Hydralazine Therapy in Severe Chronic Heart Failure: Inability of Radionuclide Left Ventricular Ejection Fraction Measurement to Predict the Hemodynamic Response

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Simultaneous hemodynamic and radionuclide angiographic assessment was made at rest and during exercise in nine patients with severe chronic congestive heart failure to determine the value of radionuclide left ventricular ejection fraction measurement in predicting the hemodynamic response to short-term treatment with oral hydralazine. Hydralazine, 50 to 100 mg orally every 6 hours, produced significant increases in cardiac index and stroke volume index at rest and during exercise (p < 0.01) and in left ventricular stroke work index at rest (p < 0.01) and during exercise (p < 0.05), significant decreases in systemic vascular resistance at rest and during exercise (p < 0.01) and significant increases in radionuclide angiographic left ventricular ejection fraction at rest (control 0.21 ± 0.06 vs. hydralazine 0.26 ± 0.07, p < 0.01) and during exercise (control 0.21 ± 0.08 vs. hydralazine 0.24 ± 0.09, p < 0.05). However, there were no statistically significant correlations between changes in radionuclide ejection fraction with hydralazine and changes in hemodynamic variables with hydralazine, either at rest or during exercise. Patients responding hemodynamically to hydralazine could not be separated from those not responding on the basis of the radionuclide ejection fraction at rest or changes in ejection fraction with hydralazine.

It is concluded that: 1) hydralazine exerts beneficial effects on cardiac index, stroke volume index, left ventricular stroke work index and systemic vascular resistance both at rest and during exercise; 2) hydralazine therapy is associated with improvement in the radionuclide left ventricular ejection fraction both at rest and during exercise; but 3) the radionuclide ejection fraction response to hydralazine does not correlate with and cannot be used to predict the hemodynamic response to hydralazine in patients with severe chronic congestive heart failure.

Various vasodilator agents have been demonstrated to produce beneficial hemodynamic responses in patients with chronic congestive heart failure. In particular, hydralazine, a vasodilator agent that acts predominantly on the arterial bed, increases cardiac output and decreases systemic vascular resistance both at rest and during exercise in patients with heart failure (1–6). Currently, evaluation of the hemodynamic effects of hydralazine therapy in patients with heart failure requires invasive monitoring with a Swan-Ganz thermodilution catheter, and as a result, necessitates hospitalization of such patients, usually in an intensive care unit, and exposes them to the potential hazards of invasive monitoring (7). Thus, an accurate noninvasive method of evaluating the hemodynamic effects of hydralazine therapy in patients with heart failure would be valuable and could obviate the need for hospitalization and invasive monitoring of such patients.

Radionuclide angiography is one noninvasive approach that has been employed with patients with heart failure to assess the effects on left ventricular performance of various drugs, including the vasodilator agents hydralazine (4,8), prazosin (9–11), captopril (12,13) and nitroprusside (14). Improvement in the radionuclide left ventricular ejection fraction, either at rest or during exercise, in response to vasodilators has been documented (8–11,13). However, the clinical utility of radionuclide angiography in assessing the
effects of vasodilators in individual patients with heart failure remains to be defined; it has been suggested that the radionuclide left ventricular ejection fraction may be insensitive in determining the response to vasodilators in patients with a markedly decreased ejection fraction and a dilated left ventricle (8,14–16).

The present study was undertaken to investigate the effects of short-term oral hydralazine therapy in patients with severe chronic heart failure, with simultaneous hemodynamic and radionuclide angiographic assessment at rest and during exercise, to determine whether or not radionuclide angiographic left ventricular ejection fraction measurement is of value in predicting the hemodynamic response in such patients.

**Methods**

**Patients.** Nine patients with chronic congestive heart failure, in New York Heart Association functional class III or IV (17), were studied (Table 1). The group included seven men and two women, ranging in age from 36 to 68 years. The cause of the heart failure was coronary artery disease in seven patients and was idiopathic in two patients (confirmed by coronary arteriography in all but one patient). Heart failure was of at least 3 months’ duration, stable (no episode of pulmonary edema in the last 10 weeks) and under treatment with stable doses of digitalis, diuretic drugs, and in some cases, nitrate preparations. All patients had moderate to severe impairment of exercise tolerance despite this medical therapy and musculoskeletal function was relatively well preserved. Left ventricular ejection fraction was less than 0.35 by either contrast left ventriculography or radionuclide angiography. Patients with myocardial infarction in the last 3 months and patients with primary valvular heart disease were excluded. A grade 2/6 mitral regurgitation murmur was heard at the time of the study in five of nine patients; mitral regurgitation was believed to be secondary to left ventricular failure in these five patients. Six of the nine patients had contrast left ventriculography within 1 year of the time of the study; only one of these six patients had angiographically demonstrable mitral regurgitation (grade I-II); this patient also had a mitral regurgitation murmur.

The study protocol was approved by the Sinai Hospital of Detroit Medical Research Committee on February 29, 1980. Informed consent was obtained from all patients. The patients were hospitalized in the cardiac intensive care unit for the duration of the study and maintained on stable schedules and doses of digitalis, diuretic drugs and nitrate preparations when applicable. Dietary sodium was restricted.

**Hemodynamic measurements.** A triple lumen Swan-Ganz thermodilution catheter was inserted percutaneously for determination of right atrial, pulmonary artery and pulmonary capillary wedge pressures. Left ventricular filling pressure was determined as either the pulmonary capillary wedge pressure or the pulmonary artery end-diastolic pressure after it was established initially that the pulmonary capillary wedge and pulmonary artery end-diastolic pressures were equivalent; the method of determining left ventricular filling pressure was constant in each patient. Cardiac output was determined in triplicate with the thermodilution technique. Heart rate was determined from the electrocardiogram simultaneously with cardiac output measurements. Arterial blood pressure was measured using sphygmomanometry of the brachial artery.

**Radionuclide left ventriculography.** Radionuclide left ventricular ejection fraction was obtained by the gated equilibrium technique, at rest and during exercise, with patients in the supine position. A dose of 25 mCi of technetium-99m pertechnetate dissolved in less than 1 ml of isotonic saline solution was injected 30 minutes after the intravenous

| Table 1. Clinical Characteristics of Nine Study Patients |
|------------|-----------|-------------|----------------|-----------------|
| Case | Age(yr) & Sex | Cause of Heart Failure | NYHA Class | Medications | Murmur of Mitral Regurgitation |
| 1 | 41M | Coronary artery disease | III | Digoxin, furosemide, quinidine | Present |
| 2 | 36F | Idiopathic | III-IV | Digoxin, furosemide, ID, NTG ointment | Present |
| 3 | 54M | Idiopathic | III | Digoxin, furosemide, ID | Absent |
| 4 | 67M | Coronary artery disease | III-IV | Digoxin, furosemide, NTG ointment | Present |
| 5 | 56M | Coronary artery disease | III | Digoxin, furosemide, NTG ointment, oral NTG, quinidine | Present |
| 6 | 68F | Coronary artery disease | III | Digoxin, furosemide, ID, NTG ointment | Absent |
| 7 | 44M | Coronary artery disease | III | Digoxin, furosemide, ID, hydrochlorothiazide, spironolactone | Absent |
| 8 | 67M | Coronary artery disease | III-IV | Digoxin, furosemide | Present |
| 9 | 65M | Coronary artery disease | III-IV | Digoxin, furosemide, ID, NTG ointment | Absent |

F = female; ID = isosorbide dinitrate, M = male; NTG = nitroglycerin; NYHA = New York Heart Association
administration of unlabeled pyrophosphate. Ten minutes was allowed for equilibration of the tracer in the blood pool. Imaging was performed using a single crystal Anger gamma scintillation camera (Ohio Nuclear Sigma 420 with a VIP 550 on-board computer) equipped with a high sensitivity, low energy parallel hole collimator, in the left anterior oblique projection which allowed for optimal visualization of the interventricular septum. Data were acquired in frame mode. Imaging at rest was performed until a count density of 400,000 counts/frame over the left ventricular region of interest had been obtained and during exercise was performed until a count density of 250,000 counts/frame had been obtained.

Data were processed by an independent observer. Background subtraction was performed utilizing a paraventricular region of interest. Left ventricular chamber edges were defined using a fixed region of interest over the left ventricle in the initial frame. End-diastolic and end-systolic images were defined as the frames containing the largest and smallest number of counts in this fixed region of interest (QMICA program). The left ventricle in the end-diastolic frame and in the three frames bracketing the end-systolic frame was then manually outlined (MMICA program).

Left ventricular ejection fraction was determined from the following formula: Left ventricular ejection fraction = end-diastolic counts − end-systolic counts ÷ end-diastolic counts. This process was performed at least three separate times for each rest and exercise left ventricular ejection fraction determination and an average value was calculated.

Study protocol. Sequential measurements at rest and during exercise were performed at the same time of day with the patient in the postabsorptive state. Hemodynamic measurements were made after 15 minutes of quiet supine rest with the patient recumbent. Radionuclide left ventricular ejection fraction at rest was measured. After these determinations, the patient’s legs were raised and secured to bicycle ergometer pedals (Quinton). On the initial day of testing (control or prehydralazine), supine bicycle exercise was begun at a work load of 200 kilopond-meters (kpm)/min and exercise was continued to a symptom-limited maximal work load attained for seven of the nine patients; it was increased to 300 kpm/min after an initial 3 minutes of exercise at 200 kpm/min for the remaining two patients (Table 2). During control testing, exercise was stopped in six patients because of fatigue and in three patients because of dyspnea. Hemodynamic variables were measured within 1 minute of peak exercise. An electrocardiographic lead was monitored continuously during exercise. The radionuclide left ventricular ejection fraction was measured at peak exercise.

Patients were then returned to the cardiac intensive care unit for continuous hemodynamic monitoring and for initiation of hydralazine therapy. A hydralazine dose of 25 mg orally was given with subsequent doses administered every 6 hours and increments of 25 mg were added to the previous dose until maximal hemodynamic response was seen. The maximal hydralazine dose ranged from 50 to 100 mg orally every 6 hours. Forty-eight hours after initiation of hydralazine therapy, patients duplicated the specific exercise protocol used on the initial day of testing (control or prehydralazine). Hemodynamic variables and radionuclide left ventricular ejection fraction were again measured at rest and during exercise at the work load and duration of exercise corresponding to the maximal work load and duration of exercise achieved on the initial day of testing. Measurements on hydralazine were made 2 to 4 hours after the previous hydralazine dose.

Calculated hemodynamic variables. Stroke volume index, left ventricular stroke work index and systemic vascular resistance were calculated from the measured hemodynamic variables as follows: 1) $SVI = CO/HR/BSA$, where $SVI$ is stroke volume index in ml/beat per m$^2$, $CO$ is cardiac output in ml/min, $HR$ is heart rate in beats/min and $BSA$ is body surface area in m$^2$. 2) $LVSWI = 0.0136 \times SVI \times (MLVSP - LYFP)$, where $LVSWI$ is left ventricular stroke work index in g·m/m$^2$, where $MLVSP$ is mean left ventricular systolic pressure in mm Hg calculated as diastolic arterial pressure + 0.8 × pulse pressure and $LYFP$ is the left ventricular filling pressure as either the pulmonary capillary wedge pressure or pulmonary artery end-diastolic pressure; the method of determining filling pressure was constant in each patient. 3) $SVR = (MAP - RA/CO) \times 80$, where $SVR$ is systemic vascular resistance in dynes·s·cm$^{-5}$, $MAP$ is mean arterial pressure in mm Hg calculated as diastolic arterial pressure + 0.33 × pulse pressure and $RA$ is right atrial pressure in mm Hg.

Statistical analysis. All data are presented as mean values ± 1 standard deviation. Comparisons between control and hydralazine therapy, both at rest and during exercise, were made using the paired $t$ test. Comparisons between rest and exercise, for both control and hydralazine therapy, were also made using the paired $t$ test. Relation of changes
in left ventricular ejection fraction to changes in cardiac index, stroke volume index, left ventricular stroke work index and systemic vascular resistance were analyzed using least-squares linear regression analysis. Significance of data was determined at the level of probability \( p < 0.05 \). Arterial blood pressure at maximal exercise on the initial day of testing was not obtained for one patient (Patient 8); corresponding left ventricular stroke work index and systemic vascular resistance values were therefore not calculated and Patient 8 was excluded from statistical comparisons and linear regression analysis involving control exercise mean arterial pressure, left ventricular stroke work index and systemic vascular resistance.

**Results**

The maximal oral hydralazine dose was 100 mg every 6 hours in four patients, 75 mg every 6 hours in three patients and 50 mg every 6 hours in two patients.

**Hemodynamic data.** Hemodynamic and radionuclide angiographic data for the nine patients studied are summarized in Table 3. Hydralazine produced significant increases in cardiac index, stroke volume index and left ventricular stroke work index and significant decreases in systemic vascular resistance, both at rest and during exercise. There were no significant changes in left ventricular filling pressure, right atrial pressure, heart rate or mean arterial pressure with hydralazine therapy, either at rest or during exercise. Cardiac index, mean arterial pressure, heart rate, left ventricular filling pressure and right atrial pressure increased significantly from rest to exercise and systemic vascular resistance decreased significantly from rest to exercise, both before and during hydralazine therapy.

**Ejection fraction.** Hydralazine therapy was associated with significant increases in left ventricular ejection fraction both at rest (0.21 ± 0.06 before hydralazine and 0.26 ± 0.07 during hydralazine therapy, \( p < 0.01 \)) and during exercise (0.21 ± 0.08 before hydralazine and 0.24 ± 0.09 during hydralazine therapy, \( p < 0.05 \)) (Fig. 1). Hydralazine therapy increased left ventricular ejection fraction in all nine patients at rest and in six of nine patients during exercise.

Changes in left ventricular ejection fraction from rest to exercise were not statistically significant, either before or during hydralazine therapy. There was no significant difference between control and hydralazine therapy in the increase in left ventricular ejection fraction from rest to exercise (0.01 ± 0.03 control and −0.02 ± 0.04 hydralazine).

**Correlation of ejection fraction and hemodynamic data.** There were no statistically significant correlations between the percent increase in left ventricular ejection fraction associated with hydralazine and either the percent increase in cardiac index, stroke volume index and left ventricular stroke work index or the percent decrease in systemic vascular resistance at rest or during exercise. Similarly, there were no statistically significant correlations between the actual increase in left ventricular ejection fraction associated with hydralazine and either the percent increase in cardiac index, stroke volume index and left ventricular stroke work index or the percent decrease in systemic vascular resistance at rest or during exercise.

**Hemodynamic responders versus nonresponders.** For the purpose of data analysis, patients were categorized as responding hemodynamically to hydralazine on the basis of whether they manifested a 20% or greater decrease in systemic vascular resistance at rest with hydralazine, or as not responding if they manifested a less than 20% decrease in systemic vascular resistance at rest with hydralazine (18). Of the nine patients studied, six responded hemodynamically and three did not. Responders and nonresponders could not be adequately separated on the basis of the control left

| Table 3. Hemodynamic and Radionuclide Angiographic Data (mean values ± standard deviation) |
|-----------------------------------------------|---------------------------------------------------|-------------------------------------------------|-----------------------------|-----------------------------|
|                                               | Control                                            | Hydralazine                                     | Statistical Significance (p value)* |
|                                               | Rest                                               | Exercise                                        | CR-HR                       | CE-HE                       |
| CI (liters/min per m²)                        | 1.8 ± 0.3                                          | 2.6 ± 0.8                                       | CR-HR                       | CE-HE                       |
| MAP (mm Hg)                                  | 93 ± 10                                            | 103 ± 13                                        | < 0.01                      | < 0.01                      |
| H.R. (min⁻¹)                                 | 85 ± 17                                            | 105 ± 24                                        | < 0.01                      | < 0.01                      |
| LVFP (mm Hg)                                 | 21 ± 11                                            | 36 ± 8                                          | NS                          | NS                          |
| RAP (mm Hg)                                  | 5 ± 5                                              | 13 ± 9                                          | NS                          | NS                          |
| SVI (ml/m²)                                  | 23 ± 8                                             | 26 ± 12                                         | NS                          | NS                          |
| LVSWI (g/m²)                                 | 29 ± 12                                            | 35 ± 19                                         | NS                          | NS                          |
| SVR (dynes/s-cm⁻²)                           | 2,155 ± 420                                        | 1,530 ± 348                                     | NS                          | NS                          |
| LVEF                                          | 0.21 ± 0.06                                        | 0.21 ± 0.07                                     | < 0.01                      | < 0.05                      |

*Patient 8 was excluded from CE-HE and CR-CE comparisons for mean arterial pressure, left ventricular stroke work index and systemic vascular resistance.

CE = control, exercise; CI = cardiac index; CR = control, rest; HE = hydralazine, exercise; HR = hydralazine, rest; H.R. = heart rate; LVEF = left ventricular ejection fraction; LVFP = left ventricular filling pressure; LVSWI = left ventricular stroke work index; MAP = mean arterial pressure; RAP = right atrial pressure; SVI = stroke volume index; SVR = systemic vascular resistance.
Figure 1. Left ventricular ejection fraction (LVEF) at rest (R) and during exercise (E) in the control study and during hydralazine therapy. Open circles and vertical bars indicate mean and range of standard deviations, respectively.

ventricular ejection fraction at rest (Fig. 2), or the percentage increase in ejection fraction with hydralazine at rest (Fig. 3).

Discussion

Effect of hydralazine on radionuclide ejection fraction. This study confirms previous observations (1–6) regarding the hemodynamic effects of short-term oral hydralazine in patients with chronic congestive heart failure. At rest and during exercise, hydralazine produced an increase in cardiac index that was a result mainly of an increase in stroke volume with an associated decrease in systemic vascular resistance. Left ventricular filling pressure was unaffected by hydralazine, both at rest and during exercise.

The increase in the radionuclide left ventricular ejection fraction with hydralazine, both at rest and during exercise, in this study contrasts with results obtained by Hindman et al. (4), who found no significant change in the radionuclide ejection fraction (by the first-pass technique) either at rest or during exercise with hydralazine in patients with coronary artery disease and severe left ventricular dysfunction despite documented hemodynamic improvement. The increase (0.05) in the radionuclide ejection fraction at rest with hydralazine in the present study is similar to the increase (0.08) in the gated equilibrium ejection fraction at rest demonstrated by Davis et al. (8) in eight patients with severe left ventricular dysfunction after a single oral dose of hydralazine.

Variability of radionuclide ejection fraction. In the analysis of the change in radionuclide ejection fraction associated with hydralazine therapy, the serial variability of the radionuclide value must be taken into account. Wackers et al. (19) demonstrated that the change in left ventricular ejection fraction in an individual patient with an abnormal ejection fraction must be at least 0.05 in order for that change to be attributed to a nonrandom physiologic variation. In the present study, five of the nine patients demonstrated an increase in left ventricular ejection fraction of 0.05 or greater with hydralazine at rest; only two of the nine showed an increase in ejection fraction of 0.05 or greater with hydralazine during exercise. However, with hydralazine, the mean ejection fraction increased by 0.05 at rest and by 0.03 during exercise. Because a change in left ventricular ejection fraction of less than 0.05 may be sufficient to demonstrate the effect of a drug or intervention in a group of patients as opposed to an individual patient (15, 19), these changes in mean ejection fraction may represent physiologically significant increases related to hydralazine therapy.

Correlation of changes in ejection fraction and hemodynamic variables. Although patients in this study exhibited statistically significant increases in left ventricular ejection fraction both at rest and during exercise with hydralazine therapy, there were no statistically significant correlations between changes in ejection fraction and changes in hemodynamic variables with hydralazine, either at rest or during exercise. Furthermore, patients responding hemodynamically to hydralazine could not be separated from those not responding to hydralazine on the basis of changes in ejection fraction with hydralazine. Davis et al. (8) described a patient who exhibited a marked increase in cardiac index in response to hydralazine with only a minimal increase in radionuclide left ventricular ejection fraction; the patient had a very large left ventricular end-diastolic volume. Firth et al. (14) recently investigated the hemodynamic and radionuclide angiographic responses to nitroprusside in 12 patients with severe congestive heart failure; only 1 patient demonstrated...
an increase in the gated equilibrium radionuclide left ventricular ejection fraction of 0.05 or greater in response to nitroprusside, while mean cardiac index in the group increased from 2.1 to 2.9 liters/min per m². Changes in radionuclide ejection fraction did not correlate with changes in hemodynamic variables, as we demonstrated in the present study with hydralazine. Similarly, Haq et al. (16) found no significant change in the radionuclide ejection fraction in response to oral vasodilators in a group of patients with refractory congestive heart failure, despite hemodynamic improvement.

**Explanations for lack of correlation.** The lack of correlation between hemodynamic and radionuclide angiographic responses to hydralazine therapy may reflect insensitivity of the radionuclide left ventricular ejection fraction technique in detecting small changes in patients with a dilated left ventricle and a markedly reduced ejection fraction (8,14–16). In such patients, a large increase in stroke volume related to hydralazine therapy would be associated with a relatively small increase in ejection fraction (because of a greatly increased left ventricular end-diastolic volume) and this small increase could be obscured by the normal serial variability of the radionuclide ejection fraction (19). For instance, in a patient with a left ventricular end-diastolic volume of 300 ml and a left ventricular ejection fraction of 0.15, the stroke volume would be 45 ml; if hydralazine therapy produced a 33% increase in the stroke volume, increasing it from 45 to 60 ml, the ejection fraction would increase from 0.15 to 0.20. This 0.05 increase in ejection fraction would be considered at the upper limit of the expected normal serial variability.

**Role of mitral regurgitation.** Another possible explanation for the lack of correlation between hemodynamic and radionuclide angiographic responses is an effect of hydralazine on the amount of mitral regurgitation in some patients in the study (five of the nine patients had evidence of secondary mitral regurgitation). In patients with mitral regurgitation, hydralazine decreases the amount of mitral regurgitation, increases cardiac index and stroke volume index and decreases systemic vascular resistance without changing the left ventricular ejection fraction (20). Of the five patients in this study with secondary mitral regurgitation, two (Patients 1 and 8) manifested marked increases in cardiac index and stroke volume index, a marked decrease in systemic vascular resistance and an increase in radionuclide ejection fraction of less than 0.05, with hydralazine therapy; hydralazine may have increased the cardiac index and stroke volume index in these patients by reducing the amount of mitral regurgitation. However, in one patient (Patient 7) without evidence of mitral regurgitation, hydralazine therapy produced marked improvement in hemodynamic variables with an increase in ejection fraction of less than 0.05. In addition, in two patients (Patients 3 and 6), hydralazine therapy was associated with minimal improvement in hemodynamic variables and an increase in ejection fraction of 0.05 or greater. Therefore, reduction in the amount of mitral regurgitation secondary to hydralazine in some patients cannot be the only explanation for the observed lack of correlation.

**Role of spontaneous changes in end-diastolic volume.** Because a change in left ventricular end-diastolic volume with no change in stroke volume can lead to a change in ejection fraction, it is possible that spontaneous changes in left ventricular end-diastolic volume occurred in some patients after hydralazine therapy had been initiated, leading to changes in ejection fraction that were not related to the hemodynamic effects of hydralazine. Direct measurement of left ventricular end-diastolic volume using radionuclide angiography may be helpful in assessing the response to vasodilators (8,14). Left ventricular end-diastolic volume was not measured in the present study. Finally, our study involved nine patients; it is possible that significant correlations between hemodynamic and radionuclide angiographic responses to hydralazine therapy would be detected in a larger series of patients.

**Conclusion.** Hydralazine exerts beneficial effects on cardiac index, stroke volume index, left ventricular stroke work index and systemic vascular resistance, both at rest and during supine bicycle exercise, and is associated with improvement in the radionuclide left ventricular ejection fraction, both at rest and during exercise. However, in this preliminary series, the radionuclide left ventricular ejection fraction response to hydralazine did not correlate with and failed to predict the hemodynamic response to hydralazine.

At present, determination of radionuclide left ventricular ejection fraction cannot supplant invasive hemodynamic monitoring to assess the hemodynamic effects of hydralazine in individual patients with severe chronic congestive heart failure. Radionuclide angiography may play an important role in assessing the effects of hydralazine and other vasodilator agents in large groups of patients.

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**References**


