Using Hydralazine and Nitrates To Treat Heart Failure

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A Treatment of Refractory HF With Nitroprusside

Guiha NH, Cohn J
NEJM 1974

Figure 1. Average Percentage Change from Control Values during Intravenous Infusion of Sodium Nitroprusside in 18 Patients with Intractable Heart Failure.
Combined oral hydralazine nitrate therapy in left ventricular failure: hemodynamic equivalency to sodium nitroprusside.

Pierpont, Cohn, Franciosa JA

Effect of Hyd-N on LV Function
Massie B Am J Cardiol 1977
Indications For Use Of Vasodilators in Chronic HFrEF

Approved indications

- African Americans patients with symptomatic HFrEF.
- All patients with HFrEF not tolerating ACEi/ARBs/Entresto due to renal insufficiency or hyperkalemia.

Practical indications

- Pregnancy.
- Reduction of PA pressure in patients monitored with the CardioMems device.
1050 AA patients with HFrEF. NYHA III-IV.
Randomized to a fixed dose Hyd/ISDN (Bidil) or placebo in addition to standard HF therapy.
Primary end point: A composite of death, hospitalizations and QOL.
### A-HeFT Study
#### Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantable cardiac defibrillator (% of patients)</td>
<td>16.6</td>
<td>17.3</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>23.9±7.3</td>
<td>24.2±7.5</td>
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<tr>
<td>LVDD (cm)†</td>
<td>6.5±0.9</td>
<td>6.5±1.0</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
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<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>127.2±17.4</td>
<td>125.3±18.1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77.6±10.3¶</td>
<td>75.6±10.5 ¶</td>
</tr>
<tr>
<td>Minnesota Living with Heart Failure Questionnaire score (range, 0 to 105)</td>
<td>50.9±24.9¶</td>
<td>50.7±25.5 ¶</td>
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<tr>
<td>Medications for heart failure (% of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>88.0</td>
<td>91.5</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>69.4</td>
<td>69.5</td>
</tr>
<tr>
<td>ARB</td>
<td>17.2</td>
<td>16.5</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>74.1</td>
<td>73.5</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>55.2</td>
<td>55.8</td>
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<tr>
<td>Digoxin</td>
<td>58.5</td>
<td>60.7</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>40.2</td>
<td>37.6</td>
</tr>
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</table>
A-HeFT Results: **Additional 39% Risk Reduction in First Hospitalization for Heart Failure When Added to Current Standard Therapies**

- **Standard Therapies + BiDil**
  - Event rate = 16.4%
  - 39% Reduction*
  - $P < 0.001$ by Log-Rank Test

- **Standard Therapies + Placebo**
  - Event rate = 24.4%
A-HeFT
Quality of Life

Change in MLHF® Questionnaire Score

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Standard Therapies + BiDil</th>
<th>Standard Therapies + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>369</td>
<td>371</td>
</tr>
<tr>
<td>6</td>
<td>307</td>
<td>305</td>
</tr>
<tr>
<td>9</td>
<td>269</td>
<td>250</td>
</tr>
<tr>
<td>12</td>
<td>226</td>
<td>218</td>
</tr>
<tr>
<td>15</td>
<td>198</td>
<td>184</td>
</tr>
<tr>
<td>18</td>
<td>198</td>
<td>528</td>
</tr>
<tr>
<td>End point</td>
<td>512</td>
<td>528</td>
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</table>

*P<0.05
†P<0.01

MLHF® Questionnaire=Minnesota Living With Heart Failure® Questionnaire.
A-HeFT Results: **Additional 43% Reduction in Mortality When Added to Current Standard Therapies**

- **Standard Therapies + BiDil**: Event rate = 6.2%
- **Standard Therapies + Placebo**: Event rate = 10.2%

*43% Reduction* (P = 0.012 by Log-Rank Test)
A-HeFT vs PARADIGM - HF

Figure 1. Kaplan–Meier Estimates of Overall Survival.
A-HeFT vs SCD-HeFT

- HeFT vs SCD
  - 12% reduction in death and hospitalization, P=0.002
  - 4.5 mg/d vs 33 mg/d, 43% improvement in survival in 10 months, P=0.01
  - 23% survival benefit with ICD in 45 months, P<0.001

*Figure 1. Kaplan–Meier Estimates of Death from Any Cause. CI denotes confidence interval.*

*Figure 1. Kaplan–Meier Estimates of Overall Survival.*
Hyd/ISDN in Patients D/C from Hospital
Mullens W et al. Am J Cardiol 2009;103;1113

80% Caucasians
SBP 108 ± 16 mmHg
Mean PWP 24 ± 8 mmHg

Freedom from all cause mortality

Freedom from mortality and hospitalizations
Hydralazine-ISDN in AA patients with HF
Ziaeian B et al JACC HF 2017

- 15% treated with Hyd-ISDN before the admission.
- Mortality at 18 months was 22% vs 25% (p=0.009) HR 0.85.
Hydralazine and Oral Nitrates
When To Use It?

- A combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality in addition to BB and ACE-inhibitors for African Americans with HF and reduced LVEF:
  - NYHA III or IV HF
    
    Strength of Evidence = A

  - NYHA II HF
    
    Strength of Evidence = B

AHA/ACC 2013 Practice Guideline
Heart Failure Readmission Penalties, Care Quality, and Outcomes
Pandey et al. JACC Heart Failure August 2016

**Figure 1** Adherence to Get With The Guidelines-Heart Failure Performance Measures Across the Study Groups

N=43,143
GWTG-HF Registry
2008-2011

- ACEI/ARB
- Measured LV Function
- Aldosterone Antagonist
- Hydralazine Nitrates
- Blood Pressure Control
- Beta Blockers
- Smoking Cessation
- Discharge Instructions
- ICD (Apr-2003)
- HF Detect-Free Care
Potential Reasons For Underutilization

- Polypharmacy.
- Concerns of BP reduction.
- Side effects.
Figure 3
Time Course of Mean SBP and DBP
Change in the Placebo and FDC I/H Groups
Change in BP in relation to baseline BP

Anand et al JACC 207;49:32-9
### Table 4. Adverse Events.*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Isosorbide Dinitrate plus Hydralazine</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations of CHF</td>
<td>8.7</td>
<td>12.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Severe exacerbation of CHF</td>
<td>3.1</td>
<td>7.0</td>
<td>0.005</td>
</tr>
<tr>
<td>Headache</td>
<td>47.5</td>
<td>19.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dizziness</td>
<td>29.3</td>
<td>12.3</td>
<td>&lt;0.001</td>
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Indications For Use Of Vasodilators in Chronic HFrEF

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- African Americans patients with symptomatic HFrEF.
- All patients with HFrEF not tolerating ACEi/ARBs/Entresto due to renal insufficiency or hyperkalemia.

Practical indications

- Pregnancy.
- Reduction of PA pressure in patients monitored with the CardioMems device.
A combination of hydralazine and ISDN can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency. *(Level of Evidence: B)*
EFFECT OF VASODILATOR THERAPY ON MORTALITY IN CHRONIC CONGESTIVE HEART FAILURE

Results of a Veterans Administration Cooperative Study*

Jay N. Cohn, M.D., Donald G. Archibald, M.Phil., Susan Ziesche, R.N., Joseph A. Franciosa, M.D., W. Eugene Harston, M.D., Felix E. Tristani, M.D., W. Bruce Dunkman, M.D., William Jacobs, M.D., Gary S. Francis, M.D., Kathleen H. Flohr, M.D., Steven Goldman, M.D., Frederick R. Cobb, M.D., Pravin M. Shah, M.D., Robert Saunders, M.D., Ross D. Fletcher, M.D., Henry S. Loeb, M.D., Vincent C. Hughes, M.D., and Bonnie Baker, M.D.

Abstract: To evaluate the effects of vasodilator therapy on mortality in 642 men with HF, at a mean EF of 30%, mean max O2 consumption 14.5 ml/Kg/min, and on digoxin and diuretics, 273 were randomized to either placebo, 183 to prazosin (20 mg/d), and 186 to HYD (300 mg/d) plus ISDN (160 mg/d). The average doses were: Hydralazine 270 mg/d, ISDN 136 mg/d.

642 men with HF,
Mean EF of 30%, mean max O2 consumption 14.5 ml/Kg/min,
On digoxin and diuretics.
Randomized to either placebo, N=273, prazosin (20 mg/d), N=183 or HYD (300 mg/d) plus ISDN (160 mg/d) N= 186.
Average doses: Hydralazine 270 mg/d, ISDN 136 mg/d.

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V-HeFt Study
Effect on all cause mortality

34% mortality Reduction for 1st 2 y with Hyd-Iso
P=0.028

Figure 1. Cumulative Mortality from the Time of Randomization in the Three Treatment Groups.
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<th>Practical indications</th>
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</thead>
<tbody>
<tr>
<td>African Americans patients with symptomatic HFrEF.</td>
<td>Pregnancy.</td>
</tr>
<tr>
<td>All patients with HFrEF not tolerating ACEi/ARBs/Entresto due to renal insufficiency or hyperkalemia.</td>
<td>Reduction of PA pressure in patients monitored with the CardioMems device.</td>
</tr>
</tbody>
</table>
The increase in mean PA pressure was $1.3 \pm 5.6$ mmHg before a HF hospitalization compared with $-0.3 \pm 5.5$ mm Hg before a non-HF hospitalization ($P=0.0034$).

### Table 10. Change in Total Daily Dose of Heart Failure Medications (Reduced EF)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline (Mean±SD)</th>
<th>6 mo (Mean±SD)</th>
<th>Change From Baseline Mean</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment (n=208)</td>
<td>Control (n=222)</td>
<td>Treatment (n=208)</td>
<td>Control (n=222)</td>
</tr>
<tr>
<td>Reduced (EF&lt;40%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrate</td>
<td>64.51±32.21</td>
<td>48.33±30.01</td>
<td>82.68±53.62</td>
<td>50.90±31.66</td>
</tr>
<tr>
<td>Diuretic loop</td>
<td>97.05±70.22</td>
<td>92.95±64.14</td>
<td>115.9±89.82</td>
<td>110.9±90.57</td>
</tr>
<tr>
<td>Diuretic thiazide</td>
<td>2.92±1.98</td>
<td>3.42±2.47</td>
<td>3.92±4.04</td>
<td>3.43±3.18</td>
</tr>
</tbody>
</table>
Hemodynamic Effects of Hydralazine/Nitrate Combination
Roth, Elkayam AHJ 1993;125:155
Limitations of Nitrate Therapy

- Nitrate resistance
- Nitrate tolerance
Nitrate Resistance

The need to increase the dose to overcome insufficient hemodynamic response to standard dose.
Nitrate Resistance in Chronic HF
Kulic D, Elkayam U JACC 1988;12:1023

- 50 patients receiving 40 mg of ISDN.
- 27 responders and 23 non responders (>20% reduction in PCW lasting for at least 2 hours)
- Only 2 of the 14 non responders to 40 mg responded to 80 mg.
- Only 8 of 20 non responders to 40 mg (8pts) and 80 mg (12 pt) responded to 120 mg.
RA pressure Non Responders 14+/−6 mmHg, Responders 10+/−6 mmHg, P<0.02
Nitrate Resistance in Chronic HF
Kulic D, Elkayam U JACC 1988;12:1023

Table 1. Baseline Characteristics of 27 Responders and 23 Nonresponders to 40 mg of Isosorbide Dinitrate

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 27)</th>
<th>Nonresponders (n = 23)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom duration (mo)</td>
<td>37 ± 40</td>
<td>22 ± 26</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (n = 45)</td>
<td>0.23 ± 0.07</td>
<td>0.24 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pressures (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA (mmHg)</td>
<td>10+/-6</td>
<td>14+/-5</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

CI (liters/min per m²) 2.1 ± 0.5 1.9 ± 0.4 NS
SVI (ml/m²) 24 ± 7 21 ± 7 NS
HR (beats/min) 91 ± 16 94 ± 16 NS
MAP (mm Hg) 95 ± 14 92 ± 14 NS
SVR (dynes-s-cm⁻⁵) 1827 ± 491 1718 ± 407 NS
PVR (dynes-s-cm⁻⁵) 398 ± 557 260 ± 146 NS
SWI (g-m/m²) 23 ± 11 18 ± 9 NS

CI = cardiac index; HR = heart rate; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; PA = pulmonary arterial pressure; PAW = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RA = right atrial pressure; SVI = stroke volume index; SVR = systemic vascular resistance; SWI = stroke work index.

Figure 3. Response to high dose (80 to 120 mg) isosorbide dinitrate (ISDN) in 23 nonresponders to the 40 mg dose. D/C = excluded from study.
Dose Requirements of Hydralazine in Patients with Chronic HF

Packer M et al Am J Cardiol 1980;45:655

**Figure 1.** Relation between the control mean right atrial pressure and the percent decrease (%↓) in systemic vascular resistance observed after the administration of single oral doses of 100 mg of hydralazine in 45 patients. Data expressed as mean ± standard error of the mean. The proportion of patients who responded to hydralazine at each level of mean right atrial pressure is shown within each bar.
Nitrate tolerance

Nitrate tolerance is the loss of effects, or the necessity to increase dosages to maintain the effects, of organic nitrates.
ISDN in HF: Dosing Intervals
Strategies to Prevent Nitrate Tolerance

- Anti oxidants (Vitamin C, Hydralazine).
- Concomitant use neurohormononal blockers (RAASi, BB).
- Nitrate free intervals.
- Escalating dose.
Strategies to Prevent Nitrate Tolerance

- Anti oxidants (Vitamin C, Hydralazine).
- Concomitant use neurohormonal blockers (RAASi, BB).
- Nitrate free intervals.
- Escalating dose.
Prevention of Nitrate Tolerance with Hydralazine in Patients with Heart Failure
Gogia H, Elkayam U. JACC 1995;26:575

*P<0.05 vs 0 hours.
Consequences of Nitric Oxide and Super Oxide Balance Disruption in Heart Failure Patients


[Diagram] Nitric oxide synthase and oxidase pathways in the context of heart failure patients. Nitric oxide and oxygen react to form peroxynitrite (ONOO−), leading to cell damage, DNA damage, oxidized proteins, and endothelial dysfunction. Isosorbide dinitrate and hydralazine inhibit these processes. L-Arginine is converted to citrulline, and cyclic guanosine monophosphate is formed through the physiologic pathway. S-nitrosylation modifies effector molecules post-translationally.
Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Organic Nitrates in Patients With Chronic Heart Failure Treated With Angiotensin-Converting Enzyme Inhibition

Uri Elkayam, MD; Janet V. Johnson, RN, BSN; Avraham Shotan, MD; Syed Bokhari, MD; Alejandro Solodky, MD; Menahem Canetti, MD; Omar Rashid Wani, MD; Ilyas Somer Karaalp, MD

Background—Organic nitrates are widely used in the treatment of chronic heart failure (CHF). No information, however, is available regarding their effect in patients already treated with ACE inhibitors.

Methods and Results—In a randomized, double-blind, crossover design, we studied the effects of high-dose (50 to 100 mg) transdermal nitroglycerin (NTG) and placebo given daily for 12 hours in 29 patients with CHF (NYHA functional classes II to III). Exercise time (4 hours after patch application) showed a progressive improvement during NTG administration, with an increase of 38±35 seconds (9±7%) at the end of the first month (P=NS), 76±28 seconds (16±6%) at the end of the second month (P=0.01), and 117±34 seconds (27±6%) at the end of the third month (P=0.003). No significant change was seen during placebo administration (12±20, 5±26, and 19±28 seconds, all P=NS). Exercise time 8 hours after NTG application measured at 3 months was also significantly longer, with a difference of 87±28 seconds (P=0.006), but not with placebo (23±36 seconds, P=0.53). Assessment of quality of life and need for additional diuretics or hospitalizations for CHF failed to demonstrate a significant difference between the 2 treatment periods. In contrast, NTG decreased left ventricular end-diastolic (−2.1±0.1%, P<0.05) and end-systolic (−3.2±1.3%, P<0.05) dimensions and augmented LV fractional shortening (24.7±10.5%, P<0.03). The effect of placebo on these parameters was not statistically significant.

Conclusion—High-dose nitrate therapy significantly improves exercise tolerance and left ventricular size and systolic function in patients with chronic, mild to moderate CHF already treated with ACE inhibitors. These findings support the role of organic nitrates as an adjunctive therapy to ACE inhibitors in patients with chronic CHF. (Circulation. 1999;99:2652-2657.)
Effect of Organic Nitrates In Chronic HFrEF

Figure 1. Study design included a single-blind placebo stabilization period of 1 week and 2 periods of 12 weeks each in which patients were randomized and crossed over to receive transdermal NTG 50 to 100 mg for 12 h/d or transdermal placebo. The 2 treatment periods were separated by 4 weeks of a single-blind placebo washout period.

Figure 3. Change in treadmill exercise time from baseline 8 hours after patch application at end of 3 months of treatment with NTG and placebo.
Effect of Organic Nitrates In Chronic HFrEF

Figure 2. Change in treadmill exercise time from baseline 4 hours after administration of NTG (△) and placebo (○).

Figure 5. Percent change in LVEDD, LVESD, and fractional shortening (FS) from baseline after 3 months of therapy with NTG (solid bars) and placebo (open bars). *Statistically significant.

Elkayam U et al Circulation 1999;99:2652-7
Escalating Dose Overcomes Nitrate Tolerance
Mehra A Elkayam U et al. Am Heart J 1995;130:798
Summary

- Hyd/ISDN combination (Bidil) is one of the most effective and underutilized intervention for the treatment of AA patients with symptomatic HFrEF.

- Use of Hyd/ISDN is recommended in pregnant women with HF and all ACEi/ARB intolerant HF patients including non AA.
Understanding the limitations of nitrate therapy can help in maximizing the hemodynamic benefits.
Use nitrates in combination with hydralazine.

Nitrate free interval – q 6 h for 3 doses.

Try escalating dose with hemodynamic monitoring.

Higher dose to patients with RA hypertension.

Borderline BP not always a contra indication.