Rest and Exercise Hemodynamic Effects of Oral Hydralazine in Patients with Coronary Artery Disease and Left Ventricular Dysfunction

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SUMMARY To determine the hemodynamic effects of afterload reduction at rest and during upright exercise in patients with coronary artery disease and left ventricular dysfunction, 12 patients were studied before and after taking 50–75 mg of oral hydralazine every 6 hours for 48 hours. Oxygen consumption and heart rate were unchanged from control both at rest and during two workloads on a bicycle ergometer. Cardiac output was significantly increased at rest and during both workloads. The arteriovenous oxygen difference was significantly reduced at rest and during exercise. Pulmonary capillary wedge pressure was also significantly lower at rest and during exercise. Systemic vascular resistance was reduced at rest, and exercise-induced vasodilation was augmented by the administration of hydralazine. Left ventricular end-diastolic volume and ejection fraction assessed by radionuclide angiocardiography were not significantly changed at rest or during exercise after hydralazine. Seven of the 12 patients have maintained clinical improvement during a follow-up of 6–12 months.

Hemodynamic improvement provided by oral hydralazine at rest is maintained during moderate exertion in patients with coronary artery disease and left ventricular dysfunction. In selected patients, chronic afterload reduction with oral hydralazine may result in increased cardiac reserve, decreased pulmonary congestion or decreased myocardial oxygen demands, thereby improving or abolishing resting or exertional dyspnea or angina.

PATIENTS with obstructive coronary artery disease may experience symptoms of low cardiac output (CO) or pulmonary congestion. Often occurring at rest or with mild exertion, these symptoms may drastically restrict activity. For patients who continue to have symptoms despite therapy with digitalis glycosides, diuretic agents and nitrates, treatment with afterload-reducing agents has become widespread. Beneficial hemodynamic effects, especially decreased left ventricular (LV) filling pressure and enhanced stroke volume (SV) and CO, have been shown with a variety of vasodilators in patients with severe cardiac failure due to many etiologies. Most studies of vasodilator therapy have been performed with parenteral agents or single doses of medication, and with patients at rest in the supine position. Though investigators have recently begun to evaluate oral vasodilators in ambulatory patients, data concerning the effects of vasodilators on the hemodynamic response to exercise are still preliminary. Because the major disability in patients with advanced coronary artery disease is usually reduced exercise tolerance caused by angina, fatigue or dyspnea, a critical evaluation of the hemodynamic effects of vasodilator therapy during moderate exertion is important if this mode of therapy is to be used rationally and safely. Therefore, we sought to determine the short-term hemodynamic effects of oral hydralazine at rest and during moderate upright exercise.

Methods

Twelve patients with coronary artery disease and LV dysfunction were studied (table 1). The patients included 11 men and one woman, ages 47–69 years. All 12 patients had had at least one documented myocardial infarction, but not within 3 months of this study. All patients were in New York Heart Association (NYHA) functional class III or IV; eight were limited by severe angina pectoris and four primarily by symptoms of congestive heart failure. Conventional therapy with digitalis glycosides, diuretic agents, nitrates and β-blocking agents had been used when appropriate.

Eleven patients had undergone cardiac catheterization with biplane left ventriculography and selective coronary arteriography that documented the existence of three-vessel coronary artery disease (≥ 75% narrowing of the luminal diameter of the coronary arteries) and severe LV dysfunction (depressed LV ejection fraction [EF]: mean 0.23, range 0.12–0.31). The one patient who had not undergone catheterization had had two myocardial infarctions and an EF of 0.22 determined by radionuclide angiocardiography. Left ventriculography revealed mitral regurgitation in 10 patients, which was mild in nine and severe in one. None had aortic valve disease. Data obtained during cardiac catheterization are summarized in table 2.

All patients gave written informed consent and were admitted to the Clinical Research Unit. Maintenance medications except nitroglycerin and long-acting nitrates were continued throughout the study. During

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Table 1. Clinical Characteristics

<table>
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<tr>
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<th>Major symptom</th>
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Abbreviations: AMI = anterior myocardial infarction; DMI = diaphragmatic myocardial infarction; NYHA class = New York Heart Association functional class; CHF = congestive heart failure; Dig = digitalis; D = diuretics; N = nitroglycerin; LAN = long-acting nitrates; P = propranolol.

Exercise Protocol

All patients were studied in the postabsorptive state without premedication. A single lead of the ECG was continuously monitored. Hemodynamic and oxygen consumption determinations were obtained and radionuclide angiography was performed with patients in the resting state seated on a bicycle ergometer (Monarch, Quinton Industries, or Fitron, Cybex Co.). Patients then exercised at a work load of 150 kilopond-meters (kpm) for 4 minutes, with hemodynamic and oxygen consumption determinations and radionuclide angiography performed during the fourth minute of exercise. After a 6-8-minute rest, during which time all hemodynamic variables returned to control values, patients exercised at a work load of 300 kpm. Repeat studies were obtained during the fourth minute at this work load.

Hemodynamic Studies

An intra-arterial Teflon catheter was inserted percutaneously into a brachial or radial artery for measurement of systemic arterial pressure and withdrawal of blood samples. A balloon-tipped, flow-directed catheter (Edwards Laboratories) was inserted percutaneously, or through a venous cutdown, into an antecubital vein and advanced under fluoroscopic control to the pulmonary artery for measurement of pulmonary artery and pulmonary capillary wedge pressures and withdrawal of blood samples. Pressures were recorded using Statham P23Db transducers and a Hewlett Packard 4588 multichannel recorder. Expired air was collected for determination of total body oxygen consumption (VO2); CO was determined by the Fick technique. Both catheters were removed at the end of the control study and reinserted for the study after administration of hydralazine.

All measurements and determinations were made with the patients at rest and during exercise in the sitting position. Heart rate (HR), systolic (SAP), diastolic (DAP) and mean arterial (MAP) pressures, mean pulmonary artery (PAP) and pulmonary capillary wedge (PCWP) pressures, VO₂, and...
pulmonary and systemic arterial oxygen content were measured or determined directly. Arteriovenous oxygen difference (AVO₂), CO and cardiac index (CI), SV and systemic vascular resistance were derived from standard formulas.

In three situations (two patients), PCWP could not be measured. The pulmonary artery diastolic pressure during 10 consecutive heart beats was measured and averaged in these cases.

Radionuclide Angiocardiography

A 20-gauge Teflon catheter was inserted percutaneously into an external jugular or antecubital vein for injection of 15 mCi of technetium-99m pertechnetate during the rest period and again at each work load (150 kpm and 300 kpm). Images were obtained from the anterior position with a Baird Atomic Seventy-seven computerized multicrystal gamma camera. Our technique for determining LV function from data obtained by the first passage of tracer through the central circulation has been reported. The method uses standard angiographic planimetry of the static LV end-diastolic volume (EDV) image. EDV is obtained by using the length-area measurement implied by the prolate ellipsoid model described by Dodge et al. A regression equation from 33 patients studied before contrast left ventriculography gave the appropriate corrected EDV. The following list summarizes mathematical techniques for determining LV function from data obtained by the first passage of tracer through the central circulation:

\[
LVEF = \frac{\text{end diastolic counts} - \text{end systolic counts}}{\text{end-diastolic counts}} \times 100
\]

\[
LVEDV = \frac{0.85A^2}{l}
\]

where the end-diastolic image was used to obtain the area (A) by planimetry and the length (l) by direct measurement.

\[
SV = LVEDV \times LVEF
\]

\[
CO = SV \times HR
\]

The accuracy and reliability of this volumetric technique has been verified in patients and normal subjects by comparison with contrast left ventriculography and dye-dilution CO. Correlation coefficients for LVEDV, LVEF and CO were 0.89, 0.89 and 0.95, respectively.

Hydralazine Dosage

After the control hemodynamic and radionuclide studies were completed, 50 mg of oral hydralazine was administered every 6 hours for a total of three doses. The dose of hydralazine was then increased to 75 mg unless HR had increased more than 20% above control (one patient) or SAP had decreased more than 20% below control (one patient). Two patients experienced an increase in HR greater than 20% above control with 75 mg of hydralazine and the dose was decreased to 50 mg. Eight doses of hydralazine were administered to each patient.

Follow-up

All patients were discharged on hydralazine. Eight of the patients were also treated with isosorbide dinitrate after discharge. Each patient was seen 1 month after initiation of oral hydralazine and then seen or followed by telephone at 1–2-month intervals for at least 6 months. NYHA functional class for angina and symptoms of cardiac failure was determined subjectively. Radionuclide angiocardiography was performed 1 month after initiation of oral hydralazine in 11 of the patients. Isosorbide dinitrate was discontinued 24 hours before restudy in these patients.

Statistical Analysis

Statistical analysis of the data was performed using the paired t test (two-tailed). Significance of data was determined at the level of \( p < 0.05 \).

Results

Hemodynamics

Control and posthydralazine hemodynamic measurements (mean ± sp) at rest and during both exercise levels are presented in table 3.

Rest

The resting V̇O₂ and HR were unchanged after hydralazine. There was an insignificant decline in MAP, from 86 ± 9 mm Hg to 80 ± 8 mm Hg. When patients were separated into two groups (angina or congestive heart failure), the response of resting arterial pressure differed (fig. 1). MAP decreased in the group with angina (from 90 ± 4 mm Hg to 80 ± 8 mm Hg, \( p < 0.05 \)), but was unchanged in the group with congestive heart failure.

CO at rest increased after hydralazine in 10 of the 12 patients, with an average overall increase of 29% (from 4.8 ± 1.0 l/min to 6.2 ± 1.3 l/min, \( p < 0.01 \)). There was also a significant reduction in the AVO₂ at rest after 48 hours of hydralazine (fig. 2).

Systemic vascular resistance was reduced significantly at rest, from 1532 ± 366 dyn-sec-cm⁻⁵ to 1105 ± 352 dyn-sec-cm⁻⁵ (\( p < 0.01 \)). Before hydralazine, the PCWP was 6–30 mm Hg at rest; after hydralazine, PCWP decreased in 10 patients. The mean PAP responded similarly to hydralazine. The responses of systemic vascular resistance and PCWP in individual patients are shown in figure 3.

Exercise

During exercise, V̇O₂, HR and arterial pressure all increased above resting values. At both exercise levels
TABLE 3. Hemodynamic Data

<table>
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<th>VO₂ (ml/min)</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Mean</th>
<th>AVO₂ (vol%)</th>
<th>CO (l/min)</th>
<th>SVR (dyn-sec/cm²)</th>
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<td>±1.8</td>
<td>±1.3</td>
<td>±201</td>
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</table>

Values are mean ± SD.

*p < 0.05 vs control.

†p < 0.01 vs control.

‡p < 0.001 vs control.

Abbreviations: C = control; H = hydralazine; Ex = exercise level; HR = heart rate; VO₂ = total body oxygen consumption; AVO₂ = arteriovenous oxygen difference; CO = cardiac output; SVR = systemic vascular resistance; PA = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure.

After 48 hours of oral hydralazine, VO₂ and HR were unchanged from control (table 3). MAP for the 12 patients during exercise was lower after hydralazine. However, in the four patients whose predominant symptom was pulmonary congestion, SAP and MAP increased during exercise after hydralazine (fig. 1).

During exercise, CO and AVO₂ increased above resting values. After hydralazine the exercise-induced increase in CO was enhanced and the AVO₂ was significantly reduced (fig. 2).

The peripheral vasodilation that occurred with exercise in the control studies was augmented after hydralazine (fig. 3). PCWP increased during both exercise levels, and during the second work load, 10 patients had control PCWPs of 18 mm Hg or greater (fig. 2). After hydralazine, the PCWP was reduced and the difference between the mean control and hydralazine values was greater during the second work load than at rest or during the first work load (fig. 4).

Radionuclide Angiography

Data obtained by radionuclide angiocardiography in nine patients are summarized in table 4. LVEDV and EF did not change significantly at rest or during exercise after hydralazine. CO increased above the mean control values at rest and during exercise 48 hours after hydralazine. One month later the increased CO was maintained during exercise but not at rest.

Clinical Response

All 12 patients completed both work loads before and after hydralazine. Symptoms did not limit the exercise performance of these patients, although two patients developed angina during the last 30 seconds.
HYDRALAZINE IN CAD AND LV DYSFUNCTION/Hindman et al.

Figure 2. Changes in arteriovenous oxygen difference (panel A) and cardiac output (panel B) from control (C) to 48 hours after continued hydralazine therapy (H) at rest and during the second exercise level (Ex2).

Table 4. Rest and Exercise Radionuclide Angiocardiography

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<tr>
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<th>CO (l/min)</th>
<th>LVEDV (ml)</th>
<th>LVEF (%)</th>
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<tr>
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<td></td>
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<td></td>
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<tr>
<td>C</td>
<td>5.1 ± 1.2</td>
<td>263 ± 88</td>
<td>26 ± 8</td>
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<tr>
<td>H</td>
<td>6.3 ± 0.8†</td>
<td>282 ± 94</td>
<td>28 ± 14</td>
</tr>
<tr>
<td>1 month</td>
<td>5.8 ± 1.1</td>
<td>277 ± 82</td>
<td>26 ± 7</td>
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<tr>
<td>Ex2</td>
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<tr>
<td>C</td>
<td>8.8 ± 1.6</td>
<td>288 ± 91</td>
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<tr>
<td>H</td>
<td>10.6 ± 2.1†</td>
<td>278 ± 73</td>
<td>31 ± 11</td>
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<td>1 month</td>
<td>10.6 ± 2.0*</td>
<td>289 ± 55</td>
<td>31 ± 7</td>
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Values are mean ± sd.
* p < 0.05 vs control.
† p < 0.01 vs control.

Abbreviations: C = control; H = hydralazine; Ex = exercise level; CO = cardiac output; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction.

Figure 3. Changes in systemic vascular resistance (panel A) and pulmonary capillary wedge pressure (panel B) from control (C) to 48 hours after continued hydralazine therapy (H) at rest and during the second exercise level (Ex2).

Figure 4. Effects of exercise and hydralazine on the pulmonary capillary wedge pressure (mean ± sd). Before hydralazine (control), wedge pressure increased progressively during the two exercise levels (Ex1 and Ex2). After therapy with hydralazine, the wedge pressure is decreased at rest and during both work loads compared with control; the difference between control and post-hydralazine pulmonary capillary wedge pressure is greatest during Ex2.
of the second work load during the control study, but not during the posthydralazine study. The responses of CO, AVO₂ and PCWP after hydralazine in these two patients were not different from those in the 10 patients who did not experience angina. Eight of these latter 10 patients experienced mild-to-moderate dyspnea during the control study, but only three reported no subjective improvement after hydralazine. None of the patients developed electrocardiographic evidence of myocardial ischemia or injury. The hospital course of each patient was uneventful.

All patients have been followed for at least 6 months after initiation of hydralazine. The patients' dosage of hydralazine, clinical status (NYHA class) during follow-up, and changes in therapy are shown in table 5. One month after initiation of hydralazine, seven of the patients with angina and three of the patients with cardiac failure experienced subjective improvement (NYHA class III or IV to class I or II). During the 6–12-month follow-up, five of the patients with angina and two of the patients with cardiac failure maintained clinical improvement. Six patients required an increase in diuretic dose because of fluid retention. One patient with angina (patient 4) dramatically improved for 6 months but then experienced a sudden increase in the severity and frequency of angina that led to major changes in therapy, including discontinuation of hydralazine. One patient with cardiac failure (patient 7) did not experience any clinical improvement but had fluid retention, and hydralazine was discontinued after 4 months.

Discussion

Although conventional pharmacologic therapy, prolonged bed rest and coronary artery bypass surgery have been beneficial for some patients with cardiomyopathy due to coronary disease, the overall response has been poor and only temporary.3, 4, 27–29 The most important recent advance in the medical management of chronic heart failure has been the use of vasodilators, which decrease LV preload or afterload or both. Improved CO and reduced pulmonary venous congestion with these agents have led to widespread use of a variety of vasodilators in the treatment of patients with refractory cardiac failure.12–17

Studies of the hemodynamic effects of hydralazine in patients with severe heart failure have shown significant improvement in cardiovascular performance. In patients at rest in the supine position, SV and CO are augmented, AVO₂ is decreased, arterial pressure is decreased slightly or does not change, and HR is increased slightly or does not change.15, 16, 20 The reported response of PCWP to oral hydralazine has been variable.15, 16, 20, 32 Chatterjee et al.16 found no significant change in filling pressure with 50–75 mg of hydralazine given every 6 hours for 24 hours, but a significant decrease in PCWP was found in two other studies using similar doses.15, 30 In eight of 15 patients treated with 50–75 mg every 6 hours, LeJemtel et al.31 found that PCWP decreased significantly over 24 hours (26 mm Hg to 14 mm Hg), associated with an increase in urinary sodium excretion. Packer et al.32 demonstrated a dose-dependent reduction in LV filling pressure after single doses of hydralazine. A significant decrease was seen after 100 mg of hydralazine, and these patients experienced a brisk diuresis. Finally, Chatterjee et al.20 showed a reduction in PCWP in patients with severe mitral regurgitation, a result of decreased systemic resistance and redistribution of LVSV so that forward SV was increased and regurgitant fraction decreased.

Many patients with LV dysfunction do not have symptoms of limited cardiac reserve at rest, but such symptoms occur during mild or moderate exertion. Thus, an important therapeutic objective in ambulatory patients is to improve exercise tolerance.

<table>
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<th>Patient</th>
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<th>Follow-up NYHA class</th>
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<td>12</td>
<td>300</td>
<td>6</td>
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Abbreviations: ↑ = increase; NYHA = New York Heart Association.
vasodilator-induced improvement in cardiac function at rest is maintained during exercise in the upright position, and hemodynamic improvement is sustained during prolonged follow-up, exercise capacity may be expected to improve. Studies have shown a decrease in PCWP and systemic vascular resistance and a small increase in CI during submaximal exercise after administration of long-acting nitrate preparations. In addition, Chatterjee et al. noted improved CI and reduced AVO₂ but no change in PCWP during exercise after treatment with hydralazine or prazosin. Franciosa et al. recently showed no difference in exercise duration, maximal total body VO₂ or maximal CO after single doses of hydralazine and isosorbide dinitrate; however, a significant increase in CO and decrease in systemic vascular resistance was noted during submaximal exercise (300 kpm/min) after this combination therapy. Other studies have shown increased exercise capacity after long-term vasodilator therapy for congestive heart failure. Investigators have also observed sustained clinical improvement with chronic hydralazine therapy and other non-parenteral agents; and sustained hemodynamic improvement has been noted with hydralazine and with isosorbide dinitrate and phenoxybenzamine.

In the present study, the patients all had coronary artery disease with a markedly depressed LVEF, and most had dilated ventricles and mitral regurgitation. Resting CO and PCWP at the time of diagnostic right- and left-heart catheterization were normal in many of the patients; however, all the patients had severely limited exercise tolerance. In a majority of the patients, disabling angina pectoris limited their tolerance for activities that would provoke symptoms of cardiac failure. After 48 hours of hydralazine in these patients with coronary disease and LV dysfunction, CO is increased, AVO₂ is reduced and PCWP and systemic vascular resistance are decreased at rest in the upright position. Exercise-induced peripheral vasodilation is augmented by hydralazine, and the enhanced CO and reduced AVO₂ at rest after hydralazine are maintained during submaximal exercise. In addition, the exercise-induced elevation of PCWP was blunted in all 12 patients after hydralazine. This beneficial change may have been a major reason for the prolonged clinical improvement of these patients, particularly because repeat radionuclide angiography after 1 month revealed that improvements in SV and CI were sustained in only three patients at rest and in four patients during exercise.

The hemodynamic improvement in these patients is probably a direct effect of hydralazine on arterial resistance. The cardiovascular response initiated by the decrease in systemic vascular resistance consisted of increased forward flow, which was not associated with reflex tachycardia or a marked drop in arterial pressure. A reduction in PCWP and an increase in CO without decreased EDV and increased LVEF may be due to a change in the ventricular pressure-volume relationship (compliance), as has been shown with nitroprusside, or it may indicate insensitivity of radionuclide angiography in detecting small changes when the ventricle is dilated and the EF markedly depressed. A reduction in the regurgitant fraction ejected across an incompetent mitral valve also may have been an important factor in the hemodynamic improvement at rest and during exercise after hydralazine in the present study.

Vasodilator therapy has been extensively studied in patients with severe heart failure (NYHA class IV) and markedly depressed CO and elevated LV filling pressure. The effects of vasodilators in ambulatory, less symptomatic patients during exercise and over long periods of time are not as well defined. The present study indicates that afterload reduction with oral hydralazine in patients with cardiomyopathy due to coronary artery disease is associated with 1) beneficial hemodynamic effects on SV, CO, AVO₂, systemic vascular resistance and PCWP at rest in the upright position; 2) persistent and sometimes greater beneficial hemodynamic changes during submaximal exercise in the upright position; and 3) sustained clinical improvement in a majority of patients. Future experimental and clinical studies need to define the metabolic and hemodynamic effects of prolonged vasodilator therapy in patients with coronary disease. Studies of large numbers of patients will be required to assess the effect of such therapy on long-term morbidity and mortality.

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