Oral Hydralazine Therapy for Chronic Refractory Heart Failure

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SUMMARY The hemodynamic effects of oral hydralazine were investigated in ten patients (nine in NYHA Class IV and one in Class III) with chronic refractory heart failure. With hemodynamic monitoring, adequate oral doses of hydralazine (50 or 75 mg) were determined and then administered every six hours. Hemodynamics were determined at 2–3, 6–8 and 24 hours on hydralazine therapy. Arterial pressure decreased slightly (5%) and systemic vascular resistance decreased significantly (42%). Cardiac and stroke volume index increased by 70 and 66%, respectively, without any significant change in heart rate, pulmonary capillary wedge or right atrial pressure. Hemodynamic improvement was associated with clinical improvement without a major complication. During the follow-up period of 3–7 months, seven of nine patients were in NYHA Class II and one in Class III. One other patient died suddenly six weeks after discharge. These findings suggest that hydralazine is an effective oral vasodilator for the treatment of refractory heart failure.

REDUCING LEFT VENTRICULAR ejection impedance with various vasodilator drugs has been shown to be a practical therapeutic approach to the management of patients with acute or chronic heart failure. The infusion of sodium nitroprusside or phentolamine increases cardiac output and decreases pulmonary and systemic venous pressure, thus decreasing the signs and symptoms of congestive failure. Such beneficial hemodynamic and clinical responses, however, are quickly reversed when intravenous vasodilator therapy is stopped. Therefore, for the long-term management of heart failure, intravenous vasodilator therapy is impractical. To circumvent this difficulty, the hemodynamic effects of various nonparenteral vasodilators (primarily the nitrates) have been investigated in the treatment of patients with chronic heart failure. Sublingual or topical nitroglycerin, and sublingual or oral isosorbide dinitrate cause a significant reduction in left ventricular filling pressure in most patients. Although an increase in cardiac output also occurs in some patients, this increase is slight. In many patients cardiac output may even decrease. The nitrates have a marked dilating effect on capacitance vessels with a lesser effect on resistance vessels. This often results in a greater reduction in ventricular preload than afterload. A significant decrease in left ventricular filling pressure, with little or no change in cardiac output, may thus be the result.

In those patients with left ventricular failure in whom a low cardiac output is the primary problem, nitrates may be less effective. A drug with a predominant effect on resistance vessels might have a greater potential for increasing cardiac output. Hydralazine, a smooth muscle relaxant, is known to cause a significant reduction in arteriolar tone, with little effect on capacitance vessels. Furthermore, hydralazine can be administered orally. The purpose of this study, therefore, was to evaluate the hemodynamic effects of orally administered hydralazine in patients with severe and chronic refractory heart failure, and also to assess the feasibility of such therapy in the long-term management of such patients.

Methods

Ten patients with severe and chronic heart failure, refractory to conventional medical therapy, form the patient population. There were five females and five males with an age range of 29 to 65 years. The etiology of congestive heart failure was cardiomyopathy of unknown cause in four, ischemic cardiomyopathy in two, and persistent heart failure, despite valve replacement (three mitral and one aortic) in the remaining four. The duration of heart failure ranged from one to seven years. Nine of ten patients were in NYHA Class IV and one was in Class III at the time of the study. All patients were chronically and adequately digitalized. All patients were taking oral furosemide, 160 to 840 mg daily. In addition, three patients were also taking...
Aldactone. Clinically, all patients had signs of severe biventricular failure, pulmonary hypertension and cardiomegaly. Five of the ten patients also had physical signs suggestive of some degree of mitral regurgitation. Two patients were in atrial fibrillation and the remaining eight were in sinus rhythm at the time of the study. Chest X-ray showed considerable cardiomegaly and evidence of pulmonary arterial and venous hypertension in all patients. Only one patient was mildly hypertensive at the time of the study.

**Hemodynamic Measurements**

In all patients, right atrial (RA), pulmonary artery (PA) and pulmonary capillary wedge (PCW) pressures were recorded with a balloon-tip triple-lumen catheter. Cardiac output (CO) was measured by thermodilution techniques with the same catheter\textsuperscript{29,30} with the use of ice cold water as the indicator. Cardiac outputs were performed in triplicate, with a variation of less than 10\%. Cardiac output computations were performed by a bedside computer (Santa Barbara Technology, Inc., Model 1700). Arterial blood pressure (AP) was obtained by cuff readings. The mean arterial pressure (MAP) was estimated from the formula MAP = D + (S - D) \times \frac{2}{3}, where S is the peak systolic and D the diastolic pressures.\textsuperscript{31} (In two patients with atrial fibrillation AP was determined from the average of several consecutive readings.) Derived hemodynamic parameters were calculated as follows:

Cardiac index (CI) = CO/body surface area (BSA) (L/min/m\(^2\))

Stroke volume index (SVI) = SV/BSA (ml/m\(^2\))

An approximation of stroke work index was calculated from the formula:

Stroke work index (SWI) = SVI \times (AP - PCW) \times 0.136 (g-m/m\(^2\))

Systemic vascular resistance (SVR) = 80 (AP - RA/CO) (dynes sec cm\(^{-5}\))

Pulmonary vascular resistance (PVR) = 80 (PA - PCW/CO) (dynes sec cm\(^{-5}\)).

**Hydralazine Therapy**

After obtaining baseline hemodynamics, 25 mg of hydralazine was administered orally and the hemodynamic measurements were repeated at two to three hours. Since there were no significant hemodynamic changes in any patients following a 25 mg dose of hydralazine, 50 mg of hydralazine was administered three hours after the 25 mg dose and the hemodynamic measurements were repeated. If there were no significant hemodynamic and clinical changes at two to three hours after the 50 mg dose, 75 mg of hydralazine was administered and the hemodynamic measurements were repeated at two to three hours. Only two patients had a significant increase in cardiac output with 50 mg of hydralazine; the remaining eight patients required 75 mg of hydralazine. After determining the appropriate dose of hydralazine based on the hemodynamic response, 50 or 75 mg of hydralazine was then administered every six hours. Hemodynamic measurements were repeated at frequent in-
tervals (every two to three hours) for more than twenty-four hours and hemodynamic monitoring was then discontinued. While evaluating the hemodynamic effects of hydralazine, diuretic therapy was temporarily withheld, but digitalis was continued. All patients were discharged on hydralazine (50 or 75 mg every six hours), in addition to digitalis and diuretic therapy. However, no patient needed more than 80 mg of furosemide a day at the time of discharge. All patients were advised to continue diuretics as continued use of hydralazine may cause sodium retention and an increase in extracellular and plasma volume.

Statistical analysis of the data utilized a two-way analysis of variance, without replication and a mixed effects model.

Results

The hemodynamic effects of hydralazine in all ten patients are summarized in Table 1. Results are tabulated at two to three hours, six to eight hours, and twenty-four hours after the continuous administration of the maximum dose of hydralazine used (50 mg in two patients, and 75 mg in eight patients). Representative hemodynamic effects of oral hydralazine in a patient (F.R., Table 1) are illustrated in Figure 1. In the group as a whole there were no significant changes in heart rate, pulmonary capillary wedge pressure, or right atrial pressure. Mean arterial and pulmonary arterial pressures decreased only slightly. There was a significant reduction in both systemic and pulmonary vascular resistance. Along with the reduction in systemic vascular resistance, there was a marked increase in cardiac output and stroke volume. Despite some reduction in arterial pressure, stroke work index increased significantly. A significant increase in stroke volume and stroke work index with little change in left ventricular filling pressure is indicative of improved left ventricular performance.

Although a favorable hemodynamic response was observed at two to three hours and six to eight hours after administration of 50 to 75 mg of hydralazine, the maximum increase in cardiac output was observed in most patients at twenty-four hours. Individual changes in heart rate, mean arterial pressure, cardiac index, left ventricular filling pressure, stroke volume and stroke work index are illustrated in Figures 2 and 3.

In two patients there was some tachycardia, while in the remaining eight patients heart rate either decreased or did not change. Mean arterial pressure decreased only moderately in five patients. Cardiac output increased significantly in all patients. Although changes in left ventricular filling pressure were inconsistent, there were significant increases in stroke volume and stroke work index.

Clinical Response

In all patients there was a significant decrease in fatigue during hydralazine therapy. Urine output remained satisfactory in the hospital despite a reduced dose of diuretics. Nine
of the ten patients continued to use hydralazine during the follow-up period (two to five months). In one patient with an aortic prosthetic valve, hydralazine was discontinued when he developed a neurological complication due to cerebral embolism. Seven of the nine patients on long-term hydralazine therapy remained significantly improved clinically and were in NYHA Class II and one in Class III at the time of the most recent follow-up (three to seven months). One patient died suddenly six weeks after discharge from the hospital, although he had had marked improvement in his effort tolerance (NYHA II) until his death. Two patients have returned to their jobs (part time), one as a garage mechanic and the other as a house painter.

Complications

No patient developed postural hypotension. Three patients had nausea in the first twenty-four hours after the initiation of hydralazine therapy, which disappeared despite continued therapy. During the short follow-up period no patient developed any clinical manifestations of the lupus syndrome.26 However, two patients gained weight slightly during follow-up period, despite a marked improvement in effort tolerance. Restriction of fluid and salt intake has prevented any further gain in weight.

Discussion

This study demonstrates that the vasodilator hydralazine can produce a significant beneficial hemodynamic response in patients with severe congestive heart failure. Thus, in all ten patients in this study, cardiac output increased within two to three hours of oral administration of hydralazine.

An increase in cardiac output and stroke volume and stroke work with little or no change in left ventricular filling pressure indicates enhanced left ventricular function. Improved cardiac performance in these patients was also associated with clinical improvement, in that all patients had relief of fatigue and other manifestations of low cardiac output. Furthermore, seven of the nine patients who were continued on hydralazine therapy were in NYHA Class II at the most recent follow-up, although eight of these nine patients were in NYHA Class IV before the initiation of hydralazine therapy. Two patients could return to part-time jobs. One patient with primary cardiomyopathy died suddenly six weeks after discharge from the hospital; the immediate cause of death is not known. However, this patient had sustained improvement in his effort tolerance until death.

The increase in cardiac output was not due to an increase in heart rate, preload, or contractility. Although one patient developed tachycardia, heart rate in general did not change significantly and there was no consistent change in left ventricular filling pressure. Furthermore, hydralazine does not possess any direct inotropic effect on the myocardium. A reflex increase in contractility was also unlikely due to the lack of reflex tachycardia in these patients. Although changes in arteriolar tone were not measured directly, the decreased systemic vascular resistance in these patients was most likely due to a direct dilating effect of hydralazine on the resistance vessels, as demonstrated in previous studies.25-28 This decrease in impedance to left ventricular ejection presumably resulted in an increase in cardiac output in these patients. A reduction in the severity of mitral regurgitation in some patients probably contributed also to the increases in cardiac output.25

Although cardiac output increased in all patients in this study, there was very little change in either pulmonary capillary wedge pressure or right atrial pressure. It appears, therefore, that hydralazine has unimportant dilating effects on the capacitance vessels as suggested by previous investigators. Franciosa and Cohn27 observed some decrease in pulmonary capillary wedge pressure following a single oral dose of 100 mg of hydralazine. The lack of change in pulmonary capillary wedge pressures in our patients may be related to the smaller dose of hydralazine used. Furthermore, variation in the metabolism of hydralazine in different patients (slow or fast acetylators) may cause variable blood levels of hydralazine and this might explain some of the differences.

In the present study the dose of oral hydralazine was increased every three hours until an adequate hemodynamic response was observed. This dose was then administered every six hours. With this method of administration, the increased cardiac output was maintained for more than twenty-four hours after the initiation of hydralazine therapy. These findings indicate that sustained hemodynamic improvement can be expected in patients with congestive heart failure on continuous hydralazine therapy. This is suggested by the fact that the clinical improvement in these patients seemed to be maintained during the follow-up period. However, this study does not provide any objective evidence to confirm the clinical impression and further investigations would be necessary for substantiation.

Because there was little or no reduction in pulmonary capillary wedge pressure in these patients, hydralazine may not relieve the symptoms of pulmonary venous congestion. Furthermore, a tendency to gain weight due to an increased intravascular volume is a known complication of hydralazine therapy. In such circumstances, however, the addition of, or an increase in the dose of a potent diuretic like furosemide, or the nitrates with their prominent venodilating

![Figure 4. Stroke work index and pulmonary capillary wedge pressure during the control period (●), with oral hydralazine alone (○), and with combined oral hydralazine and sublingual isosorbide dinitrate (▲). During hydralazine therapy, there was a marked increase in stroke work index, but only a minor decrease in pulmonary capillary wedge pressure. With the addition of sublingual isosorbide dinitrate however, there was a significant decrease in pulmonary capillary wedge pressure while the increase in stroke work index due to hydralazine was maintained.](http://circ.ahajournals.org/)

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effect, is necessary, as illustrated in figure 4. In patients with a markedly decreased cardiac output, but with only a slightly elevated left ventricular filling pressure, as illustrated in figure 1, hydralazine therapy alone may be effective.

In hypertensive patients, hydralazine produces tachycardia, along with a reduction in blood pressure.38 In this study in patients with severe and chronic congestive heart failure, however, there was no significant increase in heart rate. The mechanism of the lack of change in heart rate in these patients with chronic heart failure is not totally clear. The relatively minor decrease in arterial pressure in most patients, together with an increase in pulse pressure due to increased stroke volume, may be contributory. Furthermore, a reduced baroreceptor response has been observed in patients with chronic heart failure. It needs to be emphasized, however, that in an occasional patient significant tachycardia may occur, as in one patient in this study in whom heart rate increased from 58 to 78 beats per minute.

Nine of the ten patients in this study were normotensive and only one was slightly hypertensive. A marked reduction in arterial pressure during hydralazine therapy occurred only in the hypertensive patient. Furthermore, no patient in this study developed postural hypotension. The lack of a significant reduction in arterial pressure may be an advantage in the management of normotensive patients with heart failure due to ischemic heart disease. This will help maintain the coronary artery perfusion pressure. Since there was no significant change in heart rate or left ventricular filling pressure, a change in myocardial oxygen demand is also unlikely to have occurred in these patients. Despite the fact that no significant hypotension and its complications occurred, it is advisable to monitor changes in blood pressure during the initiation of hydralazine therapy. Although the immunologic or clinical evidence of lupus syndrome, a known complication of long-term hydralazine therapy, has not yet developed in these patients, prolonged follow-up would be necessary to determine the prevalence of this complication.

The number of patients in this study is relatively small and the duration of follow-up is short. Nevertheless, the study demonstrates that oral hydralazine is an effective vasodilator which can improve cardiac performance in patients with heart failure. Since it can be administered less frequently, oral hydralazine therapy may be a practical, feasible and effective method of treatment for patients with refractory heart failure.

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