

Prevention of Tolerance to Hemodynamic Effects of Nitrates With Concomitant Use of Hydralazine in Patients With Chronic Heart Failure

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Objectives. This study was designed to determine the effect of oral hydralazine on the development of nitrate tolerance in patients with chronic congestive heart failure.

Background. Early development of nitrate tolerance with either continuous administration of intravenous or topical nitrate preparations or frequent dosing of oral nitrates leads to significant attenuation of nitrate-mediated hemodynamic and anti-ischemic effects. In recent animal experiments, prevention of nitroglycerin-induced hemodynamic tolerance with a concomitant use of hydralazine was demonstrated. This finding may have important clinical relevance.

Methods. Twenty-eight patients with chronic heart failure due to left ventricular systolic dysfunction were randomized to receive either a continuous infusion (24 h) of nitroglycerin alone (group I, 14 patients) or concomitantly with oral hydralazine (75 mg four times a day [group II, 14 patients]). The effect of nitroglycerin in each group was evaluated by analysis of variance for repeated measures. The power of the analysis to detect a 5.4-mm Hg (20%) change in mean pulmonary artery wedge pressure was 90%.

Results. Baseline hemodynamic variables as well as the initial hemodynamic response to nitroglycerin were comparable in both

groups. Compared with the initial response to nitroglycerin, a significant attenuation of effect was found in group I at 24 h in mean (\pm SE) pulmonary artery pressure ($27 \pm 4\%$ vs. $10 \pm 3\%$, $p < 0.05$) and mean pulmonary artery wedge pressure ($40 \pm 4\%$ vs. $16 \pm 4\%$, $p < 0.05$). In group II, conversely, oral hydralazine prevented nitroglycerin-induced hemodynamic tolerance and resulted in a persistent effect on mean pulmonary artery and wedge pressures throughout the study period ($31 \pm 3\%$ vs. $27 \pm 4\%$, $p = 0.13$ and $37 \pm 4\%$ vs. $34 \pm 6\%$, $p = 0.40$, respectively). In addition, the initial effect on blood pressure was attenuated at 24 h in group I ($5 \pm 2\%$ vs. $12 \pm 3\%$, $p < 0.05$) but not in group II ($15 \pm 3\%$ vs. $17 \pm 2\%$, $p = 0.46$).

Conclusions. In patients with chronic heart failure due to left ventricular systolic dysfunction, the concomitant use of oral hydralazine prevents early development of nitrate tolerance and results in a persistent nitrate-mediated hemodynamic effect on systemic and pulmonary artery and left ventricular filling pressures. These data may support the concurrent use of hydralazine in patients with heart failure treated with organic nitrates.

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Organic nitrates have been widely used in the treatment of ischemic heart disease and congestive heart failure (1,2). However, the development of early tolerance to the vasodilatory effects of these drugs has substantially limited their therapeutic efficacy (3). The exact mechanism of nitrate tolerance has remained poorly understood (4). It is therefore not surprising that various strategies proposed for prevention of nitrate tolerance, including concomitant administration of sulfhydryl groups (5), angiotensin-converting enzyme inhibitors (6) or diuretic drugs (3,7), have not proved beneficial in patients with heart failure. Although intermittent nitrate therapy, which allows a daily nitrate

washout interval, has been effective in the prevention of nitrate tolerance, this regimen is limited by its inability to provide a continuous and uninterrupted therapeutic effect (7). In a recent study, Bauer and Fung (8) demonstrated prevention of nitrate tolerance with concurrent administration of hydralazine in a rat model of congestive heart failure. Although the combination of nitrates and hydralazine has been shown (9,10) to result in beneficial clinical effects in patients with heart failure, there is no information available regarding the potential effect of hydralazine on nitrate tolerance in humans. Therefore, the present study proposed to evaluate the effect of concomitant use of oral hydralazine on the early development of nitrate tolerance in patients with chronic heart failure.

Methods

Study patients. Patients with chronic heart failure due to left ventricular systolic dysfunction admitted to the Los Ange-

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les County/University of Southern California Medical Center for worsening symptoms were enrolled in the study after clinical stabilization.

Of 33 patients who entered the study, 28 demonstrated a hemodynamic response to intravenous nitroglycerin, completed the study and were included in the analysis (23 men, 5 women; mean [\pm SE] age 48 ± 1 years, range 24 to 68). Coronary artery disease was diagnosed in 5 patients, but the cause of heart failure was unknown in 23, 7 of whom had a history of hypertension, and 5 a history of excessive alcohol consumption. All patients were in New York Heart Association functional class III or IV on admission to the hospital and were in stable clinical and hemodynamic condition at the time of the study. The diagnosis of left ventricular systolic dysfunction was established in each patient by either contrast or radionuclide ventriculography (23 patients) or by echocardiography (5 patients). None of the patients had primary valvular disease or clinical evidence of myocardial ischemia at the time of the study.

Hemodynamic measurements and computations. Right heart catheterization was performed with a balloon-tipped, triple-lumen Swan-Ganz catheter. Right atrial, pulmonary artery and left ventricular filling pressures, determined indirectly from the mean pulmonary artery wedge pressure, were recorded using an Electronics for Medicine AR-6 recorder; mean pressures were obtained by electronic integration. Heart rate was determined from electrocardiographic recordings, and arterial blood pressure was measured by the standard cuff method. Cardiac output was determined by thermodilution, as previously described (11). Calculations of mean arterial blood pressure, cardiac index, and systemic and pulmonary vascular resistance were performed by standard formulas.

Study protocol. All patients were in stable clinical and hemodynamic condition. Vasodilators, other than hydralazine, were withheld for at least 24 h before the initiation of the study, but the usual doses of digitalis and diuretic drugs were continued throughout the study. Patients randomized to oral hydralazine therapy received 75 mg four times daily, with the first dose given at least 24 h before the study. To allow for any spontaneous hemodynamic changes (12) pulmonary artery catheters were inserted at least 16 h before the start of the study. Hemodynamic stability ($<10\%$ variation in two consecutive measurements) was ensured before the initiation of the study by consecutive readings performed at ~ 30 -min intervals. Values obtained at the last measurement were used as baseline values. Baseline hemodynamic measurements in the hydralazine group were initiated ~ 3 h after administration of the last hydralazine dose (6 AM).

After obtaining baseline measurements, an intravenous infusion of nitroglycerin regulated by an infusion pump (IVAC 530) was started at a rate of $20 \mu\text{g}/\text{min}$ through special nitroglycerin polyethylene tubing. The rate of infusion was then increased in increments of 20 to $60 \mu\text{g}/\text{min}$ every 5 min to achieve at least a 30% reduction in mean pulmonary artery wedge pressure or until a maximal dose of $560 \mu\text{g}/\text{min}$ was reached. In patients who did not respond to the maximal dose

Table 1. Baseline Variables in the Two Study Groups*

	Group I (NTG [n = 14])	Group II (NTG + HYD [n = 14])
Age (yr)	48 ± 1	48 ± 1
NTG dose ($\mu\text{g}/\text{min}$)	215 ± 50	185 ± 33
EF (%)	22 ± 1	23 ± 1
HR (beats/min)	94 ± 4	93 ± 5
CI (liters/min per m^2)	2.1 ± 0.3	2.3 ± 0.2
RA (mm Hg)	13 ± 2	12 ± 2
PA (mm Hg)	38 ± 3	42 ± 3
PAWP (mm Hg)	27 ± 2	27 ± 2
SVR ($\text{dynes}\cdot\text{s}\cdot\text{cm}^{-5}$)	$1,786 \pm 227$	$1,640 \pm 129$
PVR ($\text{dynes}\cdot\text{s}\cdot\text{cm}^{-5}$)	268 ± 53	318 ± 46

*No significant differences between groups for any variable. Data presented are mean value \pm SE. CI = cardiac index; EF = ejection fraction; HR = heart rate; HYD = hydralazine; NTG = nitroglycerin; PA = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RA = right atrial pressure; SVR = systemic vascular resistance.

of nitroglycerin, the infusion of the drug was discontinued, and these patients were excluded from the study. In those who responded to nitroglycerin, the dose required to achieve the desired hemodynamic response was maintained at the same rate for 24 h, and hemodynamic measurements were repeated at 1, 2, 4, 8, 12, 16, 20 and 24 h.

Statistical analysis. One-way repeated measures of analysis of variance and the Newman-Keuls test were used to evaluate the temporal hemodynamic effect of nitroglycerin in each group, as represented by the measured or calculated values throughout the study, or the difference in these values from baseline. Single comparisons were performed with the Student *t* test. 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. Results are expressed as mean value \pm SE; $p < 0.05$ was considered statistically significant. A previous study (3) in a similar group of patients treated with placebo for 24 h demonstrated spontaneous changes $<17\%$ in pulmonary artery wedge pressure. The power of analysis of variance to detect a 20% (5.4 mm Hg) change in pulmonary artery wedge pressure in the present study was $\sim 90\%$.

Results

Patients. Twenty-eight patients (14 in each group) demonstrated the desired hemodynamic response to nitroglycerin and completed the study. Table 1 compares the results in patients receiving nitroglycerin alone (group I) with those receiving nitroglycerin in combination with oral hydralazine (group II). No significant differences were found between the two groups for age (48 ± 1 years in both groups), left ventricular ejection fraction ($22 \pm 1\%$ in 11 group I patients, $23 \pm 1\%$ in 12 group II patients) or measured or calculated baseline hemodynamic values. The dose of nitroglycerin used to achieve the desirable

Table 2. Hemodynamic Variables at Baseline, at Peak Nitroglycerin Titration and During Nitroglycerin Administration in Patients Receiving Nitroglycerin Alone or Nitroglycerin in Combination With Oral Hydralazine

Time (h)	HR (beats/min)		BP (mm Hg)		RA (mm Hg)		PA (mm Hg)		PAWP (mm Hg)		CI (liters/min per m ²)		SVR (dynes·cm ⁻⁵)		PVR (dynes·cm ⁻⁵)	
	NTG	HYD	NTG	HYD	NTG	HYD	NTG	HYD	NTG	HYD	NTG	HYD	NTG	HYD	NTG	HYD
Baseline	94 ± 4	93 ± 5	84 ± 3	90 ± 4	13 ± 2	12 ± 2	38 ± 3	42 ± 3	27 ± 2	27 ± 2	2.1 ± 0.3	2.3 ± 0.2	1786 ± 227	1649 ± 129	267 ± 53	318 ± 46
0	94 ± 5	98 ± 7	73 ± 3*	75 ± 4*	9 ± 2*	7 ± 1*	28 ± 2*	28 ± 2*	17 ± 1*	17 ± 2*	2.5 ± 0.2*	2.8 ± 0.2*	1164 ± 96*	1188 ± 98*	192 ± 22*	182 ± 34*
1	92 ± 5	91 ± 6	70 ± 3*	72 ± 3*	9 ± 1*	6 ± 1*	28 ± 2*	28 ± 2*	18 ± 1*	17 ± 2*	2.7 ± 0.3*	2.9 ± 0.3*	1115 ± 113*	1160 ± 96*	173 ± 25*	206 ± 39*
2	92 ± 5	93 ± 4	70 ± 3*	71 ± 2*	9 ± 2*	6 ± 1*	27 ± 2*	28 ± 2*	19 ± 2*	16 ± 2*	2.6 ± 0.4*	3.0 ± 0.2*	1165 ± 125*	1089 ± 86*	151 ± 25*	186 ± 26*
4	94 ± 5	96 ± 4	73 ± 3*	74 ± 2*	9 ± 1*	6 ± 1*	28 ± 2*	28 ± 2*	20 ± 2*	17 ± 2*	2.5 ± 0.3*	2.8 ± 0.2*	1195 ± 108*	1174 ± 97*	157 ± 30*	186 ± 28*
8	95 ± 4	98 ± 6	78 ± 3*	79 ± 4*	10 ± 2*	8 ± 1*	32 ± 3*	32 ± 3*	21 ± 1*	17 ± 2*	2.7 ± 0.4*	2.9 ± 0.2*	1260 ± 139*	1169 ± 84*	195 ± 47*	177 ± 30*
12	94 ± 5	94 ± 5	76 ± 4*	76 ± 3*	10 ± 2*	7 ± 1*	30 ± 3*	28 ± 2*	21 ± 2*	16 ± 2*	2.7 ± 0.3*	2.7 ± 0.2*	1239 ± 160*	1269 ± 117*	152 ± 35*	203 ± 20*
16	94 ± 5	98 ± 6	73 ± 3*	72 ± 3*	10 ± 1*	7 ± 2*	32 ± 2*	31 ± 3*	22 ± 1*	18 ± 2*	2.5 ± 0.3*	2.9 ± 0.3*	1241 ± 140*	1091 ± 98*	189 ± 46*	201 ± 130*
20	94 ± 4	95 ± 4	76 ± 3*	76 ± 3*	11 ± 2*	7 ± 1*	32 ± 3*	30 ± 2*	22 ± 2*	17 ± 2*	2.5 ± 0.3*	3.0 ± 0.2*	1252 ± 134*	1102 ± 87*	183 ± 33*	195 ± 110*
24	96 ± 4	94 ± 5	80 ± 4*	75 ± 3*	10 ± 2*	7 ± 1*	34 ± 2*	30 ± 2*	23 ± 1*	18 ± 2*	2.7 ± 0.3*	2.8 ± 0.2*	1284 ± 152*	1159 ± 78*	187 ± 36*	202 ± 98*

*p < 0.05 versus baseline. †p < 0.05 versus 0 h. Data presented are mean value ± SE. BP = systemic blood pressure; 0 h = peak nitroglycerin (NTG) titration; other abbreviations as in Table 1.

reduction in mean pulmonary artery wedge pressure was 215 ± 50 μg/min in the nitroglycerin group and 185 ± 33 μg/min in the nitroglycerin plus hydralazine group; this difference was not statistically significant.

Hemodynamic changes over time. Titration of nitroglycerin dose to achieve a ≥30% reduction in mean pulmonary artery wedge pressure resulted in a significant decrease in mean right atrial and pulmonary and systemic arterial blood pressures and an increase in cardiac index. There was no significant change in heart rate (Table 2). Initial changes from baseline in all hemodynamic variables, as seen at peak nitroglycerin titration, were similar between the two groups and demonstrated no statistically significant difference. Analysis of hemodynamic changes over time revealed the following findings: mean right atrial pressure decreased by 39 ± 6% at peak nitroglycerin titration (from 13 ± 2 to 9 ± 2 mm Hg) in group I and by 46 ± 8% (from 12 ± 2 to 7 ± 1 mm Hg) in group II (p = 0.17). These hemodynamic changes persisted throughout the study in both groups without an indication for attenuation of effect (Table 2). At 24 h, mean right atrial pressure was reduced by 25 ± 7% in group I and by 25 ± 20% in group II (p = 0.98). The initial change in cardiac index was also preserved in both groups (Table 2). Cardiac index increased by 35 ± 10% in group I (from 2.1 ± 0.3 to 2.5 ± 0.2 liter/min per m²) and by 29 ± 13% in group II (from 2.3 ± 0.2 to 2.8 ± 0.2 liter/min per m²) at peak titration and remained augmented at 24 h (39 ± 10% and 26 ± 9%, respectively). Similarly, systemic and pulmonary vascular resistances were reduced by 25 ± 9% and 13 ± 9% (from 1,786 ± 227 to 1,164 ± 96 dynes·cm⁻⁵ and from 267 ± 53 to 192 ± 22 dynes·cm⁻⁵, respectively) in group I and by 25 ± 6% and 39 ± 80% (from 1,640 ± 129 to 1,188 ± 98 dynes·cm⁻⁵ and from 318 ± 46 to 182 ± 34 dynes·cm⁻⁵) in group II. These changes remained unattenuated at the end of the study.

Nitroglycerin titration resulted in a comparable mean arterial blood pressure reduction in both groups (Table 2), with a 12 ± 3% reduction in group I (from 84 ± 3 to 73 ± 3 mm Hg) and a 17 ± 2% reduction in group II (from 90 ± 4 to 75 ± 4 mm Hg). Unlike the persistent effect on right atrial pressure and cardiac index seen for the duration of the study, the effect on systemic blood pressure was progressively attenuated in group I during the study, with a difference of only 5 ± 2% in mean blood pressure from baseline at 24 h (Fig. 1). In contrast, the effect on mean blood pressure in group II remained unattenuated throughout the study, with a 15 ± 3% reduction still seen at 24 h (p < 0.05 vs. group I). A similar and statistically significant difference was found between the two groups in the persistence of initial changes in mean pulmonary artery and wedge pressures (Figs. 2 and 3). At peak nitroglycerin titration, mean pulmonary artery pressure (Fig. 2) demonstrated a similar reduction in both groups (27 ± 4% in group I [from 38 ± 3 to 28 ± 2 mm Hg], 31 ± 3% in group II [from 42 ± 3 to 28 ± 2 mm Hg]). Although the reduction in mean pulmonary artery pressure persisted for the duration of the study in group II (27 ± 4% at 24 h), the change in this hemodynamic variable was significantly attenuated in group I,

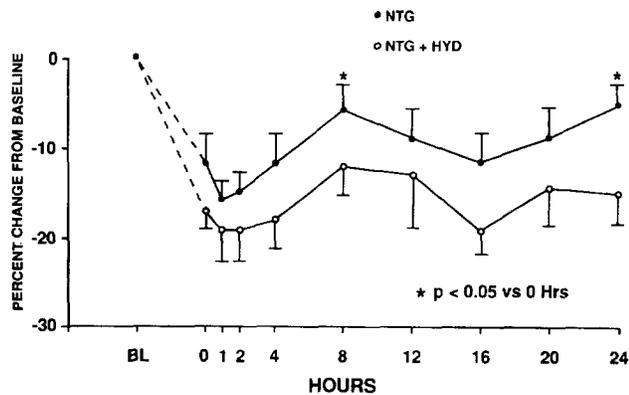


Figure 1. Effect of 24 h of nitroglycerin infusion alone (NTG; 14 patients) or in combination with hydralazine (NTG + HYD; 14 patients) on mean systemic arterial pressure. * $p < 0.05$ versus 0 h.

with a value of only $10 \pm 3\%$ at 24 h ($p < 0.01$ vs. group II). In addition, difference from baseline, as found at 8 and 16 h ($15 \pm 4\%$ and $15 \pm 3\%$, respectively), was significantly smaller than the difference found at 0 h (Fig. 2). The initial reduction in mean pulmonary artery wedge pressure (Fig. 3) was $40 \pm 4\%$ in group I (from 27 ± 2 to 17 ± 1 mm Hg) and $37 \pm 4\%$ in group II (from 27 ± 2 to 17 ± 2 mm Hg). This initial change in wedge pressure was gradually attenuated in group I, leading to a statistically significant increase from the value obtained at 0 h to that as early as 4 h of nitroglycerin infusion ($16 \pm 4\%$ vs. $40 \pm 4\%$, $p < 0.05$). In contrast, an initial reduction in mean pulmonary artery wedge pressure was maintained for the duration of the study in group II and was $34 \pm 6\%$ at 24 h ($p = 0.40$ vs. 0 h, $p < 0.05$ vs. group I).

Discussion

The results of the present investigation are in accordance with previous reports (5,13,14) of early development of tolerance to the initial hemodynamic effects of nitroglycerin when

Figure 2. Effect of 24 h of nitroglycerin infusion alone (NTG) or in combination with hydralazine (NTG + HYD) on mean pulmonary artery pressure (14 patients in each group). * $p < 0.05$ versus values obtained at peak nitroglycerin titration (0 h).

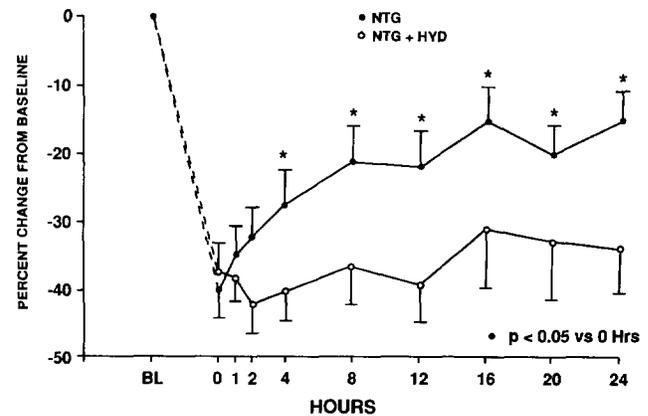
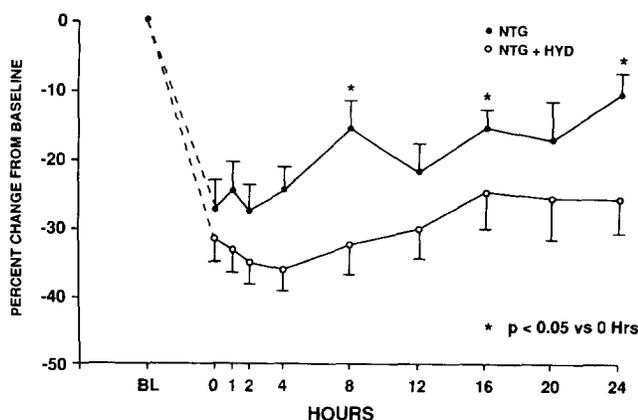


Figure 3. Effect of 24 h of nitroglycerin infusion alone (NTG) or in combination with hydralazine (NTG + HYD) on mean pulmonary artery wedge pressure. * $p < 0.05$ versus 0 h.

given as a continuous infusion to patients with heart failure. In the present study, a marked attenuation of nitroglycerin effect on systemic and pulmonary arterial pressures and left ventricular filling pressure occurred when the drug was given alone within the first 24 h of therapy. This attenuation is evidenced by a statistically significant increase in these pressures compared with values obtained at peak nitroglycerin titration (Table 2, Fig. 1 to 3). Although changes in mean right atrial pressure, cardiac index and both systemic and pulmonary vascular resistance seemed to remain unattenuated, these findings are most likely related to the limited duration of the study period. This assumption is supported by the results of previous studies (14) demonstrating a complete loss of effect on these parameters within 48 h of continuous nitroglycerin infusion.

Previous attempts to prevent nitrate tolerance. Because of the potential role of nitrate tolerance in limiting the therapeutic effects of these drugs, an extensive effort has been made in recent years by numerous investigators to develop effective strategies for the prevention of this phenomenon (3,15). Because depletion of tissue sulfhydryl groups has been considered a likely mechanism of nitrate tolerance (16), sulfhydryl-containing compounds have been used in conjunction with organic nitrates to prevent tolerance. Although sulfhydryl donors, such as *N*-acetylcysteine and methionine, have been reported to reverse nitrate tolerance (14,17) in patients with heart failure, the effect was only partial and the administration of *N*-acetylcysteine in the nontolerant stage failed to prevent tolerance development (5).

Because activation of neurohumoral, vasoconstrictive mechanisms has been considered a potential cause of nitrate tolerance (3,5,14), angiotensin-converting enzyme inhibitors have been used in combination with organic nitrates in an attempt to prevent the development of tolerance (18). Although prolongation of nitrate-mediated hemodynamic action has been reported with a concomitant administration of angiotensin-converting enzyme inhibitors by some investiga-

tors (19), others failed to demonstrate prevention of nitrate tolerance with the same drugs (6,20). Therefore, more information is needed to determine the clinical role of angiotensin-converting enzyme inhibitors in the prevention of nitrate tolerance in patients with heart failure.

An increase in blood volume has been reported (5) in patients receiving nitrate therapy and has been suggested (3,5) as a mechanism for early attenuation of the hemodynamic effects. The concomitant use of diuretic drugs in normal volunteers (21) and in patients with ischemic heart disease (22) and heart failure (13,23,24) failed to prevent the development of nitrate tolerance.

Interaction between nitroglycerin and hydralazine. A recent study by Bauer and Fung (8) demonstrated a beneficial interaction between nitroglycerin and hydralazine, with prevention of nitrate tolerance in a rat model of heart failure. The results of the present investigation extend these findings and demonstrate a potential role for hydralazine in the prevention of nitrate tolerance in patients with heart failure. Unger et al. (25) demonstrated in an *in vitro* experiment a potentiation of nitroglycerin-induced vasorelaxation with hydralazine in isolated rat aortas rendered *in vivo* nitrate tolerant and suggested an interaction between hydralazine and pyridoxal as the mechanism responsible for this effect. Pyridoxal has been shown to enhance the availability of sulfhydryl groups in vascular smooth muscle by inducing a breakdown of sulfhydryl-containing amino acids and may thereby potentiate the response to nitroglycerin. However, Bauer and Fung (8) failed to demonstrate hydralazine-induced prevention of vascular tolerance to nitroglycerin in an isolated rat aorta and concluded a low likelihood for a cellular interaction between the two drugs.

Nitrate administration has been shown to decrease renal blood flow in both animals and humans with heart failure (26,27). This change in renal perfusion may be responsible for neurohumoral activation (5,14), a possible mechanism of nitrate tolerance (3). In contrast, the administration of hydralazine was found to cause a significant increase in renal blood flow in patients with heart failure (26,28). On the basis of these findings, Bauer and Fung (8) suggested a prevention of the nitrate-mediated decrease in renal blood flow and neurohumoral stimulation with hydralazine as a possible explanation for prevention of nitrate tolerance. However, further investigations will be needed to evaluate the validity of this potential mechanism of nitrate-hydralazine interaction in patients with chronic heart failure.

Hydralazine has been shown to exert a hemodynamic effect in patients with chronic heart failure (29-35). It could therefore be argued that the persistent hemodynamic effect in patients receiving nitrates plus hydralazine may reflect a beneficial hemodynamic effect of hydralazine despite the development of nitrate tolerance. However, this argument is not supported by the results of the present and previous studies. Lack of difference in hemodynamic response to nitroglycerin in both groups suggests only a small or no hemodynamic effect of hydralazine in our patients. This suggestion is further supported by a previously published report (29) demonstrating

failure to show hemodynamic response to 75 mg of oral hydralazine (dose used in the present study) in 41 of 45 patients with chronic heart failure. In addition, a persistent, substantial reduction in left ventricular filling pressure is unlikely to be due to hydralazine. This drug has a predominant effect on the arteriolar circulation and has demonstrated only a small and often insignificant effect on left ventricular filling pressure (30-35).

Summary. The results of the present investigation demonstrate prevention of early attenuation of nitroglycerin-mediated effects on systemic and pulmonary artery pressures and left ventricular filling pressure with the concomitant administration of oral hydralazine in patients with chronic congestive heart failure. Our results support a recently published study reporting prevention of nitrate tolerance with concurrent use of hydralazine in an animal model of heart failure. Although the mechanism for the favorable interaction between hydralazine and organic nitrates remains unclear, our findings may provide an explanation for the beneficial effect of isosorbide dinitrate when used in combination with hydralazine, on left ventricular function, exercise capacity and survival in patients with chronic heart failure, as demonstrated in the Veterans Heart Failure Trials (V-HeFT) (9,10). The results of the present study may indicate a rationale for the concomitant use of hydralazine in patients with heart failure receiving nitrate therapy.

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