

# Effects of Nitrates and Hydralazine in Heart Failure: Clinical Evidence Before the African American Heart Failure Trial

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The initial rationale for use of organic nitrates and hydralazine (HYD) in combination was their complementary “nitroprussidelike” hemodynamic effect caused by the predominant venodilatory action of organic nitrates and the arterial-dilatory effect of HYD. This combination leads to a significant improvement in cardiac function, with a concomitant reduction in right and left ventricular filling pressures and augmentation of cardiac output. Based on this hemodynamic profile, the Vasodilator Heart Failure Trial (V-HeFT) was designed to examine the effect of this drug combination on the outcome of patients with congestive heart failure (CHF). Results from V-HeFT I showed improvements in left ventricular ejection fraction (LVEF), exercise tolerance, and survival in patients treated with isosorbide dinitrate (ISDN) and HYD compared with those treated with placebo. A retrospective analysis of V-HeFT I and V-HeFT II showed that the benefit of ISDN-HYD was seen mainly in African Americans. This observation led to the design of the African American Heart Failure Trial (A-HeFT), which confirmed the benefit of these drugs in combination in African American patients with CHF. There are a number of potential mechanisms responsible for the beneficial therapeutic effects of combination ISDN-HYD in patients with CHF, including favorable hemodynamic effects and improvement in left ventricular systolic function. Data from V-HeFT II showed a significant improvement in LVEF with combination ISDN-HYD, greater than the effect of the angiotensin-converting enzyme inhibitor enalapril. This increase in LVEF was associated with a favorable effect on survival. Prevention of nitrate tolerance with HYD may also be responsible for the favorable therapeutic effects of combination ISDN-HYD. Frequent administration of ISDN has been shown to result in the early development of nitrate tolerance. Concomitant use of HYD with a nitrate, both in an animal model and in patients with CHF, has been shown to prevent the development of nitrate tolerance and maintain the favorable hemodynamic effect of nitrates. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:37i–43i)

Recent results of the African American Heart Failure Trial (A-HeFT) have demonstrated a survival benefit in African American patients with chronic congestive heart failure (CHF) treated with BiDil (NitroMed; Lexington, Massachusetts), a fixed-dose combination of isosorbide dinitrate (ISDN) and hydralazine (HYD).<sup>1</sup> This new development brings to the forefront the use of this drug combination for treating CHF.

The initial use of nitrates in combination with HYD was based on a hemodynamic concept designed to achieve a “nitroprussidelike” effect, with a combined preload and afterload reduction caused by the predominant venodilatory effect of organic nitrates and the arterial dilatory effect of HYD.<sup>2</sup> This hemodynamic rationale

was the basis for the Vasodilator Heart Failure Trial (V-HeFT), which evaluated the effect of the combination of ISDN-HYD on the outcome of patients with chronic symptomatic CHF.<sup>3,4</sup> In the first part of that study, which enrolled 642 men, the use of oral ISDN at a maximum dose of 160 mg/day with HYD (300 mg/day) resulted in a significant reduction in mortality compared with results in patients treated with either placebo or prazosin (20 mg/day), a vasodilator with  $\alpha$ -adrenergic–blocking activity (Figure 1A), at 2 years, a prespecified time point.<sup>3</sup> At 1 year, the cumulative mortality rate in patients receiving the ISDN-HYD combination was reduced by 38% compared with that in the placebo group (12.1% vs 19.5%). The difference in mortality between the 2 groups persisted for 3 years. The annual mortality rate was higher in patients with coronary artery disease (CAD) ( $p < 0.02$ ); however, the beneficial effect of ISDN-HYD was comparable in patients with and without CAD. Although the overall mortality reduction in patients receiving ISDN-HYD achieved only borderline statistical significance, the survival curve in V-HeFT II<sup>4</sup> was nearly identical to that in V-HeFT I (Figure 1B), substantiating

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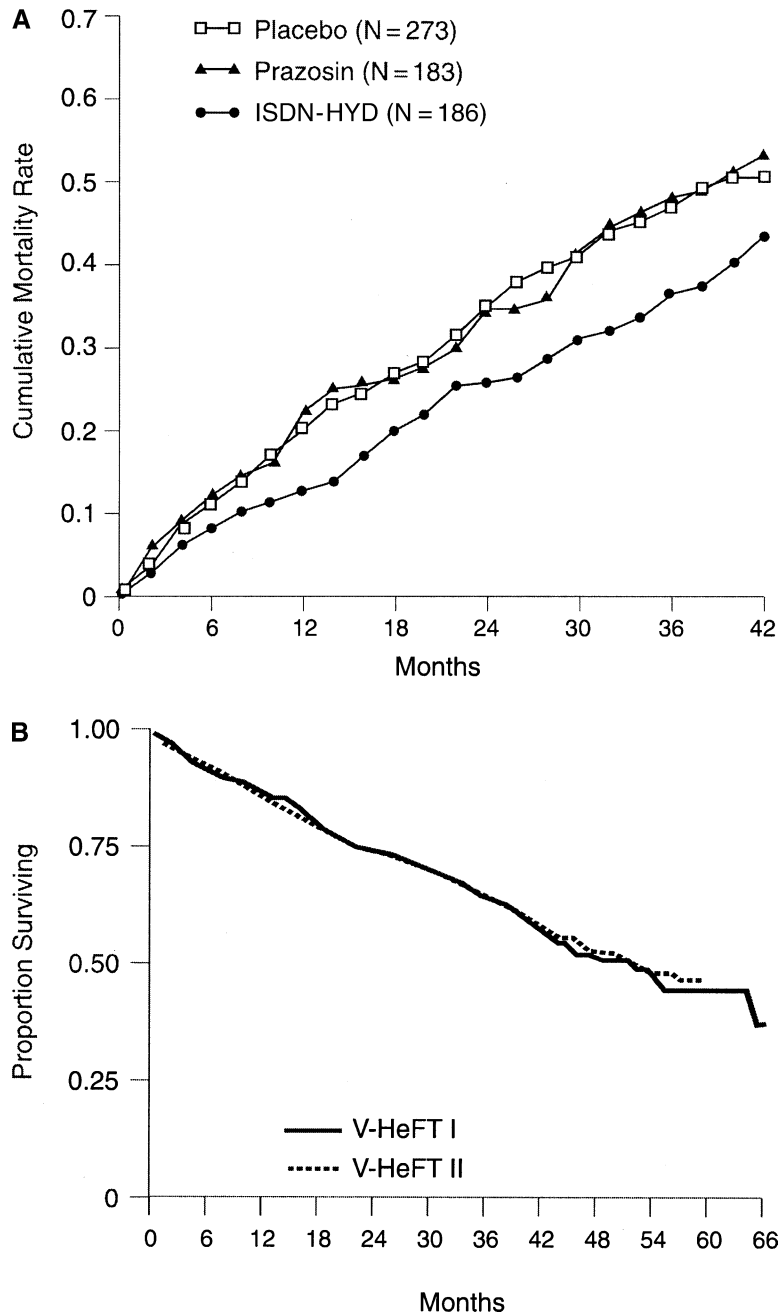


Figure 1. (A) Cumulative mortality from time of randomization to placebo, prazosin, or isosorbide dinitrate–hydralazine (ISDN-HYD) in the Vasodilator Heart Failure Trial (V-HeFT) I;  $p = 0.093$  on the log-rank test and  $p = 0.046$  on the generalized Wilcoxon test, which gives more weight to treatment differences occurring in the earlier part of the mortality curves and less weight to the latter part of the curves, where the numbers are smaller. (B) Survival curve for the isosorbide dinitrate and hydralazine arm in V-HeFT I superimposed on the survival curve for the same regimen in V-HeFT II. (Reprinted with permission from *N Engl J Med*.<sup>3,4</sup>)

the benefit of this therapeutic approach over placebo. The V-HeFT II study (804 patients) was designed to compare the effects of direct vasodilation with ISDN-HYD (160 to 300 mg/day) with those of angiotensin-converting enzyme (ACE) inhibition with enalapril (maximum dose 20 mg/day).<sup>4</sup> The results of this study demonstrated that when given to patients with mild-to-moderate symptomatic CHF, enalapril had a greater effect on survival than

the combination of ISDN-HYD. Lower mortality in the enalapril group was the result of a lower incidence of sudden death, whereas no difference was seen between the 2 treatment regimens with respect to mortality from worsening CHF. The results of these studies clearly demonstrate that ACE inhibition in patients with New York Heart Association (NYHA) class II or III CHF provides a stronger survival benefit than direct vasodilation.

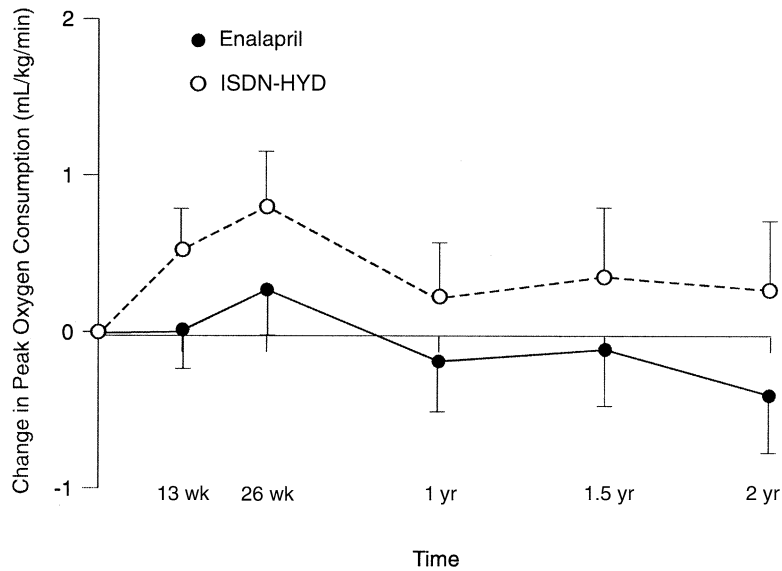


Figure 2. Mean change from baseline in peak oxygen consumption over 2 years in the Vasodilator Heart Failure Trial (V-HeFT) II. The increase in the isosorbide dinitrate–hydralazine (ISDN-HYD) arm was significant for the first 6 months ( $p < 0.01$ ) and was greater than in the enalapril arm. (Reproduced with permission from *N Engl J Med*.<sup>4</sup>)

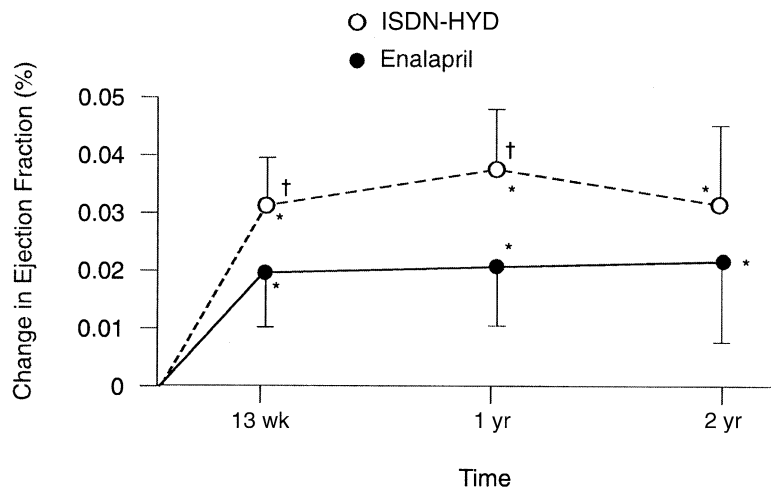


Figure 3. Mean change from baseline in left ventricular ejection fraction over 2 years in the Vasodilator Heart Failure Trial (V-HeFT) II. ISDN-HYD = isosorbide dinitrate–hydralazine. \* $p < 0.0001$  versus baseline; † $p < 0.05$  versus enalapril. (Reproduced with permission from *Drugs*.<sup>6</sup>)

### Effects of Isosorbide Dinitrate and Hydralazine on Markers of Cardiac Function

In addition to the survival benefit observed in patients with CHF, the combination of ISDN-HYD has been shown to improve other markers of cardiac function, including exercise tolerance and left ventricular ejection fraction (LVEF).

**Effect on exercise tolerance:** The results of the V-HeFT trials demonstrate a small but significant ( $p < 0.05$ ) improvement in peak oxygen consumption in patients treated with ISDN-HYD.<sup>4,5</sup> Improvement in peak oxygen consumption with this drug combination was seen for the first 6 months of the follow-up period and was greater than the effect of the ACE inhibitor enalapril (Figure 2).<sup>4</sup>

**Effect on LVEF:** Data from V-HeFT II<sup>6</sup> demonstrate a significant improvement in LVEF with the combination of ISDN-HYD (Figure 3). Similar to the effect on peak oxygen consumption, the effect of this drug combination was superior to that of enalapril. A relation was demonstrated between improvement in LVEF and survival in patients treated with ISDN-HYD. In patients whose LVEF increased by  $>10\%$ , there was a very favorable effect on long-term survival (80% at 5 years), whereas survival in patients whose LVEF remained unchanged or decreased during the first 6 months of the study was only 30% at 5 years.

Thus, although patients with CHF achieved a greater survival benefit with enalapril, the combination of ISDN-HYD improved exercise tolerance and LVEF significantly more than enalapril in these patients.

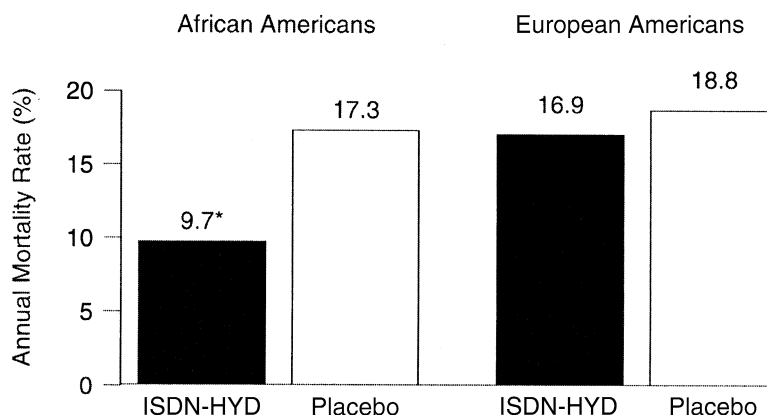


Figure 4. Annual mortality rate in the Vasodilator Heart Failure Trial (V-HeFT) I among African Americans and European Americans treated with isosorbide dinitrate-hydralazine (ISDN-HYD) or placebo. \* $p = 0.04$ . (Adapted from *J Card Fail.*<sup>7</sup>)

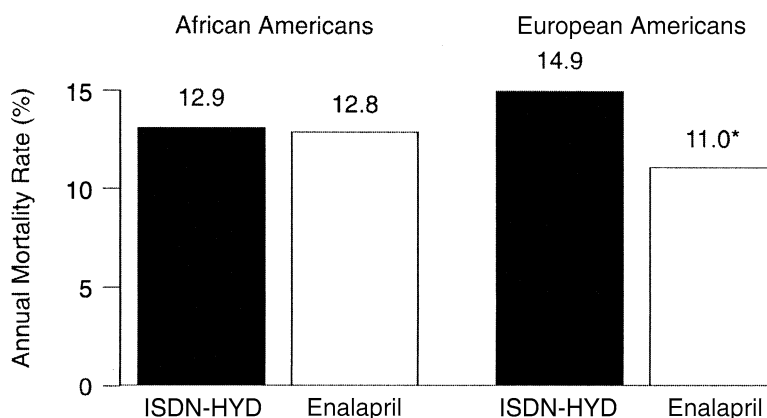


Figure 5. Annual mortality rate in the Vasodilator Heart Failure Trial (V-HeFT) II among African Americans and European Americans treated with isosorbide dinitrate-hydralazine (ISDN-HYD) or enalapril. \* $p = 0.02$ . (Adapted from *J Card Fail.*<sup>7</sup>)

### Effect of Isosorbide Dinitrate-Hydralazine in African Americans with Congestive Heart Failure in the Vasodilator Heart Failure Trials

African Americans constitute 180 of 642 patients in V-HeFT I, and 215 of 804 patients in V-HeFT II.<sup>3,4,7</sup> A retrospective analysis<sup>7</sup> of the outcome of African Americans compared with European Americans in V-HeFT I showed a significant 56% lower annual mortality rate in African American patients who were treated with ISDN-HYD than with placebo (9.7% vs 17.3%;  $p = 0.04$ ) (Figure 4). Administration of ISDN-HYD was also associated with a greater effect on oxygen consumption, which increased by 1.25 mL/kg per min in African Americans treated with ISDN-HYD compared with a decrease of 0.4 mL/kg per min in African Americans receiving placebo. The difference between the 2 groups was borderline significant.

Despite a superior effect of enalapril on survival in the overall V-HeFT II study population,<sup>4</sup> the effect of ISDN-HYD was comparable to that of enalapril in African American pa-

tients (12.9% vs 12.8%;  $p = \text{NS}$ ) (Figure 5).<sup>7</sup> In addition, compared with enalapril, ISDN-HYD significantly improved the quality of life in African Americans ( $p < 0.043$ ). When peak oxygen consumption was analyzed using a longitudinal model that took into account all data collected during the entire year, ISDN-HYD performed slightly better than enalapril compared with these drugs at baseline ( $p < 0.067$ ). Collectively, these results demonstrate that ISDN/HYD is more effective than placebo and as effective as enalapril in reducing mortality in African Americans compared with European Americans and is significantly more effective at improving quality of life than enalapril in these patients, despite only modest improvements in oxygen consumption.

### Effect of Hydralazine on Nitrate Tolerance

Multiple studies have clearly demonstrated that frequent administration of oral nitrates or continuous administration of intravenous or topical nitrates results in early develop-

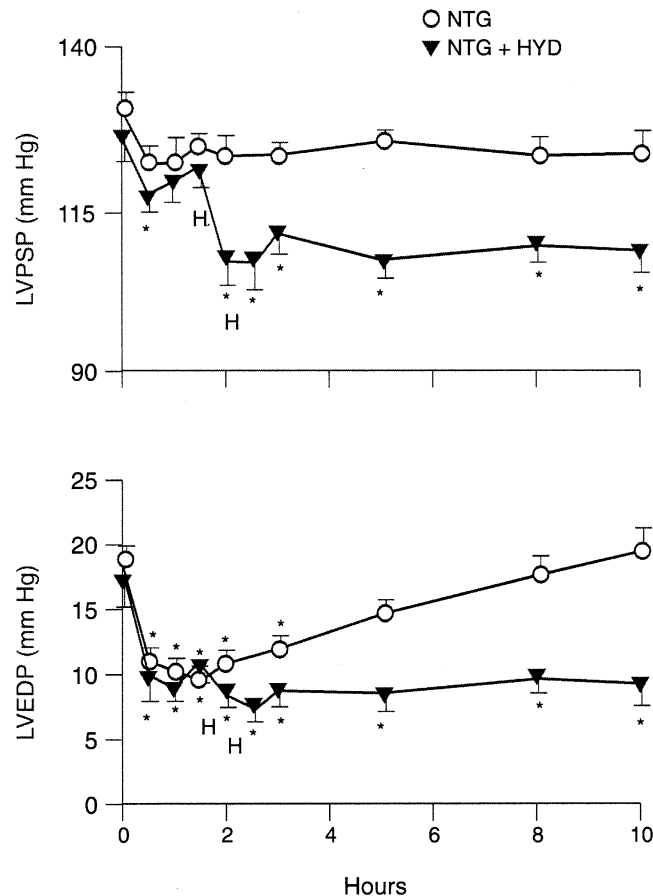


Figure 6. Effects of nitroglycerin (NTG) infusion alone ( $n = 7$ ) or in combination with hydralazine (HYD) ( $n = 8$ ) on left ventricular hemodynamics in rats with heart failure. NTG was infused at  $10 \mu\text{g}/\text{min}$  in both groups. Hydralazine (H) was administered at 1.5 and 2 hours (0.1-mg bolus) during NTG infusion. NTG alone produced initial reductions in left ventricular end-diastolic pressure (LVEDP), but had no effect on left ventricular peak systolic pressure (LVPS). LVEDP returned to baseline by 8 hours, indicating tolerance development. HYD caused significant reductions in LVPS, which were maintained throughout the remainder of the NTG infusion. Hemodynamic tolerance to NTG did not occur during coadministration with HYD. Values are expressed as mean  $\pm$  SEM. \*Statistically significant differences from baseline ( $p < 0.05$ ). (Reproduced with permission from *Circulation*.<sup>16</sup>)

ment of nitrate tolerance with marked attenuation of the initial hemodynamic effect.<sup>8,9</sup> It is therefore not surprising that various strategies have been proposed and attempted for preventing nitrate tolerance. These strategies include concomitant administration of sulfhydryl groups, an ACE inhibitor, or diuretics.<sup>10</sup> However, these methods have not been proven beneficial in patients with CHF.<sup>10–12</sup> Intermittent nitrate therapy, allowing a daily nitrate washout interval of at least 12 hours, has been effective in preventing nitrate tolerance,<sup>8,13</sup> but such a regimen is limited by its inability to provide a continuous and uninterrupted therapeutic effect. Interaction between HYD and nitrates was first reported by Unger and colleagues,<sup>14</sup> who demonstrated potentiation of nitroglycerin response with HYD incubation in isolated aortic rings rendered tolerant *in vivo* to nitroglycerin. Münzel and colleagues<sup>15</sup> later showed the ability of HYD to inhibit vascular superoxide production and prevent nitrate tolerance *in vitro*. The results of these investigations suggest that the antioxidant properties of HYD may be responsible for preventing nitrate tolerance. In 2 studies performed approximately 10 years ago, in an *in vivo* animal model of

CHF<sup>16</sup> and in patients with CHF,<sup>17</sup> it was also demonstrated that concomitant administration of HYD is useful in preventing nitrate tolerance.

In the first study, Bauer and Fung<sup>16</sup> produced CHF in Sprague-Dawley rats by ligating the left coronary artery, producing a myocardial infarction at the left ventricular free wall and apex. They then allowed the rats to recover for at least 6 weeks. The development of myocardial infarction resulted in elevated venous pressure and reduced cardiac output similar to the hemodynamic changes observed in patients with CHF. Infusion of nitroglycerin to the rats with CHF produced a reduction in left ventricular end-diastolic pressure of  $46\% \pm 3\%$ . However, with continuation of nitroglycerin infusion, the initial hemodynamic effect was not maintained, and left ventricular end-diastolic pressure returned to near baseline values within 6 hours as a result of the development of tolerance. Coadministration of HYD, which was given intravenously ( $2 \times 0.1\text{-mg}$  bolus injections) at 1.5 and 2 hours during nitroglycerin infusion, prevented the development of nitrate tolerance (Figure 6), and the initial reduction in left ventricular end-diastolic

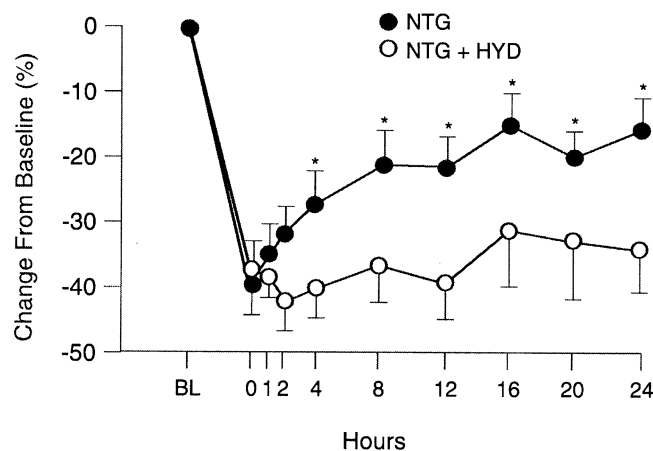


Figure 7. Mean pulmonary artery wedge pressure measured over time during 24-hour continuous administration of nitroglycerin (NTG) alone or in combination with oral hydralazine (HYD). \* $p < 0.05$  versus 0 hour. (Reproduced with permission from *J Am coll Cardiol*.<sup>17</sup>)

pressure with nitroglycerin was maintained throughout the 10-hour nitroglycerin infusion period. The plasma concentrations of nitroglycerin and dinitrate metabolites before and after HYD dosing were not significantly different. Because of the potential therapeutic value of these study results,<sup>17</sup> a similar experiment to evaluate the effect of oral HYD on the development of nitrate tolerance was conducted in 28 patients with chronic CHF (New York Heart Association [NYHA] functional class III or IV).<sup>17</sup> Patients were randomized to receive a continuous infusion of nitroglycerin for 24 hours either alone (14 patients, group 1) or concomitantly with oral HYD (14 patients, group 2) given at a dose of 75 mg 4 times daily and begun  $\geq 24$  hours before the study. Therapy with nitroglycerin was started in both groups at a rate of 20  $\mu\text{g}/\text{min}$ . The rate of infusion was increased in increments of 20 to 60  $\mu\text{g}/\text{min}$  every 5 minutes to achieve at least a 30% reduction in mean pulmonary artery wedge pressure or until a maximum dose of 560  $\mu\text{g}/\text{min}$  was reached. The dose required to achieve the desired hemodynamic response was maintained at the same rate for 24 hours, and hemodynamic measurements were repeated periodically throughout the study. Continuous infusion of nitroglycerin alone resulted in a gradual and significant attenuation of the initial effect of therapy (group 1) on mean pulmonary artery pressure ( $27\% \pm 4\%$  at 0 hour vs  $10\% \pm 3\%$  at 24 hours;  $p < 0.05$ ) and mean pulmonary artery wedge pressure ( $40\% \pm 4\%$  at 0 hour vs  $16\% \pm 4\%$  at 24 hours;  $p < 0.05$ ) (Figure 7). In contrast, in group 2, concomitant administration of oral HYD prevented nitroglycerin-induced hemodynamic tolerance and resulted in persistent effects on mean pulmonary artery and wedge pressures throughout the study period ( $31\% \pm 3\%$  at 0 hour vs  $27\% \pm 4\%$  at 24 hours [ $p = \text{NS}$ ] and  $37\% \pm 4\%$  vs  $34\% \pm 6\%$  [ $p = \text{NS}$ ], respectively). In addition, the initial effect on blood pressure reduction was attenuated at 24 hours in group 1 ( $12\% \pm 3\%$  at 0 hour vs  $5\% \pm 2\%$  at 24 hours;  $p < 0.05$ ), but not in group 2 ( $17 \pm 2\%$  at 0 hour vs  $15\% \pm 3\%$  at 24 hours;  $p = \text{NS}$ ). The results of this study support the observations made by Bauer and Fung<sup>16</sup> in animals,

indicating the ability of HYD to prevent early development of nitrate tolerance and maintain nitrate-mediated favorable hemodynamic effects.

## Conclusion

In both in vivo animal models of CHF and patients with chronic CHF, preview reports have demonstrated prevention of nitrate tolerance and preservation of nitrate-induced hemodynamic effects with concomitant administration of HYD. Studies with in vitro models of nitrate tolerance have demonstrated that HYD potentiates the vasorelaxing effect of nitroglycerin and reduces the formation of nitrate-mediated vascular superoxide that leads to nitrate tolerance. These data, in addition to the results of the V-HeFT and A-HeFT studies, which demonstrated a beneficial effect of ISDN-HYD on cardiac function, exercise tolerance, and survival, provide strong support for the combined use of nitrates with HYD in patients with CHF.

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