Early Tolerance to Hemodynamic Effects of High Dose Transdermal Nitroglycerin in Responders With Severe Chronic Heart Failure

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Transdermal systems for delivery of nitroglycerin have been shown to provide sustained blood levels of the drug for at least 24 hours. Investigations of hemodynamic effects of transdermal nitroglycerin in patients with heart failure have demonstrated a transient reduction in pressure lasting less than the expected 24 hours. These findings could be due to the development of circulatory tolerance to the vasodilatory effects of nitroglycerin or to insufficient drug dosing. In the present study, we compared the hemodynamic effects of the first and the second doses of high dose (120 mg) transdermal nitroglycerin given 24 hours apart in 11 responders (≥20% reduction in mean pulmonary artery wedge pressure lasting ≥2 hours).

Initiation of nitroglycerin therapy resulted in a significant reduction in mean right atrial pressure lasting for 14 hours and in a reduction in mean pulmonary artery and mean pulmonary artery wedge pressures lasting 24 hours. After administration of the second dose, mean right atrial pressure at 2 hours (9 ± 5 versus 7 ± 4 mm Hg), 4 hours (8 ± 5 versus 6 ± 4 mm Hg) and 8 hours (8 ± 5 versus 6 ± 3 mm Hg) was higher than after the first dose (p < 0.05). Both mean pulmonary artery and mean pulmonary artery wedge pressures were significantly higher after the second nitroglycerin dose. Mean pulmonary artery pressure after the second dose was 32 ± 8 versus 28 ± 7 mm Hg at 2 hours (p < 0.05), 32 ± 7 versus 27 ± 7 mm Hg at 4 hours (p < 0.01), 33 ± 10 versus 27 ± 6 mm Hg at 6 hours (p < 0.05) and 31 ± 8 versus 26 ± 7 mm Hg at 8 hours (p < 0.05). Mean pulmonary artery wedge pressure was 22 ± 7 versus 17 ± 7 mm Hg at 2 hours (p < 0.01), 21 ± 8 versus 16 ± 6 mm Hg at 4 hours (p < 0.01), 19 ± 8 versus 16 ± 7 mm Hg at 6 hours (p < 0.05) and 20 ± 9 versus 15 ± 6 mm Hg at 8 hours (p < 0.01).

It is concluded that in patients with chronic congestive heart failure, the initial hemodynamic changes seen after the administration of high dose transdermal nitroglycerin are significantly attenuated within hours of the first dose. These findings suggest that circulatory tolerance to the effect of sustained nitroglycerin therapy develops early and should be taken into consideration when transdermal nitroglycerin is used in short- and long-term therapy of chronic heart failure.

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Methods

Study patients. We studied 18 patients with chronic severe congestive heart failure due to left ventricular systolic dysfunction who were admitted to the hospital for worsening transient effect lasting less than the expected 24 hours, even with high doses. These findings raise the possibility of circulatory tolerance to the effects of sustained serum levels of nitroglycerin, but could also be due to insufficient drug dosing.

Our study was designed to further evaluate the persistence of the circulatory response to sustained nitrate therapy in patients with heart failure by using large dose transdermal nitroglycerin and by comparing the effects of the first and second doses of the drug.

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of symptoms. Eleven of these patients demonstrated a hemodynamic response to transdermal nitroglycerin (>20% reduction in mean pulmonary artery wedge pressure seen within 4 hours after drug administration and lasting ≥2 hours) and were included in our study. There were six women and five men aged 21 to 77 years (mean ± SD 55 ± 18). The diagnosis of left ventricular systolic dysfunction was based on a reduced ejection fraction (measured in eight patients; range 0.15 to 0.37, mean 0.24 ± 0.08) or echocardiographic findings (three patients). Duration of heart failure ranged between 1 and 8 years and the cause was believed to be dilated cardiomyopathy in 10 patients and coronary artery disease in 1. Six patients with dilated cardiomyopathy had a history of excessive chronic alcohol intake. No patient had primary valvular disease or clinical evidence of active myocardial ischemia at the time of the study. Three patients had atrial fibrillation and eight had sinus rhythm. All patients were in New York Heart Association functional class III or IV and were in stable clinical and hemodynamic condition at the time of study.

The study was started at least 24 hours after the insertion of a balloon-flotation pulmonary artery catheter. All patients were treated with digoxin, 0.25 mg daily, and all but one (Patient 1) received oral furosemide, 40 mg three times daily; the dosage of these drugs was maintained constant throughout the study. The administration of long-acting vasodilator agents was discontinued at least 24 hours before the initiation of therapy.

Hemodynamic measurements and computations. Right heart catheterization was performed using a balloon-tipped, triple-lumen, Swan-Ganz catheter, which allowed for measurements of right atrial, pulmonary artery and pulmonary artery wedge pressures. The reference point for the procedure was at the midchest level with the patient in a supine position. All pressures were recorded on an Electronics for Medicine AR6 or VR12 recorder and mean pressures were measured with the use of electronic integration. Heart rate was determined by electrocardiographic recordings and systemic blood pressures were determined by the standard cuff method. Cardiac output was determined by thermodilution and systemic blood pressures were calculated using standard formulas (10).

Drug protocol. Baseline hemodynamic values were measured at least 24 hours after the insertion of the pulmonary artery catheter. Hemodynamic stability (<10% variation) in heart rate, blood pressure, mean pulmonary artery wedge pressure and cardiac output was ensured for at least 1 hour by two or more hemodynamic measurements before the initiation of therapy. Hemodynamic values determined at the last measurement were used as baseline values. A transdermal nitroglycerin system, 30 cm² (Transderm-Nitro, Ciba-Geigy), was used in this study; this system is claimed by the manufacturer to release 15 mg of nitroglycerin over a 24 hour period (11). Because our previous experience demonstrated a lack of significant hemodynamic response to 30 to 60 (12) and 90 mg (8) in most patients with severe heart failure, eight 30 mg patches were applied to the chest wall of each patient in this study to provide the release of 120 mg of nitroglycerin per 24 hours. Hemodynamic measurements were repeated 1, 2 and 4 hours after the application of transdermal nitroglycerin. In 11 patients who demonstrated hemodynamic response (>20% reduction in mean pulmonary artery wedge pressure lasting >2 hours), measurements were repeated every 2 hours for 24 hours. At that time, the nitroglycerin patches were removed and replaced by the same number of fresh transdermal systems. Hemodynamic measurements were repeated every 2 hours for 8 hours after the application of the second dose. At that point, the nitroglycerin patches were removed and hemodynamic measurements were repeated in 10 of the patients 1 and 2 hours after discontinuation of therapy.

Statistical analysis. One way repeated measures analysis of variance (ANOVA) and the Newman-Keuls test (13) were used to evaluate the temporal hemodynamic effects of 120 mg of transdermal nitroglycerin. Single comparisons were performed with Student’s t test for paired values. Analyses were performed using 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 probability (p) value of <0.05 was considered statistically significant.

Results

Effect of first dose 120 mg transdermal nitroglycerin. Heart rate, mean blood pressure, cardiac index and systemic and pulmonary vascular resistance demonstrated no significant change throughout the 24 hours after the first nitroglycerin dose (Fig. 1). A significant reduction was noted in mean right atrial pressure after the application of nitroglycerin (Fig. 2). This value fell from 10 ± 4 at baseline to 6 ± 4 mm Hg at 4 hours (p < 0.05) and remained significantly lower than the control value for 14 hours after nitroglycerin administration. Mean pulmonary artery pressure was 38 ± 7 mm Hg at baseline and demonstrated a significant reduction to 31 ± 8 mm Hg at 1 hour, with maximal reduction at 8 hours (26 ± 7 mm Hg). After 8 hours, mean pulmonary pressure increased gradually but remained significantly lower than the control value at 24 hours after initiation of therapy (31 ± 6 mm Hg). Mean pulmonary artery wedge pressure demonstrated a similar response to transdermal nitroglycerin. The initiation of therapy resulted in a significant decrease from 26 ± 6 to 19 ± 5 mm Hg at 1 hour with peak effect at 8 hours (15 ± 6 mm Hg). The reduction of this
variable persisted for the entire 24 hours (19 ± 7 mm Hg, p < 0.05).

Comparison between hemodynamic effect during the first 8 hours after the administration of the first and the second doses of transdermal nitroglycerin (Fig. 3 and 4). A comparison of the hemodynamic values at 2, 4, 6 and 8 hours after the administration of both nitroglycerin doses demonstrated no significant difference in heart rate, mean blood pressure, cardiac index and systemic and pulmonary vascular resistances. Mean right atrial pressure was significantly higher (p < 0.05) after the second than after the first nitroglycerin dose at 2 hours (9 ± 5 versus 7 ± 4 mm Hg), 4 hours (8 ± 5 versus 6 ± 4 mm Hg) and 8 hours (8 ± 5 versus 6 ± 3 mm Hg). At 6 hours the difference between the two values was not statistically significant (9 ± 6 versus 6 ± 3 mm Hg). Both mean pulmonary artery and mean pulmonary artery wedge pressures were significantly higher after the second than after the first dose of nitroglycerin. The respective values for mean pulmonary artery pressure were 32 ± 8 versus 28 ± 7 mm Hg at 2 hours (p < 0.05), 32 ± 7 versus 27 ± 7 mm Hg at 4 hours (p < 0.01), 33 ± 10 versus 27 ± 6 mm Hg at 6 hours (p < 0.05) and 31 ± 8 versus 26 ± 7 mm Hg at 8 hours (p < 0.05). Mean pulmonary artery wedge pressures showed similar differences: 22 ± 7 versus 17 ± 7 mm Hg at 2 hours (p < 0.01), 21 ± 8 versus 16 ± 6 mm Hg at 4 hours (p < 0.01), 19 ± 8 versus 16 ± 7 mm Hg at 6 hours (p < 0.05) and 20 ± 9 versus 15 ± 6 mm Hg at 8 hours (p < 0.01).

Figure 3 demonstrates changes from control in right atrial, pulmonary artery and pulmonary artery wedge pressures after the administration of the two nitroglycerin doses given 24 hours apart. The reduction in mean right atrial pressure at 2, 4 and 8 hours was significantly larger after the first dose than after the second dose. The reduction in both mean pulmonary artery and mean pulmonary artery wedge pressures was significantly and progressively larger at each measured interval after the first nitroglycerin dose. The individual values for mean pulmonary artery wedge pressure as measured in all 11 patients after the first and second nitroglycerin doses are demonstrated in Figure 4. Complete attenuation of initial effect was seen in three patients (Patients 3, 9 and 11). Partial attenuation was seen in five patients (Patients 4, 5, 7, 8 and 10). Patients 1, 2 and 6 demonstrated a persistent effect after the second dose.

Hemodynamic effect of abrupt discontinuation of nitroglycerin therapy. Figure 5 shows mean hemodynamic values as measured at baseline, at 32 hours of continuous nitroglycerin administration and then 1 and 2 hours after

![Figure 2. Sequential values in 11 patients of mean right atrial pressure (RA), mean pulmonary artery (MPA) and mean pulmonary artery wedge (PAW) pressures as measured at baseline (C) and after the first (solid lines) and second (broken lines) doses of 120 mg transdermal nitroglycerin. Shaded areas represent difference from control values. * p < 0.05.](image)
removal of the patches in 10 patients. Mean pulmonary artery and wedge pressures at 32 hours of nitroglycerin therapy were still significantly lower than baseline values. Abrupt discontinuation of nitroglycerin administration resulted in return of these variables to baseline values. No hemodynamic value recorded after discontinuation of therapy was statistically different from baseline values, demonstrating no demodynamic rebound.

Discussion

Early attenuation of nitroglycerin effect. Attenuation of early hemodynamic action has been a limiting factor in the use of vasodilator drugs for short- and long-term treatment of heart failure (14–16). In contrast to other vasodilator agents, the use of oral nitrates has been reported (2) to result in a persistent hemodynamic effect without tolerance in patients with chronic congestive heart failure. However, oral administration of nitrates has certain limitations, including a relatively short duration of action and sharp peaks and valleys of blood levels, resulting in a need for frequent drug dosing and a potential for great fluctuations in the degree of effectiveness and safety during the dosage interval. The recent attempt (11) to use the transdermal route for administration of nitroglycerin has demonstrated the ability to attain a relatively constant blood level of nitroglycerin for at least 24 hours. Our results, however, demonstrate that a significant attenuation of initial hemodynamic improvement occurs within the first day of therapy with large dose transdermal nitroglycerin. The reduction in pulmonary pressure and right and left ventricular filling pressures that started within 60 minutes of first dose nitroglycerin administration demonstrated a gradual attenuation after reaching a peak at 4 to 8 hours of therapy. The administration of a second dose 24 hours after initiation of therapy resulted in either no response or a significantly attenuated response in most patients when compared with the effect of the initial nitroglycerin dose. A similar attenuation of transcutaneous nitroglycerin effect was recently demonstrated by other investigators, (6,7) and by us (8) using lower doses of the drug. Our study extends previous findings and demonstrates that the early diminution of hemodynamic effects of nitroglycerin cannot be fully restored with repeat administration of the same dose of the drug and therefore is not likely to
be related to a decline in plasma level due to an insufficient drug dose. This is supported by the work of Jordan et al. (17), who recently documented persistence of the plasma concentration of nitroglycerin for 24 hours after application of 60 mg/24 h dosage of the drug in patients with heart failure.

Our findings are based on the assumption that baseline hemodynamics before the administration of the second nitroglycerin dose at 24 hours of therapy were comparable in our patients with those measured before initiation of the study. Because our study was designed to test the hypothesis that steady state nitrate levels were associated with early development of tolerance, a discontinuation of nitrate therapy to reestablish baseline hemodynamics could potentially prevent the development of tolerance, and was therefore not performed. However, the relative stability of hemodynamics in the same patient population using a similar protocol over a period of 24 hours has been previously demonstrated (7,18).

In a recent randomized crossover comparison of hemodynamic effects of hydralazine and nifedipine in patients with severe chronic heart failure, we (18) found comparable hemodynamic data before the administration of both drugs given approximately 24 hours apart. Jordan et al. (7), who evaluated the hemodynamic response to transdermal nitroglycerin in comparison with placebo in a similar patient population, found no statistically significant change in any hemodynamic variable over 24 hours in patients treated with placebo. In addition, hemodynamic measurements after discontinuation of continuous nitroglycerin therapy in our patients revealed values comparable with those obtained at baseline before the initiation of therapy, indicating baseline hemodynamic stability (Fig. 5).

Mechanisms of development of tolerance to nitroglycerin. The exact mechanism responsible for early reduction in efficacy of vasodilator drugs is not entirely clear; however, cardiocirculatory tolerance to the vasoactivity of these drugs seems to be a highly likely explanation. The issue of tolerance development to circulatory effects of nitrates is not new and was first noted in animal studies (19,20).

Clinical studies (21,22) in patients with angina pectoris have resulted in conflicting information; however, there is a large body of recent data (22–27) supporting a development of tolerance to hemodynamic as well as to anti-ischemic effects of nitrates after continuous administration in patients with angina pectoris. Although only limited information is available regarding long-term therapy in patients with heart failure, it seems that a long-term clinical effect is maintained. Franciosa and Cohn (2) reported persistence of hemodynamic effects of isosorbide dinitrate for 3 months without the development of tolerance. Leier et al. (3) demonstrated persistent improvement in exercise capacity and in pulmonary capillary wedge pressure, pulmonary artery pressure and pulmonary vascular resistance. These investigators, however, found the development of tolerance to the effect of the drug on both systemic vascular resistance and arterial blood pressure. On the basis of these findings, a preferential tolerance to the systemic arterial effect without attenuation of the venous and pulmonary vascular effects of nitrates was suggested when these drugs were used as therapy for congestive heart failure.

Figure 5. Group values in 11 patients for heart rate (HR), mean blood pressure (MBP), mean right atrial pressure (RA), mean pulmonary artery wedge pressure (PAW), mean pulmonary artery pressure (MPA) and systemic vascular resistance (SVR) at baseline before initiation of nitroglycerin therapy (C), at 32 hours of continuous nitroglycerin administration (32 HR) and 1 hour (1 HR P) and 2 hours (2 HR P) after abrupt discontinuation of nitroglycerin. There is no evidence of a hemodynamic rebound phenomenon.
(23–30). These clinical findings have been in accordance with experimental studies that demonstrated the development of tolerance to the vasorelaxing effect of nitroglycerin after continuous exposure to the drug. The tolerance to nitroglycerin has been suggested (20) to be due to conversion of sulphydryl groups found in nitroglycerin receptors in vascular smooth muscle to disulfides which demonstrate lower affinity for nitrates.

Activation of vasoconstrictor mechanisms resulting from stimulation of the sympathetic nervous system and renin-angiotensin system has been suggested (15) to offset vasodilatory effects and thus to cause tolerance to vasodilator therapy. This speculative mechanism of action has been supported by a significant hemodynamic rebound reported with discontinuation of vasodilators including nitrates (31,32). Our experience with the use of high dose transdermal nitroglycerin in patients with heart failure in the present study and in previous studies (8,12) has demonstrated an absence of rebound hemodynamic response after removal of nitroglycerin systems in the majority of the patients. This finding, in addition to a lack of change in plasma catecholamine level or renin concentration during transdermal nitroglycerin therapy (8,32), suggests that counterregulatory arterial vasconstriction is an unlikely mechanism for the observed attenuation of nitroglycerin-mediated vasodilation in most patients with chronic congestive heart failure.

Our data demonstrate continued attenuated effect on both the pulmonary artery and left ventricular filling pressures in spite of the tolerance to transdermal nitroglycerin. These findings contradict previous findings by others (7) and by us (8) demonstrating only short-lasting hemodynamic effects with transdermal nitroglycerin in patients with heart failure. This contradiction is probably due to the very large doses used in our study and to the fact that only data in patients who demonstrated an initial response (“responders”) were reported. Although there is attenuation of effect, the actual level of the wedge pressure for the duration of our study represents a positive response and could be beneficial to patients responding to the drug. Further studies are necessary to assess the long-term effect of high dose transdermal nitroglycerin and the effect of nitrate-free intervals on the restoration of nitroglycerin action in patients with chronic heart failure.

Conclusion. This study demonstrates that in patients with chronic severe heart failure who respond to high dose transdermal nitroglycerin (120 mg), there is a rapid and significant reduction in pulmonary pressures and in right and left ventricular filling pressures after initiation of therapy. However, a substantial attenuation of this response occurs several hours after application of the first nitroglycerin dose and cannot be reversed by administration of a second dose. These findings suggest early development of tolerance to the vasodilatory effect of transdermal nitroglycerin in most patients with severe chronic heart failure and demonstrate a limitation of sustained, continuous therapy with nitroglycerin for patients with chronic heart failure.

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