26.0</td>
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<td>12.4</td>
<td>15.7</td>
<td>6.7</td>
<td>0.52</td>
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</table>

CAD = coronary artery disease; CHF = congestive heart failure; CI = cardiac index; CTR = cardiothoracic ratio; HR = heart rate; ICC = idiopathic congestive cardiomyopathy; LVDD = left ventricular diastolic dimension; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; PCW = pulmonary capillary wedge pressure.

patients was not caused by resistance to the drug but by apparent inability to absorb nitroglycerin transcutaneously in sufficient amounts.

**Part II.** The effects of transdermal nitroglycerin at a dose of 60 mg/24 hr in a single application (120 cm²) were compared with those of a similar application of placebo patches (120 cm²). The two groups were comparable at baseline with similarly increased cardiac dimensions, reduced left ventricular ejection fraction, elevated pulmonary capillary wedge pressure, and low cardiac index (table 2). No differences between groups were significant except that in right atrial pressure, which was higher in placebo-treated patients for unknown reasons. Among the eight patients given transdermal nitroglycerin, all were men, all were taking maintenance digoxin and diuretics, and two were also taking isosorbide dinitrate, which was discontinued at least 24 hr before study. Of the seven patients given placebo, three were women. All of these patients were receiving maintenance diuretics, but only four had

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**FIGURE 1.** Effects of incremental doses of transdermal nitroglycerin on pulmonary capillary wedge pressure (PCW) in patients with congestive heart failure. Values expressed as peak reduction observed within 4 hr of drug administration. Dose was titrated until three consecutive patients experienced at least a 30% fall in PCW.
TABLE 2
Baseline characteristics of patients with heart failure given transdermal nitroglycerin or placebo

<table>
<thead>
<tr>
<th></th>
<th>Transdermal nitroglycerin</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>No. of patients</td>
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<td>7</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56±15</td>
<td>62±15</td>
</tr>
<tr>
<td>Cause of CHF</td>
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<td>CAD</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>ICC</td>
<td>3</td>
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<tr>
<td>CTR (%)</td>
<td>59±6</td>
<td>59±8</td>
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<td>LVDD (mm)</td>
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<td>65±6</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>21±11</td>
<td>38±20</td>
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<tr>
<td>HR (bpm)</td>
<td>83±14</td>
<td>83±11</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>91±8</td>
<td>89±13</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>7±2</td>
<td>17±6*</td>
</tr>
<tr>
<td>MPA (mm Hg)</td>
<td>33±7</td>
<td>42±8</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>22±7</td>
<td>26±5</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.6±0.3</td>
<td>2.5±0.7</td>
</tr>
<tr>
<td>PVR (units)</td>
<td>7±2</td>
<td>11±5</td>
</tr>
<tr>
<td>SVR (units)</td>
<td>18±4</td>
<td>19±3</td>
</tr>
</tbody>
</table>

RAP = right atrial pressure; PVR = total pulmonary vascular resistance; SVR = systemic vascular resistance; MPA = mean pulmonary arterial pressure; other abbreviations as in table 1.

\*p < .01.

TABLE 3
Hemodynamic effects of transdermal nitroglycerin in patients with heart failure (mean ± SD)

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<th>Time after drug administration (hr)</th>
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<tr>
<td>TDN</td>
<td>83±14</td>
<td>85±16</td>
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<tr>
<td>PL</td>
<td>83±10</td>
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<td>84±9</td>
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<td>85±10</td>
<td>82±9</td>
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<tr>
<td>MAP (mm Hg)</td>
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<td></td>
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<td>RAP (mm Hg)</td>
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TDN = transdermal nitroglycerin; PL = placebo; other abbreviations as in tables 1 and 2.

Statistical comparisons (intragroup and intergroup): \*p < .05; \*\*p < .01.
reduction in pulmonary capillary wedge pressure after administration of transdermal nitroglycerin was maximal after 4 hr (−8 ± 6 mm Hg; p < .01) and persisted to be significant through 12 hr. By 18 and 24 hr after transdermal nitroglycerin, the decreases in pulmonary capillary wedge pressure of 3 ± 5 and 4 ± 6 mm Hg were no longer statistically significant.

Placebo did not alter any hemodynamic parameter in a statistically significant manner. However, the time course of changes in pulmonary capillary wedge pressure after administration of placebo tended to parallel those observed after administration of transdermal nitroglycerin (figure 2). Thus pulmonary capillary wedge pressure tended to be reduced, although not significantly, 24 hr after administration of placebo. Therefore changes at 24 hr were not significantly different either between groups or within groups. Changes in other hemodynamic variables in the two treatment groups also tended to parallel each other so that differences between groups were not significant and tended to offset apparent changes within a given group (table 3).

Discussion

Nitrates were among the first vasodilators to be evaluated for the treatment of congestive heart failure and today remain among the clinically effective vasodilator agents used in treating patients with heart failure.1, 2, 7 Efficacy of other vasodilators has been questioned because of problems with tolerance, side effects, or inability to ameliorate clinical status despite hemodynamic improvement.15–17 Of the presently available vasodilators, only those with venodilating ability, such as nitrates and angiotensin-converting enzyme inhibitors, have produced sustained hemodynamic effects, increased exercise tolerance, and improved symptomatic status in controlled trials in patients with heart failure.1–4, 6 Thus there is a continuing interest in developing a nitrate delivery system that circumvents the problems of first-pass hepatic metabolism and limited duration of action of nitrates. The recent development of convenient transdermal delivery systems for nitroglycerin suggests the possibility of a once-daily dosing schedule for long-term nitrate administration.9–12

In this study a transdermal system that delivers nitroglycerin topically via a rate-limiting membrane produced hemodynamic effects greater than those of placebo in patients with congestive heart failure. The predominant hemodynamic effects were reduction of pulmonary capillary wedge, pulmonary arterial, and right atrial pressures with little or no effect on systemic
hemodynamics. These were the expected responses based on previous observations that nitrates are predominant venodilators in heart failure.1, 2, 5-8 Our major findings were that large doses of transdermal nitroglycerin, at least 60 mg/24 hr or 120 cm², were required to produce consistent hemodynamic responses in these patients and that even with this dose the duration of hemodynamic effect, although prolonged, was considerably less than 24 hr. Previous studies of transdermal nitroglycerin delivery systems in patients with heart failure have also found significant hemodynamic effects,9, 10 but these studies were uncontrolled and recent evidence suggests that significant spontaneous hemodynamic changes may occur during periods of prolonged hemodynamic monitoring in such patients.13 Thus previous claims of duration of action as long as 24 hr after application of transdermal nitroglycerin may be misleading, since nitratelike hemodynamic effects may have occurred spontaneously. Indeed, our placebo-treated patients experienced a fall in pulmonary capillary wedge pressure, and significant differences from the nitroglycerin-treated patients could not be demonstrated by 18 or 24 hr after drug administration. Earlier studies of transdermal nitroglycerin in patients with heart failure also used high doses (in the range of 15 to 40 mg/24 hr) to obtain hemodynamic effects. In this study a dose of transdermal nitroglycerin equivalent to 60 mg released over 24 hr (120 cm²) was required to produce a consistent response. Our finding of this even higher dose requirement might reflect our study design, which called for a dose titration until three consecutive patients met our criteria for response. Previous studies titrated the dose of transdermal nitroglycerin based on response to an infusion of nitroglycerin or used fixed doses.9, 10 We did observe considerable individual variability in responses at lower doses. Thus there appear to be individual differences in transcutaneous absorption of nitroglycerin among patients with heart failure. Nevertheless, our patients who did not respond to transdermal nitroglycerin did respond to sublingual nitroglycerin, thereby excluding resistance as a mechanism of their lack of response.

The time course of hemodynamic activity of transdermal nitroglycerin in our study revealed an onset of action within 2 hr of application, with peak effects occurring at 4 hr. The effects appear to wane by 18 hr, suggesting either altered absorption or the development of tolerance. As mentioned above, previous studies reporting hemodynamic effects lasting for 24 hr were not placebo controlled and the hemodynamic changes observed at 24 hr were returning toward baseline.9, 10 Thus the apparent effects observed by these other investigators may not have been due entirely to transdermal nitroglycerin but could have reflected spontaneous changes. Evidence for a shorter duration of action of transdermal nitroglycerin is also provided by a recent study in patients with angina. In a placebo-controlled trial, Reichek et al.11 compared exercise performance of patients given nitroglycerin delivered by a membrane system or a polymer system. Increased exercise capacity was apparent at 4 and 8 hr but not at 24 hr for either preparation.

It is interesting to speculate on the reasons for the observed attenuation of response to transdermal nitroglycerin. Since previous studies have indicated that measurable plasma levels of nitroglycerin persist for at least 24 hr after a single application of transdermal nitroglycerin, tolerance is more likely than altered absorption to explain the loss of hemodynamic responsiveness before 24 hr.18, 19 Tolerance to nitrates has been a controversial question and recent evidence suggests that tolerance is more likely to develop when high doses of nitrates are administered frequently enough to result in sustained high plasma nitrate levels.14, 20-22 Apparently such tolerance can be rapidly resolved by allowing blood nitrate levels to fall to zero for a brief period of time, after which responsiveness is promptly restored.22 If such is truly the case, then transdermal nitroglycerin may be very useful since efficacy could be maintained by simply removing the patches well before 24 hr after application, at bedtime, for example. The duration of action of transdermal nitroglycerin, even if only between 12 and 18 hr, is still much longer than other available forms.

Another possible mechanism to explain the relatively short duration of action of transdermal nitroglycerin is an alteration in the absorption of nitroglycerin caused by changes in the properties of the membrane or local skin circulation during prolonged exposure to nitroglycerin. This possibility cannot be excluded in our patients since plasma nitroglycerin levels were not available. Studies to resolve this problem are in progress.

In conclusion, we have shown that a transdermal nitroglycerin system can produce significant hemodynamic responses comparable to those of other nitrates in patients with congestive heart failure. The duration of action of nitroglycerin administered by the transdermal delivery system is considerably shorter than that previously suggested. Nevertheless, the duration of action is sufficiently longer than that of other available forms of administration. If tolerance can be avoided by properly adjusting the dosing interval, then transdermal nitroglycerin may indeed be suited to once-daily
administration. Since other available nitrates and the other effective vasodilators used in treating patients with heart failure, angiotensin-converting enzyme inhibitors, are shorter acting, transdermal nitroglycerin could become a very useful agent for long-term vasodilator therapy. It is already apparent that much larger doses of transdermal nitroglycerin than currently used in routine practice, i.e., at least 60 mg/24 hr, must be applied. This introduces potential cost problems that must be resolved, along with the questions concerning possible tolerance and the proper method and frequency of administration, before the ultimate role of transdermal nitroglycerin preparations can be defined. In the meantime, these agents should not be discarded since results such as ours are encouraging while stressing the need to learn more about the proper use of transdermal nitroglycerin delivery systems.

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