Vasodilator treatment with isosorbide dinitrate and hydralazine in chronic heart failure

Differing haemodynamic responses at rest and during upright exercise

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SUMMARY Several reports have suggested that because isosorbide dinitrate and hydralazine have different and additive haemodynamic effects at rest in patients with chronic heart failure, these agents should be administered in combination. Some studies, however, indicate that they are effective individually as well. Since most patients with heart failure are symptomatic only with activity, we examined the haemodynamic effects of these drugs given individually and in combination, at rest and during upright bicycle exercise. As has been noted previously, at rest isosorbide significantly lowered both ventricular filling pressures and did not change cardiac output; hydralazine increased cardiac output and had only a slight effect on pulmonary capillary wedge pressure; combined treatment produced both beneficial effects. In contrast, during exercise isosorbide dinitrate also raised cardiac output while hydralazine more dramatically lowered the wedge pressure. Combined treatment produced significantly greater improvement in each haemodynamic index than either drug alone, with a resulting 54 per cent increase in exercise cardiac output, and a 33 per cent reduction in exercise wedge pressure. Maximal oxygen consumption increased acutely during combined treatment.

These findings suggest that isosorbide dinitrate and hydralazine may each be effective in some patients, but that they are even more beneficial in combination.

In recent years, a great deal of experience with vasodilator treatment in chronic heart failure has accumulated.1–3 A number of currently available drugs have been shown to improve supine, resting haemodynamic measurements.3–19 Yet these haemodynamic changes have not always predicted the subsequent clinical response to treatment.16–17 20 21 Since most heart failure patients experience symptoms predominantly with activity, several groups have begun to examine the haemodynamic effects of vasodilators during exercise.25–27 Indeed, at least one commonly used agent, prazosin, appears to have a greater effect during exercise than at rest.28

Hydralazine and isosorbide dinitrate have frequently been used for vasodilator treatment.6 7 9–17 Some studies indicate that these drugs have different circulatory and resting haemodynamic effects and suggest that an optimal response can be obtained only by using them in combination.18–14 None the less, several papers have reported clinical improvement with hydralazine and nitrates used individually.7 8 10 16 29 We therefore undertook the present study to assess the exercise haemodynamic responses to short-term treatment with hydralazine and isosorbide dinitrate, given individually and in combination. In so doing, we hoped to learn more about the optimum use of these drugs.

Methods

PATIENT POPULATION

The study population consisted of 13 patients admitted for vasodilator treatment with severe (New
Exercise haemodynamics during vasodilator treatment

York Heart Association class 3 or 4) chronic congestive heart failure. All were on stable doses of digoxin and diuretics, which were continued throughout the study. The aetiology of myocardial decompensation was ischaemic heart disease in eight patients, primary cardiomyopathy in four, and hypertensive heart disease in the last. The patients' mean age was 59, with a range of 41 to 72.

STUDY DESIGN
The patients were admitted to hospital at least two days before the study in order to ensure dietary and drug compliance. On the day before catheterisation, each subject was instructed in the use of an inertial bicycle ergometer. After a period of practice, the patients exercised upright to a symptom-limited maximum, beginning at a 200 kpm/min work load and increasing by 100 kpm/min every three minutes. During the subsequent haemodynamic studies, measurements were performed in the final two minutes at the highest work load completed during the preliminary test. During subsequent tests, if the patients were able, exercise was then continued until a symptom-limited maximum to permit measurement of maximal oxygen consumption.

The following day, a balloon-tipped thermodilution catheter was placed in a pulmonary artery and a radial artery was cannulated. After several hours during which haemodynamic stability was established, supine resting and upright exercise measurements of heart rate, systolic, diastolic, mean arterial pressure, pulmonary artery pressure, right atrial pressure, pulmonary capillary wedge pressure, and cardiac output were performed. In both positions, the transducer was placed at a level 5 cm vertical distance below the sternal angle. The electrocardiogram, systemic arterial, and pulmonary artery pressures were recorded continuously during exercise. Right atrial, pulmonary capillary wedge, and mean pressures were recorded at one minute intervals. Arterial and pulmonary artery blood gases were drawn at peak exercise for calculation of oxygen consumption (see below).

Isosorbide dinitrate was then begun with an initial 5 mg sublingual dose. Subsequently, the dosage was increased until the supine pulmonary capillary wedge pressure was consistently lowered below 15 mmHg 30 to 60 minutes later or limiting side effects (generally headache) occurred. After a minimum of 12 hours of continuous nitrate administration, the resting and upright exercise haemodynamic measurements were then repeated at the anticipated time of peak effect. Then, the isosorbide dinitrate was temporarily discontinued and oral hydralazine begun at a dosage of 50 mg every six hours. The amount of hydralazine given was increased by 25 mg every third dose to a maximum of 100 mg or until the resting cardiac index exceeded 2.5 l/min per m². After at least 24 hours of oral hydralazine treatment another set of resting and exercise haemodynamic measurements was recorded two to three hours after hydralazine dosing. Lastly, the two drugs were administered in combination and a final set of measurements performed at a time when the peak effects of both drugs coincided. The final dosages of these medicines ranged from 50 to 100 mg hydralazine every six hours and 5 to 15 mg sublingual isosorbide dinitrate every two hours. The order of drug administration was not varied and new control measurements were not obtained between drugs because of practical constraints. The duration of catheterisation was 72 hours in most patients even without allowing the 24 to 48 hours needed for the hydralazine effect to disappear. It was also not possible to perform more than five exercise tests in these patients in the time available.

Measurements were performed by the same investigators in the same relation to meals and diuretic administration (always at least six hours earlier) as the baseline study. Body weight was monitored daily during the procedure and did not fluctuate more than 1 kg.

CALCULATIONS AND STATISTICAL ANALYSIS
The following variables were derived from the measured haemodynamic variables:
Cardiac index (CI) = Cardiac output/body surface area
Stroke volume index (SVI) = CI/HR
Stroke work index (SWI) = (SAP-PCW) x 0.0136 where SAP = SAP-(SAP-DAP)/3
Systemic vascular resistance (SVR) = (MAP-RA)/CO x 80
O₂ content = O₂ saturation x haemoglobin concentration x 1.34
O₂ consumption = (arterial O₂ content–venous O₂ content) x CO

The arterial and mixed venous (pulmonary artery) oxygen saturations were derived from the PO₂ measurements, using a standard nomogram. 39 The statistical significance of the haemodynamic changes produced by the three drug regimens was determined by two-way analyses of variance and the Neumann–Keuls multiple range test.

Results
HAEMODYNAMIC CHANGES AT REST
The effects of isosorbide dinitrate and hydralazine
given alone and in combination on the resting haemodynamic measurements are shown in Fig. 1 and Table 1. Heart rate was not affected. Arterial pressure fell slightly with hydralazine and combined treatment. Both pulmonary capillary wedge and right atrial pressures were lowered by isosorbide dinitrate and not greatly changed by hydralazine. Pulmonary capillary wedge pressure fell from 26.3±4.8 to 18.9±4.1 mmHg (p<0.001) with isosorbide dinitrate and by a similar amount, to 18.6±5.2 mmHg (p<0.001), on the combination. Hydralazine produced a small, but significant (p<0.05) drop as well, to 22.7±4.5 mmHg. In contrast, hydralazine and combined treatment, but

Table 1  Haemodynamic effects of isosorbide dinitrate and hydralazine at rest

<table>
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<tr>
<th>Case no.</th>
<th>Heart rate (beats/min)</th>
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<th>Cardiac output (l/min)</th>
<th>Stroke volume index (ml/m²)</th>
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Abbreviations: Con, control; ID, isosorbide dinitrate; HY, hydralazine; Comb, combined treatment.

Significance levels: * <0.01; † <0.001; ‡ <0.05.
Exercise haemodynamics during vasodilator treatment

not isosorbide dinitrate alone, improved cardiac output and stroke volume index conspicuously and lowered systemic vascular resistance. Cardiac output rose by about 50 per cent with hydralazine and combined treatment, from 4.1 ± 1.1 to 5.9 ± 1.2 and 6.4 ± 1.4 l/min, respectively, and stroke volume rose to a similar degree.

HAEMODYNAMIC CHANGES DURING EXERCISE

During exercise, the haemodynamic effects of isosorbide dinitrate and hydralazine were more comparable (Fig. 2, Table 2). Measurements were recorded in the control state and on vasodilators at the same predetermined level of near maximal exercise. Heart rate at that time was unchanged, while mean arterial pressure was lowered only by combined treatment. Isosorbide dinitrate resulted in significantly lower right atrial and pulmonary capillary wedge pressures at this level of exercise, just as at rest. In addition, however, it produced a small but significant increase in cardiac output and stroke volume index. During exercise, hydralazine not only produced pronounced increases in cardiac output and stroke volume index and lowering of systemic vascular resistance, but it also significantly lowered right atrial pressure and decreased pulmonary capillary wedge pressure by a substantially greater amount, comparable to the effect of the isosorbide dinitrate. Combined treatment resulted in additive effects, so that on these drugs cardiac output and stroke volume index were both 50 per cent higher and pulmonary capillary wedge pressure was 34 per cent lower than before vasodilators at the same level of exercise. Fig. 3 shows the pulmonary capillary wedge and stroke volume index findings in the individual patients. It can be seen that most patients manifested similar responses to these agents.

The data are plotted in the format of ventricular function curves in Fig. 4. At rest, isosorbide dinitrate produced predominantly a shift to the left, while during exercise the change was clearly upward as well as to the left. Hydralazine had only a small effect on pulmonary capillary wedge pressure at rest and thus produced predominantly an upward shift, whereas during exercise the change was clearly leftward and upward. Combined treatment in both situations produced additive benefit, but this was particularly impressive during exercise. During exercise, the improvement in most indices was significantly greater with hydralazine plus isosorbide dinitrate than with either agent alone.

ACUTE EFFECTS OF VASODILATOR TREATMENT ON EXERCISE CAPACITY

In addition to the haemodynamic measurements at the predetermined near maximal level of exercise, cardiac output and arteriovenous oxygen difference were determined at peak exercise, allowing the calculation of maximal oxygen consumption. These findings are illustrated in Fig. 3. The slight increase in oxygen consumption with isosorbide dinitrate was not statistically significant. This variable, however, did increase during treatment with both hydralazine alone and hydralazine plus isosorbide dinitrate, from 799 ± 202 to 934 ± 333 and 1017 ± 373 ml/min, respectively.

Discussion

RATIONALE FOR STUDY OF EXERCISE HAEMODYNAMICS

Conceptually, vasodilators used in the treatment of heart failure have been divided into those that act predominantly on the venous capacitance vessels, those that act predominantly on the arteriolar resistance vessels, and those with both actions.\textsuperscript{2} \textsuperscript{3} \textsuperscript{12} \textsuperscript{31} Haemodynamic studies at rest have shown that venodilators more effectively lower ventricular filling pressures while the arteriolar dilators produce greater reductions in systemic vascular resistance and increase in cardiac output.\textsuperscript{6} \textsuperscript{15} \textsuperscript{31} Since most patients with severe chronic heart failure have both raised filling pressures and low cardiac output, it has generally been felt that an optimal vasodilator regimen should affect both vascular beds.
Several reports, however, have suggested that individual treatment with either predominant venodilators, such as the nitrates, or arteriolar dilators, such as hydralazine, may be clinically effective. This may reflect indirect effects of these agents, such as a reduction in mitral regurgitation or an increase in renal blood flow. Another likely explanation for this discrepancy is that heart failure patients may differ in their haemodynamic responses to exercise, and that these agents may have different haemodynamic effects during exercise than at rest. Since most patients experience symptoms primarily with activity, the need to examine the effect of drugs during exercise as well as at rest has been in-

Table 2 Haemodynamic effects of isosorbide dinitrate and hydralazine during exercise

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Abbreviations: Con, control; ID, isosorbide dinitrate; HY, hydralazine; Comb, combined treatment. Significance levels: *<0-05; †<0-01; ††<0-001.
creasingly appreciated. For example, rapid tachyphylaxis to the resting haemodynamic effects of prazosin has been frequently noted, yet in some of these same subjects improvement persists during exercise.\(^8\)\(^9\)\(^{33–35}\) Several studies have indicated that prazosin does improve exercise tolerance in patients with chronic heart failure.\(^{19}\)\(^{36}\)\(^{37}\) Other reports indicate that the resting haemodynamic changes produced by vasodilators do not always predict the subsequent clinical response,\(^{15–17}\)\(^{20}\)\(^{21}\) and some preliminary data suggest that exercise haemodynamics may be more helpful.\(^{28}\)

**FINDINGS OF PRESENT STUDY**

This is the first study in which the exercise haemodynamic effects of isosorbide dinitrate and hydralazine have been compared in the same patients. Our results indicate that the resting and exercise responses to these drugs do differ. In our patients and in several other studies, isosorbide dinitrate substantially lowered ventricular filling pressures at rest,\(^6\)\(^7\)\(^9\) but did not alter peripheral resistance or cardiac output. In contrast, during exercise significant increases in cardiac output, stroke volume index, and stroke work index were present after treatment with this agent. Increases in cardiac output during exercise with nitrates have been previously reported, primarily in patients with coronary disease.\(^{22}\)\(^{23}\) This could reflect prevention of ischaemia, but the findings in our patients without coronary disease (cases 2, 3, 9, 11, 12) were similar to the remainder of the group.

At rest, hydralazine conspicuously improved cardiac output, stroke volume index, and stroke work index, and had only a small effect on pulmonary capillary wedge pressure. Previous studies with this agent have reported variable, but generally small, changes in filling pressures at rest.\(^{10–12}\)\(^{14}\)\(^{16}\)\(^{39}\) In contrast, hydralazine lowered exercise wedge pressure to the same level as nitrates. A reduction in exercise wedge pressure with hydralazine has also been recently reported by Hindman et al.\(^{57}\) but was not noted in the patients of Rubin et al.\(^{26}\) who exercised supine rather than upright.

As has been previously noted at rest, combined treatment with isosorbide dinitrate and hydralazine produced additive beneficial effects. During exercise, as opposed to rest, however, combined treatment produced a greater improvement in each haemodynamic variable than treatment with either agent alone. Exercise capacity, as assessed by calculated maximal oxygen consumption, also improved on combined treatment and, to a lesser de-
This figure illustrates the changes in left ventricular function, expressed as the relation between stroke work index and pulmonary capillary wedge pressure, at rest and during exercise. At rest, the effects of isosorbide dinitrate (I) and hydralazine (H) are different and additive. During exercise, these drugs produce more similar changes, and combined treatment results in greater improvement than either drug alone.

Degree, on hydralazine alone. This finding requires further corroboration, since our study was not controlled and oxygen consumption did increase with successive exercise tests, raising the possibility of a “training effect”. It should be noted, however, that the control measurements were performed after a preliminary maximal exercise test, and the duration of exercise did not significantly differ between the preliminary and control exercise tests. Other investigators have not observed an acute increase in exercise capacity with vasodilator therapy and have speculated that it may take time to develop. We did not measure oxygen consumption directly, as have some workers, but rather derived it from the cardiac output and calculated oxygen saturation. Though vasodilators may lower arterial oxygen saturation by producing functional intrapulmonary shunting, this should not affect the calculated oxygen consumption.

Our differing findings probably reflect variations in study procedure and patient population. Some studies have only used a single standardised dose; whereas, we treated our patients continuously for several days with individualised dosages. Rubin’s patients were treated for 48 hours, but he used supine bicycle exercise and his subjects were more incapacitated. If our results are corroborated, it suggests that improvement in exercise capacity was significantly improved by both hydralazine and combined treatment. The abbreviations are the same as in Fig. 1.
**Exercise haemodynamics during vasodilator treatment**

Performance may occur rapidly in some patients but develop over a period of time in others.

**Implications**

These findings show the importance of examining exercise as well as resting haemodynamic measurements in evaluating drug treatment for heart failure. Since both isosorbide dinitrate and hydralazine each lower wedge pressure and raise cardiac output during exercise, they may be efficacious individually in treating some patients. Combined treatment produces striking improvement during exercise and at rest, and thus our findings further support the use of this vasodilator regimen.

**References**

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Requests for reprints to Dr Barry Massie, Department of Medicine (111C), Veterans Administration Medical Center, 4150 Clement Street, San Francisco, California 94121, USA.
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B M Massie, B Kramer, E Shen and F Haughom

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