Effect of Apparent Elimination Half-Life on Nitroglycerin-Induced Hemodynamic Rebound in Experimental Heart Failure

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Hemodynamic rebound after abrupt withdrawal may be an important consideration associated with nitroglycerin (NTG) monotherapy. This phenomenon may arise from unopposed neurohormonal vasoconstriction because of rapid elimination of NTG. The role of NTG pharmacokinetics in the development of hemodynamic rebound was examined using a rat model of congestive heart failure. NTG was infused for 90 min, then the dose was either abruptly stopped ($n = 8$) or gradually reduced by 20% every 20 min ($n = 7$). Abrupt withdrawal caused rebound elevations of left ventricular end-diastolic pressure (LVEDP) to about 25% above baseline values, at 30–60 min after drug termination ($P < 0.01$), but this was completely avoided by graded NTG withdrawal. A positive correlation was observed ($P < 0.05$) between the percentage reduction in LVEDP during infusion and the maximum percentage rebound in rats after abrupt withdrawal but not after graded withdrawal. These results suggest that NTG-induced hemodynamic rebound is related to its short biological half-life and that this phenomenon is consistent with a mechanism of neurohormonal compensation.

KEY WORDS: nitroglycerin; congestive heart failure; hemodynamic rebound.

INTRODUCTION

Organic nitrate vasodilators, such as nitroglycerin (NTG) and isosorbide dinitrate, are useful for the treatment of angina and congestive heart failure (CHF). Their predominant venodilating effects, relative safety and the convenience of transdermal dosage forms have made nitrate therapy popular (1,2), but the long-term efficacy of these drugs has been questioned because of the development of pharmacologic tolerance (3–5). Nitrate tolerance is a well-recognized clinical problem which is not completely understood, and methods to avoid tolerance have not been entirely successful. Intermittent NTG administration (i.e., 12 hr "on," 12 hr "off") has been proposed as a method to reduce or avoid tolerance development (6), but this approach is not ideal since the patient is left untreated during much of the "dose-off" period.

Another important, yet less studied, problem in nitrate therapy is the occurrence of rebound events after abrupt drug withdrawal (6). Rebound decreases in cardiac index, increases in blood pressure, and elevations in pulmonary and systemic vascular resistances have all been observed in CHF patients after abruptly stopping NTG (4,7,8). Similarly, intermittent NTG monotherapy for the treatment of angina has been shown to increase the incidence of ischemic episodes during the "dose-off" phase (9). Therefore, while intermittent nitrate therapy may be advantageous in avoiding tolerance development, it may (in some circumstances) precipitate rebound and be hazardous to the patient. A better understanding of the factors involved in nitrate rebound may provide a rational approach for avoiding this phenomenon.

Although the mechanism of NTG rebound has not been clearly defined, it has been proposed that abrupt withdrawal results in unopposed neurohormonal vasoconstriction (7,10). According to this hypothesis, the rapid disappearance of NTG-induced vasodilation after abrupt withdrawal may be an important factor in controlling the magnitude and time course of hemodynamic rebound. If this hypothesis is valid, then a more gradual reduction in NTG plasma concentrations may lead to some reduction or total avoidance of rebound. In this study, we tested this hypothesis using an established rat model of CHF, which we have shown to mimic the behavior of CHF patients toward NTG hemodynamic response and tolerance (11–13). The experimental protocol involved an examination of left ventricular hemodynamic effects of NTG during and after an intravenous infusion, which was stopped either abruptly or gradually over a period of 80 min.

MATERIALS AND METHODS

Animal Model

Congestive heart failure was produced in rats secondary to ligation of the left coronary artery and myocardial infarct development, as described previously (11). After at least 6 weeks, polyethylene catheters were implanted in the femoral vein for drug infusion and in the left ventricle (via the right carotid artery) for the recording of left ventricular pressure tracings (12,13). Left ventricular peak-systolic pressure (LVPSP), left ventricular end-diastolic pressure (LVEDP), and heart rate (HR) were measured. LVEDP is typically elevated in CHF rats compared to control rats, and this elevation is related to the size of the left ventricular infarct produced (12). Cardiac output and LVPSP are reduced and vascular resistence is elevated in this animal model as well (14). All experiments were conducted 1 day after implantation of catheters, and infusions were initiated between 8 AM and 10 AM. Baseline hemodynamics were measured at least three times over 30–60 min prior to NTG infusion. Previous studies have shown that left ventricular pressures are stable typically for 2 days in this animal preparation, and infusion of vehicle (5% dextrose solution) has no hemodynamic effect (11).

Infusion Experiments

CHF rats were infused at 10, 15, or 18 μg/min NTG in an attempt to produce significant and varied initial reductions in LVEDP. Infusions were maintained for 90 min, after which NTG was either abruptly stopped or the infusion rate was changed by 20% decrements every 20 min. Hemodynamic parameters were measured every 30 min during the initial

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infusion, then every 10 min after the abrupt stop for 80 min. Measurements were also made every 10 min throughout the period of graded withdrawal and for 80 min after termination of the infusion.

Five of the 13 CHF rats studied were available for both treatments, which were given on consecutive days, with a washout period greater than 15 hr. Three rats received the abrupt withdrawal treatment first, while two animals received NTG in the opposite order. Previous studies in CHF rats have shown that a 12-hr washout is adequate to regain complete responsiveness to NTG (11). The limited number of animals crossed over in this study was due to failure of left ventricular catheter to provide high-quality pressure tracings on day 2 or death during the washout phase, presumably due to overt heart failure.

Data Analysis

Comparison of the maximal values during the postinfusion period against baseline was made via paired t tests. Otherwise, evaluation of other hemodynamic effects was performed using one-way analysis of variance (ANOVA), followed by Duncan's multiple-range test (15). Statistically significant differences were assigned at $P < 0.05$. The power of the ANOVA analyses was estimated to be 0.99 and 0.76 for the abrupt NTG withdrawal regimen (during infusion and after abrupt withdrawal, respectively) and 0.95 and 0.46 for graded withdrawal. The magnitude of maximal rebound in LVEDP was tested for possible relation to initial hemodynamic effects during NTG infusion by bivariate correlation analysis (15).

RESULTS

Figure 1 shows data from a representative CHF rat which received both abrupt and graded NTG withdrawal on two occasions, separated by a 15-hr washout. Shown also are the 95% confidence intervals for baseline values, based on values observed during the 2 days of experimentation. Initial infusion of NTG (15 μg/min for 90 min) produced pronounced reductions in LVEDP with only slight effects on LVPSP. Stopping the NTG infusion abruptly caused LVEDP to rise above baseline, peaking at 30–40 min and subsequently returning to baseline. A slight rise in LVPSP was also observed. No significant changes in HR were observed either during or after NTG infusion (data not shown). Despite similar initial hemodynamic effects in this animal, graded withdrawal of NTG dramatically reduced the rebound response in LVEDP observed after abrupt cessation of NTG.

Figure 2 shows the mean hemodynamic data of all CHF rats in which at least a 15% initial reduction in LVEDP was achieved over the initial 90-min infusion (abrupt withdrawal, $n = 8$; graded withdrawal, $n = 7$). Baseline hemodynamic parameters did not differ between these two groups prior to infusion (LVPSP113 ± 3 mm Hg abrupt vs 115 ± 3 mm Hg graded; LVEDP21 ± 2 mm Hg vs 23 ± 3 mm Hg; HR378 ± 11 vs 365 ± 14 beats/min). Similar initial reductions in

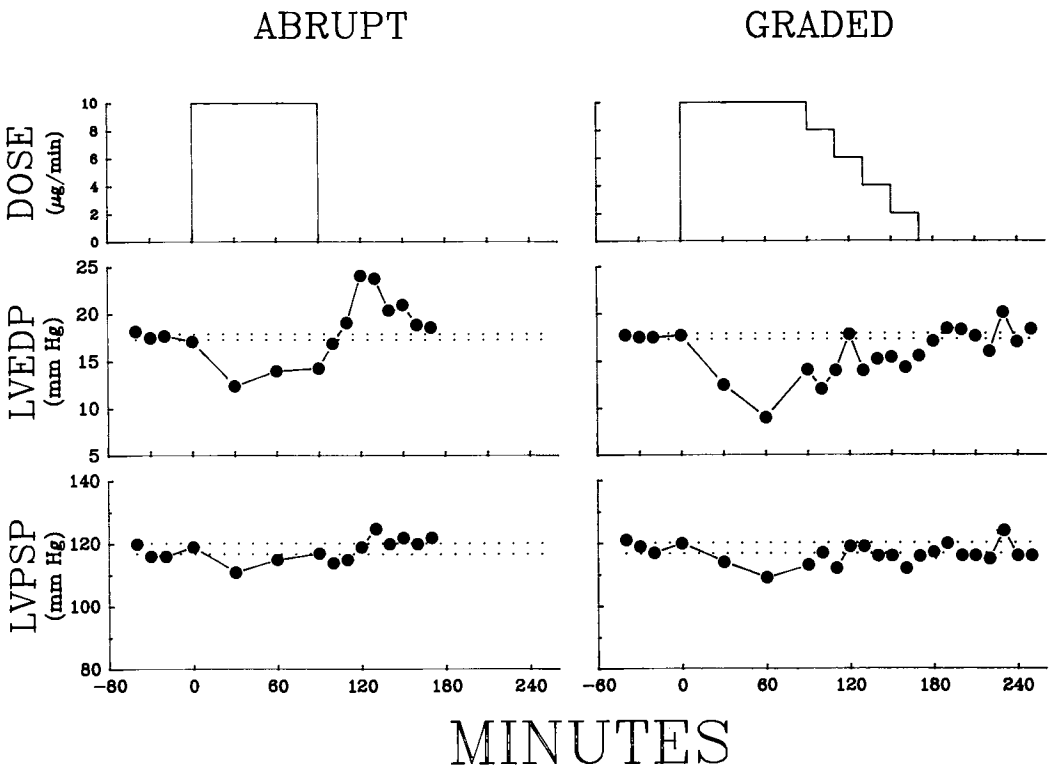

Fig. 1. Hemodynamic data from a representative CHF rat which received both abrupt and graded NTG withdrawal on separate occasions, separated by a 15-hr washout. The infusion dosing regimens (μg/min) employed are depicted in the top panels; left ventricular end-diastolic pressure (LVEDP) and left ventricular peak-systolic pressure (LVPSP) are presented as mm Hg. The dotted lines encompass the 95% confidence interval of the baseline hemodynamic values determined on both days.

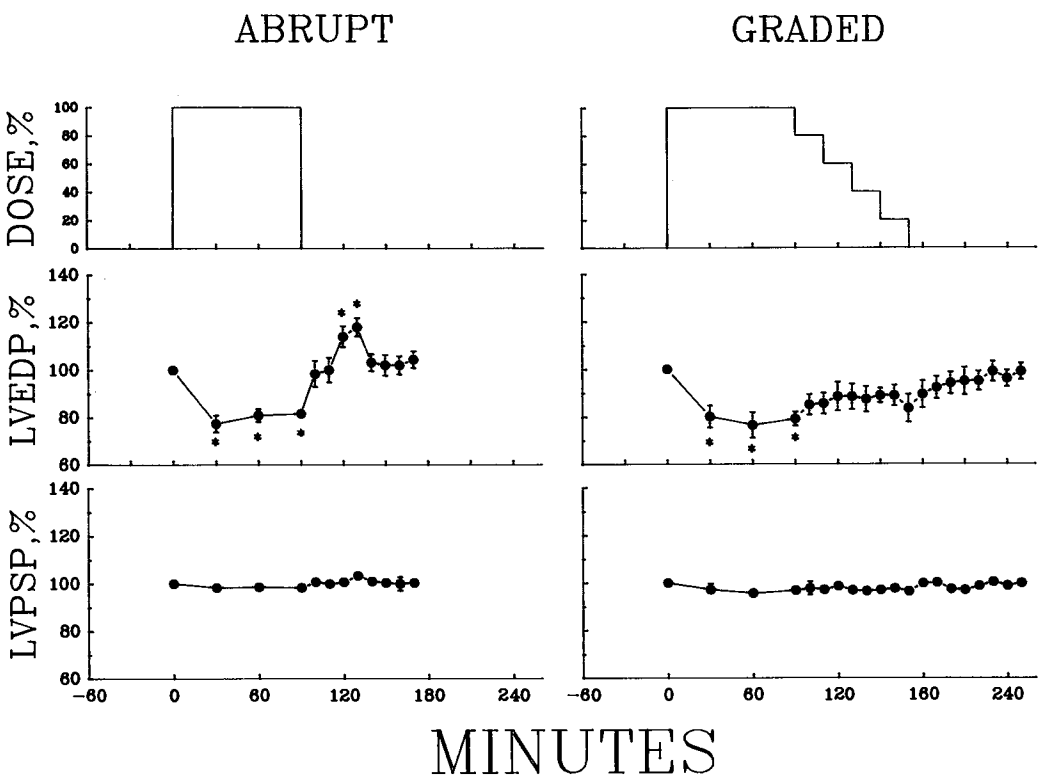

Fig. 2. Mean hemodynamic (±SE) data of CHF rats receiving abrupt or graded NTG withdrawal (abrupt, n = 8; graded, n = 7). Hemodynamic parameters are presented as percentages of initial baseline values. (*) $p < 0.05$.

LVEDP were achieved in both groups. After abrupt withdrawal of NTG, mean values of LVEDP rose significantly ($p < 0.05$) above baseline 30 and 40 min after stopping the infusion and returned to baseline within 60–80 min. These changes, expressed as the mean LVEDP increase, were blunted in magnitude because hemodynamic rebound for individual animals peaked at different times, ranging from 20 to 40 min postinfusion. In comparison, graded withdrawal of NTG did not produce any observable rebound rise in LVEDP. LVPSP (Fig. 2) and HR (data not shown) were not significantly changed for either infusion regimen during the course of the experiment.

Since the peak hemodynamic changes did not coincide in all animals, the maximal rebound values of left ventricular hemodynamics after abrupt and graded withdrawal were compared to baseline (Fig. 3). Rebound elevations of LVEDP were observed in all animals after abruptly stopping the NTG infusion, whereas no statistically significant change in LVPSP was observed. Graded withdrawal of NTG did not produce any rebound increase in LVEDP during the 80-min postinfusion period. Maximal LVPSP during postinfusion was also not statistically different from initial control. For the five rats in which both withdrawal regimens were carried out, a significant difference between peak rebound LVEDP values was observed (125 ± 3.2 vs 103 ± 5.1% of initial baseline, abrupt vs graded withdrawal, respectively, $p < 0.05$), while there was no significant difference between peak LVPSP values (104 ± 1.4 vs 103 ± 2.0% of initial baseline, NS).

Figure 4 shows the relationship between initial percentage reduction of LVEDP during NTG infusion (average of three measurements over 90 min) and maximal elevation of LVEDP above baseline in individual rats after abrupt or graded withdrawal. Results from all rats examined in this study (i.e., including poor responders) were used in this plot. A significant linear correlation was observed for the abrupt

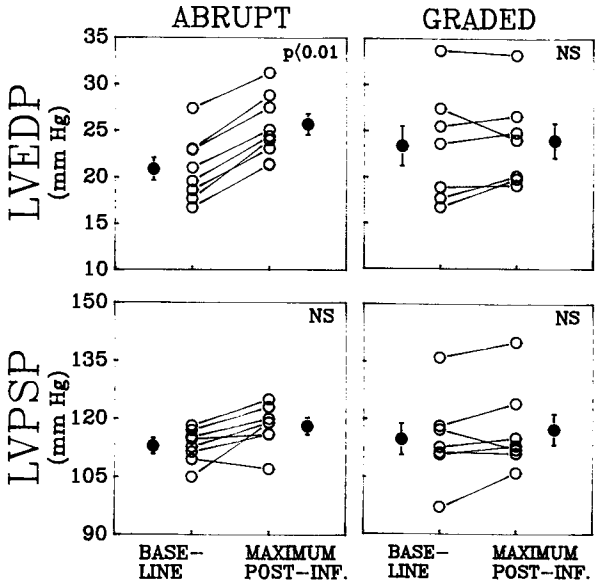

Fig. 3. Maximal change in left ventricular pressures (mm Hg) in CHF rats after abrupt and graded NTG withdrawal. Open circles denote individual animals; filled circles are mean data ± SE.

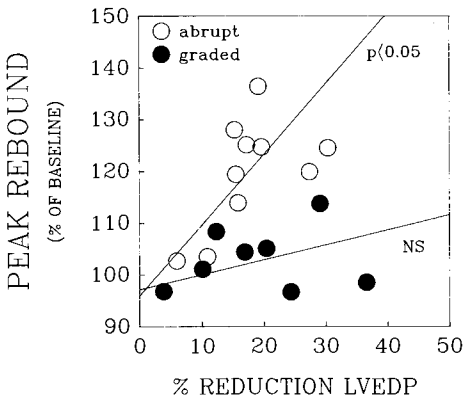

Fig. 4. Relationship between hemodynamic effect achieved during NTG infusion and maximal elevation in LVEDP after abrupt or graded drug withdrawal in CHF rats.

withdrawal group ($r = 0.635$, $p < 0.05$). In contrast, no correlation was observed following graded NTG withdrawal ($r = -0.08$, NS).

DISCUSSION

Abrupt NTG withdrawal has been associated with rebound clinical events in both CHF and angina therapy. In two separate studies, Olivari *et al.* (7) and Packer *et al.* (8) have shown that abrupt cessation of transdermal NTG in CHF patients produced rebound decreases in cardiac index and increases in mean arterial pressure and systemic, pulmonary, and forearm vascular resistences. In a recent study examining intermittent versus continuous NTG monotherapy for stable angina, Ferratini *et al.* (9) found that during a 15-day period, a total of 11 night angina attacks occurred in 6 of the 10 patients during the NTG-free interval, and most of these occurred within the first 3 hr. No angina attacks occurred during continuous NTG or during the "NTG-on" interval.

The existence of nitrate rebound as a result of withdrawal is not a new finding. It was first observed in munitions workers who were exposed to nitrates for long periods (16,17). Reports of "nitrate dependence" in these workers and the occurrence of several deaths attributed to NTG withdrawal in otherwise healthy individuals underscore the potentially dangerous situation of nitrate rebound (18,19). While the mechanism of nitrate rebound is not entirely clear, it has been suggested that it is the result of unopposed neurohormonal vasoconstriction (7,10). The pharmacodynamic implications of this likely hypothesis point toward several important factors which may determine the incidence and magnitude of rebound. These factors include the degree of neurohormonal activation developed during drug administration, the rate of disappearance of drug after cessation (i.e., plasma half-life), the rate of decline of vasoconstrictive substance(s), and the concentration–effect relationships of both the vasodilator and the vasoconstrictor(s) (i.e., their potencies to cause vascular effects). The relative roles of these factors in the development of nitrate-induced hemodynamic rebound have not been previously investigated. In this study, we have selectively examined the role of the short biological half-life of NTG [which has been observed in both rats (20) and humans (21)] in the development of rebound, using an established rat model of CHF as our study tool.

Results of this study showed that NTG infusion produced significant reductions in LVEDP, with little or no effect on LVPSP or HR. This observation is consistent with the predominant venous action of NTG and has been observed previously in this model (11,12). Although the doses used here were quite high (approximately 17–32 μg/kg/min), the hemodynamic effects achieved are similar to those observed in CHF patients [namely, 10–50% reductions in LVEDP, as shown by Elkayam *et al.* (22)]. Therefore, the difference in dose is likely to be due to interspecies differences in nitrate sensitivity.

Our results also showed a significant positive correlation between the initial hemodynamic effect during NTG infusion and the maximal extent of rebound after abrupt withdrawal. This relationship is consistent with the "neurohormonal constriction" hypothesis of nitrate rebound and suggests that the compensatory drive developed during infusion is a function of the magnitude of the hemodynamic effect achieved. Although the relationship between NTG-induced rebound and NTG tolerance development was not investigated here, the fact that rebound occurred after a short-term (2-hr) infusion of NTG suggests that neurohormonal activation occurs during drug administration, even when hemodynamic tolerance is not yet readily apparent.

When NTG was withdrawn gradually, the initial hemodynamic effect did not relate to the degree of rebound observed. This result suggests that during the stepwise reductions in NTG infusion (i.e., increasing the effective plasma half-life of NTG), the degree of neurohormonal activation might also be gradually reduced. Thus, a longer vasodilator half-life may allow adequate time for neurohormonal compensatory mechanisms to reset gradually and prevent the appearance of rebound during drug withdrawal. Further investigation of the role of vasodilator pharmacokinetics in the development of hemodynamic rebound appears to be warranted.

In conclusion, we have found the CHF rat to be a useful model for the study of NTG-induced hemodynamic rebound. Since graded NTG withdrawal avoided rebound, the short biologic half-life of NTG appears to be an important determinant in rebound development. This phenomenon may be important when considering implementation of the intermittent dosing strategy to avoid nitrate tolerance, particularly during monotherapy, in which abrupt NTG withdrawal is instituted daily. These results also suggest that nitrates with longer elimination half-lives, e.g., isosorbide dinitrate, may cause less hemodynamic rebound upon abrupt drug withdrawal. Similarly, transdermal nitroglycerin patches which provide a gradual drug decline during intermittent therapy may also be beneficial in reducing the incidence or severity of hemodynamic rebound. The benefits of these approaches in clinical nitrate therapy, however, remain to be established in man.

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