The Effect of Hydralazine on the Development of Tolerance to Continuous Nitroglycerin

JOHN D. PARKER, ANDREA B. PARKER, BERNICE FARRELL and JOHN O. PARKER

Division of Cardiology (J.D.P.), Department of Medicine, University of Toronto, Mount Sinai Hospital, Toronto, Ontario, Canada and SOCAR Research SA (A.B.P.), Givrins, Switzerland and The Division of Cardiology (B.F., J.O.P.), Department of Medicine, Queen’s University, Kingston General Hospital, Kingston, Ontario, Canada

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ABSTRACT

It has been reported that nitroglycerin (GTN) tolerance can be prevented by the concurrent administration of hydralazine. Although the mechanism of this effect remains unknown, it is possible that hydralazine modifies counter-regulatory responses to nitrate administration. To address this question, we examined the impact of hydralazine therapy on the development of tolerance during sustained therapy with GTN. Twenty normal volunteers and 18 patients with chronic heart failure (mean ejection fraction 30 ± 2%) were treated for 1 week with hydralazine or placebo in a randomized, double-blind fashion. Hydralazine therapy (or placebo) was continued, and subjects then received continuous transdermal GTN for 5 to 7 days. On the first and last day of transdermal GTN therapy, standing HR, systolic blood pressure and hematocrit responses were assessed. HR and blood pressure responses to sublingual GTN (0.6 mg) were also evaluated before and during sustained transdermal GTN therapy. Significant loss of the hemodynamic effects of transdermal GTN occurred during sustained therapy in both the normal volunteer and heart failure groups. Hydralazine had no effect on the development of tolerance to the hemodynamic effect of GTN in either group. In both, transdermal GTN therapy was associated with a significant fall in hematocrit that persisted for the entire treatment period. Hydralazine had no effect on this response. These data suggest that hydralazine therapy does not prevent loss of systemic arterial effects or prevent plasma volume expansion during sustained transdermal GTN therapy.

The phenomenon of tolerance to the organic nitrates continues to be an important clinical and investigative problem in cardiology. The organic nitrates are commonly used in the therapy of angina, although loss of efficacy during continuous therapy remains a significant problem (Parker and Fung, 1984; Parker et al., 1983; Parker et al., 1984; Reichek et al., 1984; Thadani et al., 1982; Thadani et al., 1986; Zimrin et al., 1988). In the setting of congestive heart failure (CHF), therapy with the combination of hydralazine and isosorbide dinitrate has been demonstrated to be associated with both improved survival and enhanced functional capacity (Cohn et al., 1986; Cohn et al., 1991). Although the efficacy of this combination in the setting of CHF is well recognized, the impact of hydralazine therapy on the development of traditional measures of GTN tolerance has not been fully explored. In an animal model of CHF, Bauer and Fung (1991) demonstrated that the concurrent administration of hydralazine was effective in preventing the loss of hemodynamic effects of GTN. Although the mechanism of this effect was not clear, the authors postulated that it could not have occurred secondary to sulphydryl group donation (Ignarro et al., 1981) and that it may have been secondary to modification of counter-regulatory responses associated with GTN therapy (Dupuis et al., 1990; Imhof et al., 1989; Packer, 1990; Packer et al., 1987; Parker et al., 1991). In another animal model, it has been reported that hydralazine prevents nitrate tolerance by inhibiting vascular superoxide anion production by the endothelium (Münzel et al., 1995a,b). Finally, in patients with heart failure, Gogia et al. (1995) have reported that the concurrent administration of hydralazine prevented the development of tolerance to the hemodynamic effects of a 24-h infusion of GTN. Although this report is of interest, the effect of hydralazine on GTN tolerance during truly sustained GTN therapy remains uncertain. Furthermore, this interaction between hydralazine and GTN deserves further study, because investigations in this area may offer further insight into the mechanisms of nitrate tolerance (Münzel et al., 1995a,b; Unger et al., 1993).

In light of this, we evaluated the effects of concurrent hydralazine therapy on hemodynamic responses to continuous transdermal GTN in a group of patients with heart failure. A group of patients with New York Heart Association (NYHA) functional class II and III symptoms were investigated, because this was representative of the V-Heft popula-
tion where the combination of nitrates and hydralazine has been shown to be of clinical benefit. We contrasted observations in patients with heart failure to those seen in a group of normal volunteers to determine whether an interaction between hydralazine and GTN was specific to the heart failure state. Finally, to determine whether hydralazine prevents the increase in plasma volume seen with continuous GTN therapy (Dupuis et al., 1990; Imhof et al., 1989; Parker et al., 1991) we measured serial changes in hematocrit in both groups after acute and sustained therapy. These observations concerning therapy with the combination of continuous GTN and hydralazine may provide new information about counter-regulatory responses to nitrate therapy and possible strategies for the prevention of tolerance.

Methods

Subjects. The study population consisted of two groups. The first group included 20 patients with heart failure secondary to primary systolic dysfunction. There were 18 males and two females (mean age 61 ± 3 years). These patients suffered from moderate heart failure: 10 were in NYHA functional class II, and 10 were in NYHA class III. All patients had an ejection fraction of less than 40% by either quantitative two-dimensional echocardiography or radionuclide angiography within 6 months of entering the study (mean ejection fraction 30 ± 2%). The etiology of their heart failure syndrome was idiopathic in two and ischemic in 18. All patients were in sinus rhythm. Patients were treated with vasodilators, digitalis glycosides and/or diuretics, and all had been stable for at least 2 months before entry into the study. Patients with heart failure had all vasodilator medications withheld for a minimum of 7 days before entry into the study protocol. Ten of the patients with heart failure were taking digoxin in doses that ranged from 0.125 to 0.375 mg/day. Twelve heart failure patients were taking furosemide in doses that ranged from 20 to 120 mg/day. Both digoxin and furosemide were continued throughout the study period. None of the study patients were taking beta-adrenergic blocking drugs at the time of the study.

Group 2 consisted of 20 normal male volunteers ranging in age from 20 to 24 years. There was no history of renal or cardiac disease. All subjects had a normal physical examination, electrolytes, blood urea nitrogen, creatinine, hematocrit and urinalysis. None of the subjects were taking medications at the time of the investigation.

The study protocol was approved by the Ethics Committee of Queen’s University, Kingston, Ontario, Canada, and written informed consent was obtained in all cases. After giving written informed consent, both normal volunteers and patients with heart failure underwent a screening medical history and physical examination. A schematic presentation of the protocol design can be found in figure 1.

Visit 1. Patients and normal volunteers returned to the laboratory and received a 25-mg test dose of hydralazine. HR and blood pressure were recorded before administration of the test dose and every 30 min thereafter for a period of 3 hr. Once the test dose was completed and well tolerated, the subjects were randomized to therapy with either hydralazine or matching placebo in a double-blind fashion. Hydralazine (or matching placebo) was provided in 25-mg capsules. The dose of p.o. study medication was titrated. Each subject took 1 capsule three times daily on the first day and 2 capsules three times daily on the second day. Normal subjects then continued to take either hydralazine (50 mg three times day) or placebo for the remainder of the study period. A similar dose titration was carried out in patients with heart failure, although they received double-blind medication four times daily and achieved a final dose of hydralazine (or matching placebo) of 75 mg four times daily. The dosing frequency in the heart failure group was chosen to correspond to that employed in the V-Heft studies (Cohn et al., 1986; Cohn et al., 1991).

Visit 2. After a period of 7 days, subjects returned to the cardiovascular laboratory at 7:30 A.M. At 8:00 A.M. standing HR and blood pressure were determined, and the p.o. study medication was administered. Blood pressure was measured by trained personnel using a sphygmomanometer. Three measurements separated by 1 min were made, and the results were averaged. HR was determined from a 1-min count of the pulse. Subsequently, standing HR and blood pressure were measured at 9:00 A.M., 10:00 A.M. and 12:00 P.M.. After the measurements at 12:00 P.M., 0.6 mg sublingual GTN was administered, and the subject was instructed to remain standing. HR and blood pressure were recorded 3, 6 and 9 min after the administration of GTN.

Visit 3. The following day, subjects returned to the cardiovascular laboratory at 7:15 A.M., at which time an 18-gauge heparin lock was established in the nondominant forearm to allow venous blood sampling. After the subjects rested quietly for 30 min, standing HR and blood pressure were determined, and a venous blood sample for hematocrit determination was drawn at 8:00 A.M. When these measurements had been completed, a 0.8-μg/hr GTN patch (Transderm Nitro, Ciba-Geigy Corporation Mississauga, Ontario) was applied, and subjects were given their p.o. study medication. Subsequent hemodynamic measurements and blood samples were taken at 9:00 A.M., 10:00 A.M. and 12:00 P.M. At this point the heparin lock was removed, and subjects were given a supply of transdermal GTN patches to be applied once daily and left in place for 24 hr.

Visit 4. After a period of 5 to 7 days, subjects returned to the cardiovascular laboratory at 7:15 A.M., and venous access was again established. After the subjects rested quietly for 30 min, measurements similar to those obtained at visit 3 were performed at 8:00 A.M. At that point the GTN patch was changed, the p.o. study medication was administered and repeat measurements made at 9:00 A.M., 10:00 A.M. and 12:00 P.M. After the measurements at 12:00 P.M., 0.6 mg sublingual GTN was administered, and subjects were instructed...
to remain standing. HR and blood pressure were recorded 3, 6 and 9 min after the administration of GTN.

Statistical methods. All data are presented as the mean ± S.E.M. Data were analyzed by repeated-measures analysis of variance, using a general linear modeling procedure within SAS (SAS release 6.10, SAS Institute Inc., Cary, NC). Changes across days, hours and/or minutes were analyzed as within-subject effects, with treatment group (hydralazine vs. placebo) and disease state (normal vs. heart failure) defined as between-subject effects. This design yielded tests of 1) whether mean values on these measurements varied significantly across days, hours or minutes, 2) whether the daily effect varied as a function of the time at which values were measured, 3) whether the day, hour or minute effects varied as a function of treatment with hydralazine vs. placebo and 4) whether these effects varied as a function of disease state (normal vs. heart failure). In cases where significant F values were found, specific preplanned comparisons between baseline and subsequent data points were performed. For HR and blood pressure responses to transdermal GTN, visit 2 served as baseline for the day effect, and 8:00 A.M. served as base line for the hour effect. In the case of hematocrit values, visit 3 served as baseline for the day effect, and 8:00 A.M. served as base line for the hour effect. Finally, for responses to sublingual GTN, visit 2 served as baseline for the day effect and time 0 as base line for the minute effect. Differences were considered significant if the null hypothesis could be rejected at the .05 probability level.

Results

Hydralazine and transdermal GTN therapy. A total of 20 normal volunteers were randomized; 10 received hydralazine 50 mg three times daily, and the remainder received matching placebo. In two subjects, the dose of p.o. medication was reduced to 25 mg four times daily because of persistent headache. In both cases, the subjects were receiving hydralazine. In one subject, the dose of transdermal GTN was reduced to 0.4 mg/24 hr.

In the heart failure group, 20 patients were randomized; 10 received hydralazine, and the remainder received matching placebo. In two subjects randomized to hydralazine, the maximal tolerated dose was 25 mg four times daily, and the remainder received 75 mg four times daily. In five patients with heart failure, the dose of transdermal GTN was limited to 0.4 mg/24 hr because of headache; three of these patients were receiving hydralazine, and two were taking placebo.

All of the normal volunteers who were randomized completed the investigation. Of the 20 randomized patients in the heart failure group, two who were taking hydralazine discontinued study medications because of side effects. These patients had not yet received transdermal GTN, so their data were not included in the analysis. Base-line characteristics of heart failure patients receiving placebo were similar to those of patients receiving hydralazine (table 1).

| Age (yr) | 60 ± 4 | 62 ± 3 | NS |
| Sex | 9 males, 1 female | 8 males | — |
| EF (%) | 28 ± 2 | 32 ± 3 | NS |
| HR (bpm) | 77 ± 3 | 72 ± 3 | NS |
| SBP (mm Hg) | 130 ± 5 | 130 ± 3 | NS |

Blood pressure and HR responses in normal volunteers (figs. 2 and 3). In the normal volunteer group, standing systolic blood pressure on visit 2, the day before initial transdermal GTN therapy, was not affected by treatment with hydralazine as compared with placebo. Baseline HR at 10:00 and 12:00 A.M. was slightly higher in those receiving hydralazine (P = .04), although there was no difference in HR between the treatment groups at other times of the day.

In the normal volunteer group, the initial application of transdermal GTN (visit 3) was associated with a significant decrease in systolic blood pressure that persisted for the 4-hr observation period (P < .001). This was accompanied by a significant increase in HR that also was seen throughout the observation period (P < .001). The analysis of variance revealed no differences in the response of those receiving hydralazine as compared with placebo. At 8:00 A.M. on visit 4, after 5 to 7 days of continuous GTN therapy, systolic blood pressure and HR had returned to baseline values and were not significantly different from those observed on visit 2. After patch application on visit 4, there was no significant change in either systolic blood pressure or HR in either the placebo or the hydralazine therapy group.

Blood pressure and HR responses in patients with heart failure (figs. 2 and 3). In patients with heart failure, standing systolic blood pressure was also similar in the hydralazine and placebo therapy groups at base line (visit 2). HR tended to be lower in those treated with hydralazine, and the difference attained statistical significance at 9:00 and 10:00 A.M. on this day (P = .04).

In patients with heart failure, the initial application of transdermal GTN (visit 3) was associated with a significant decrease in systolic blood pressure that persisted for the 4-hr observation period (P < .001). This effect was accompanied by a significant increase in HR that also was seen throughout the observation period (P < .001). The analysis of variance revealed no differences between the response of those receiving hydralazine and that of those receiving placebo. At 8:00 A.M. on visit 4, after 5 to 7 days of continuous GTN therapy, systolic blood pressure and HR had returned to baseline values and were not significantly different from those observed on visit 2. After patch application on visit 4, there was no significant change in either systolic blood pressure or HR in either those receiving placebo or those receiving hydralazine.

The analysis of variance reveals that the response of patients with heart failure was generally similar to that observed in normal volunteers. As can be seen in figures 2 and 3, tolerance to the blood pressure and HR responses to transdermal GTN developed in both the normal volunteer and the heart failure groups and was not affected by the concurrent administration of hydralazine. There was a significant difference between the normal volunteer group and the heart failure group in terms of the systolic blood pressure response on different days. This interaction was observed because the decrease in blood pressure after the first application of transdermal GTN at 9:00 A.M. on visit 3 was greater in the normal volunteer group than in patients with heart failure (P = .02). It is notable that this interaction between the blood pressure response and disease state did not vary as a function of treatment with hydralazine vs. placebo. The analysis of variance also revealed a difference in the hourly HR effect between the normal volunteer and heart failure groups. In this
case, the increase in HR observed at 9:00 A.M. as compared with 8:00 A.M. was greater in the normal volunteer group than in the heart failure group (P < .001). This difference did not vary across different testing days and was not affected by treatment with hydralazine.

Blood pressure and HR responses to sublingual GTN in normal volunteers (figs. 4 and 5). The acute administration of 0.6 mg of sublingual GTN on visit 2 (while subjects were in the nitrate-free state) was associated with a significant decrease in standing systolic blood pressure accompa-
nied by a significant increase in HR (P < .001). These changes persisted throughout the 9-min observation period. The observed hemodynamic responses to sublingual GTN were similar in those taking hydralazine and those taking placebo. After 5 to 7 days of sustained transdermal GTN therapy, the administration of sublingual GTN continued to be associated with a significant decrease in systolic blood pressure and a significant increase in HR, although these responses were significantly less than those seen during the administration of sublingual GTN in the nitrate-free state.
(P < .001, interaction between the effect of days and minutes). Once again, the analysis of variance revealed that these responses did not vary as a function of treatment with hydralazine.

**Blood pressure and HR responses to sublingual GTN in patients with heart failure (figs. 4 and 5).** In this group, the acute administration of 0.6 mg of sublingual GTN on visit 2 also caused a significant decrease in systolic blood pressure accompanied by a significant increase in HR that lasted for the 9-min observation period (P < .001). After sustained transdermal GTN therapy, sublingual GTN continued to have substantial effects on both blood pressure and HR. In contrast to what we found in the normal volunteer group, the analysis of variance revealed no difference in the HR or blood pressure responses to sublingual GTN between visit 2 and visit 4. Therefore, there was no attenuation of the response to sublingual GTN during sustained, continuous GTN therapy in the heart failure group. As in the normal volunteer group, therapy with hydralazine had no effect on these responses to sublingual GTN. The difference in the response of both HR and blood pressure to sublingual GTN in the normal volunteer as compared with the heart failure group was detected in the analysis of variance as a significant interaction between the effect of days and that of disease state (P = .006).

**Hematocrit responses to transdermal GTN in normal volunteers (fig. 6).** Baseline hematocrit at 8:00 A.M. on visit 3 was similar in those treated with hydralazine and those treated with placebo. On visit 4, after 5 to 7 days of sustained GTN therapy, hematocrit values in both the hydralazine-treated and the placebo-treated volunteers were significantly lower than they were at baseline throughout the entire 4-hr observation period (P < .01, significant effect in days in analysis of variance). The pattern of hematocrit change was not affected by treatment with hydralazine as compared with placebo.

**Hematocrit responses to transdermal GTN in patients with heart failure (fig. 6).** Baseline hematocrit at 8:00 A.M. on visit 3 was similar in those treated with hydralazine and those treated with placebo. On visit 4, after 5 to 7 days of sustained GTN therapy, hematocrit values in both the hydralazine- and the placebo-treated patients with heart failure remained significantly lower than they were at baseline throughout the entire 4-hr observation period (P < .001, significant effect in days in analysis of variance). The pattern
of hematocrit change was not affected by treatment with hydralazine as compared with placebo.

The analysis of variance revealed no difference between the hematocrit responses of the normal volunteer group and those of the heart failure group.

**Discussion**

The combination of hydralazine and isosorbide dinitrate has been demonstrated to improve both morbidity and mortality in patients suffering from mild to moderate CHF (Cohn *et al.*, 1986; Cohn *et al.*, 1991). Despite this therapeutic success, there have been no studies documenting the long-term hemodynamic effects of this combination therapy in patients suffering from CHF. The possibility that therapy with the combination of hydralazine and nitrate preparation prevents tolerance has been studied both *in vitro* (Münzel *et al.*, 1995a; Unger *et al.*, 1993) and in an animal model of tolerance (Bauer and Fung, 1991). More recently, these observations have been extended to patients with CHF (Gogia *et al.*, 1995). These investigations may have important clinical implications. Furthermore, understanding the nature of the interaction between nitrates and hydralazine may help to further our understanding of the mechanism of tolerance to the organic nitrates.

Bauer and Fung reported that hydralazine could successfully prevent the development of tolerance to the preload-reducing effects of i.v. GTN in a rat model of CHF (Bauer and Fung, 1991). The mechanism of this alteration in the hemodynamic response to GTN was not clear. The authors demonstrate that it was not secondary to alterations in GTN metabolism, and their *in vitro* experiments do not suggest a synergistic effect of the two compounds at the vascular smooth muscle level. They hypothesize that the balanced vasodilator effect of the combination of hydralazine and GTN prevented decreases in renal blood flow and resultant hormonal and sodium balance changes (Dupuis *et al.*, 1990; Leier *et al.*, 1983; Packer *et al.*, 1987; Parker *et al.*, 1991). As a nonthiol-containing compound, hydralazine could not have had its effect *via* sulfhydryl group donation (Ignarro *et al.*, 1981), although it has been suggested that hydralazine modifies the metabolism of thiol-containing compounds within vascular tissue (Unger *et al.*, 1993). More recently, Münzel *et al.* (1995a) have reported that hydralazine prevents tolerance to the vascular effects of GTN in an rabbit model of tolerance. The findings suggested that hydralazine eliminated GTN-induced superoxide anion production by the endothelium, thus preventing development of tolerance (Münzel *et al.*, 1995a,b). In humans, Gogia *et al.* (1995) have
reported the results of a study examining the effects of hydralazine on the hemodynamic response to GTN in the setting of CHF. In this study, concomitant hydralazine therapy prevented tolerance to the effects of continuous i.v. GTN on pulmonary artery mean and wedge pressure as well as systemic arterial pressure.

The findings of the present investigation show that hydralazine does not modify the systemic hemodynamic effects of prolonged therapy with transdermal GTN. HR and blood pressure responses were not modified by concurrent hydralazine therapy, and evidence of significant volume expansion was seen in both the placebo- and the hydralazine-treated groups. In contrast to the observations of Gogia et al. (1995), we found that hydralazine did not prevent tolerance to the systemic arterial effects of continuous GTN. Left ventricular filling pressures were not measured in the present study, and it is possible that hydralazine prevented tolerance to the effects of GTN on this parameter. It seems unlikely, however, that persistent effects on preload would have occurred in the absence of any observable difference in HR and blood pressure. It should be noted that in previous studies, this model of GTN tolerance has been successful in documenting both the development of tolerance during sustained GTN therapy (Parker et al., 1992; Parker and Parker, 1993) and its prevention during intermittent therapy (Parker et al., 1991).

Notably, hydralazine did not prevent the decrease in hematocrit that occurs during continuous GTN therapy. Therefore, in both normal volunteers and patients with heart failure, hydralazine therapy did not prevent the development of plasma volume expansion that has been shown to occur in response to GTN therapy both in subjects with CHF (Dupuis et al., 1990) and in those with normal hemodynamics (Imhof et al., 1989; Parker et al., 1991; Parker et al., 1992). Previous studies in this area have suggested that the hydralazine might prevent plasma volume expansion in response to GTN therapy because of its favorable effects on renal blood flow and sodium retention (Bauer and Fung, 1991; Gogia et al., 1995). The fact that hydralazine did not prevent the devel-
opment of plasma volume expansion is not surprising, because it has been clearly shown in both normal volunteers (Parker et al., 1992; Parker and Parker, 1993) and patients with heart failure (Dupuis et al., 1990) that GTN-induced plasma volume expansion is not caused by sodium retention but is a reflection of a transvascular fluid shift. Whether hydralazine administration modifies neurohumoral responses to nitrate therapy was not addressed in this investigation. Recent studies suggest that neurohumoral activation secondary to GTN therapy is not a prominent effect during sustained GTN therapy in either normal subjects (Parker and Parker, 1993) or patients with heart failure (Dupuis et al., 1990). Therefore, it seems unlikely that neurohumoral responses play an important role in the development of tolerance.

There are numerous differences between the Bauer study (Bauer and Fung, 1991) and the present investigation. First, the Bauer study examined the development of tolerance and its prevention with hydralazine over period of only 10 hr. Although there was clear prevention of the attenuation of the preload-reducing effects of GTN over this time period, it is possible that therapy over a longer time course would have had different results. Second, their study examined rats with CHF secondary to experimental myocardial infarction. The difference between pharmacologic responses in different animal models is emphasized by the fact that the rats in the Bauer experiment responded to extremely small doses of i.v. GTN. This differing species sensitivity to GTN may have important implications for the development of tolerance and its reversal with hydralazine that might explain these disparate results.

In a recent report, Münzel and colleagues (1995a) demonstrate that hydralazine has a favorable impact on GTN tolerance. Previously, these authors have made the intriguing observation that GTN therapy is associated with increased superoxide anion production by the endothelium and that this increase in free radical production may be an important mechanism in the development of tolerance (Münzel et al., 1995b). Interestingly, hydralazine prevented this increase in free radical production in response to GTN, and the authors postulate that it is through this mechanism that hydralazine modifies tolerance (Münzel et al., 1995a). It is important to note methodologic differences that may explain why the results of our study in humans differ from their observations in rabbit vascular tissue. Importantly, the dose of GTN that they employed (1.5 μg/kg/min) was approximately 8 times greater than that used in the present study. Furthermore, the hydralazine dose used was approximately 2 times greater than that used in our study. Finally, vascular responses to GTN examined using an in vitro, vascular ring presentation cannot be assumed to be equivalent to in vivo responses.

There are also differences between our study and the report of Gogia et al. (1995). First, the patient populations in the two investigations were different. Patients studied by Gogia et al. had severe heart failure, all patients being NYHA functional class III and IV. Patients in the present investigation suffered from mild to moderate heart failure and were all NYHA functional class II or III. This population was specifically chosen because it is in this situation where the combination of nitrates and hydralazine has been shown to have a beneficial effect (Cohn et al., 1986; Cohn et al., 1991). It should be emphasized that the patient population of the present study is similar to that of the V-Heft studies in terms of functional class and other baseline characteristics. For example, in V-Heft II the ejection fraction of the two treatment groups was 29%, whereas in our study the mean ejection fraction was 30%. In the V-Heft II study, the HR at baseline was 78 bpm in both treatment groups and the mean systolic blood pressure was 126 mm Hg. In the present investigation, these values were 75 bpm and 130 mm Hg, respectively. Another important difference is that the Gogia investigation involved a 24-hr infusion of GTN. As the authors point out, this may be why tolerance to the effects of GTN was not observed for a number of hemodynamic variables in either treatment group. It is also possible that the observed difference in the response of those receiving hydralazine would have been different after a more prolonged period of continuous therapy with GTN. A confounding factor in the study by Gogia et al. (1995) is the fact that the hemodynamic effect of hydralazine alone was not examined. Because hydralazine can have independent effects on ventricular filling pressure in patients with heart failure (Fitchett et al., 1979; Franciosa et al., 1977; Leier et al., 1983), it is not possible to conclude that the responses observed in the hydralazine and GTN group were secondary to a unique effect of hydralazine on the development of GTN tolerance.

The present study demonstrates that concomitant administration of hydralazine does not prevent the development of tolerance to sustained therapy with continuous transdermal GTN. If hydralazine did modify long-term responses to the organic nitrates, an understanding of the mechanism of this effect might provide insight into the mystery of nitrate tolerance (Packer, 1990). The present study serves to confirm that the role of organic nitrates in the therapy of chronic heart failure requires more investigation. The efficacy of the combination of hydralazine and isosorbide dinitrate in the therapy of heart failure is now clear (Cohn et al., 1986; Cohn et al., 1991). Whether this represents an independent effect of one agent or some unique synergy of the combination is open to question. The results of the present investigation suggest that hydralazine does not modify the long-term systemic arterial blood pressure and HR responses to continuous transdermal GTN. Further investigations concerning the role of long-acting nitrates in the therapy of chronic heart failure are required.

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