Effect of vasodilator drugs on exercise performance in cardiac failure

Comparison of hydralazine and prazosin

D H FITCHETT, M PATHÉ, R PARDY, P DESPAS

From the McGill University Clinic of the Royal Victoria Hospital, Montreal, PQ, Canada

SUMMARY Although vasodilator drugs cause haemodynamic improvement at rest, their effect on the overall exercise response is uncertain. Nine patients with severe diuretic dependent cardiac failure were studied before and during upright bicycle exercise, after the double blind administration of equi-hypotensive doses of hydralazine (H) 75 mg, prazosin (Pr) 3 mg, and placebo (P). The ventilatory response and oxygen uptake were monitored continuously. Cardiac output was measured during the third minute of steady state exercise by the CO₂ rebreathing method.

At rest when the treatment groups were compared with placebo, there was a 25 per cent increase in cardiac index, placebo 1.9±0.1, hydralazine 2.3±0.1, prazosin 2.4±0.1, and 23 per cent decrease in the arteriovenous oxygen content difference, placebo 9.1±0.7, hydralazine 7.3±0.4, and prazosin 6.9±0.7 ml O₂/100 ml. After progressive exercise to symptom limited maximum, there was no significant difference in the exercise duration, oxygen uptake, peak heart rate, or blood pressure. Even during steady state exercise (at two-thirds maximum), heart rate, blood pressure, cardiac index, stroke volume, stroke work, and arteriovenous oxygen content did not differ in the treatment or placebo periods.

After the acute oral administration of hydralazine or prazosin in doses which produce a significant haemodynamic improvement at rest, there were no changes in the cardiorespiratory response during exercise.

Vasodilator drugs are effective in both short- and long-term treatment of patients with severe heart failure.¹–³ Though their effects on resting haemodynamics are well defined, it is not yet clear whether they improve the exercise performance of such patients. Some reports have suggested an improvement in exercise capacity and haemodynamic reserves after the acute administration of a vasodilator drug,⁴⁵ whereas others showed no change in maximal exercise capacity, but improved pump function at submaximal workloads.⁶

In the present study, we have compared the effects of the predominantly arteriolar vasodilator hydralazine with the arteriolar and venodilator agent prazosin on the cardiac output and ventilatory responses during maximal and steady state exercise and on the time over which such exercise can be tolerated.

Patients and methods

Nine patients with chronic congestive heart failure and class II to III symptomatology (New York Heart Association criteria) were included in the study. Their ages ranged from 27 to 65 years (mean 47 years); seven were men and two were women. All were taking optimal doses of diuretics and digoxin which were continued in unchanged doses throughout the study. The patients’ symptoms and weight were also unchanged for four weeks before the study.

Heart failure was attributed to coronary artery disease in three patients, hypertension in one, cardiomyopathy in four, and mitral valve replacement with poor left ventricular function in one. No patient had severe angina pectoris, recent myocardial infarction (less than six months), or significant mitral regurgitation.

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The exercise studies were performed on three mornings within seven days. The patients attended the hospital after taking a light breakfast. Informed written consent was obtained from all patients.

**DATA COLLECTION AND ANALYSIS**

Heart rate and electrocardiogram were monitored continuously and blood pressure was measured at one-minute intervals by sphygmomanometer. Inspired air volumes were measured continuously with a Parkinson Cowan gas meter linked to a linear potentiometric resistor. Expired air passed through a mixing chamber from which a continuous aliquot was withdrawn for measurement of carbon dioxide content using a Beckman Medical Gas Analyzer LB2 and oxygen content using a Beckman Oxygen Analyzer OM11. The outputs from the gas meter potentiometer and the gas analysers were recorded continuously on a Sanborn 350 chart recorder. Cardiac output was measured during steady state exercise using the carbon dioxide rebreathing method. This method has been shown to compare well with dye dilution methods of determining cardiac output. It provides reliable measurements of cardiac output both at rest and during exercise in patients with congestive heart failure.

### Table 1 Observations at rest (seated on bicycle ergometer)

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Oxygen uptake (ml/min)</th>
<th>Heart rate (b/min)</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Cardiac index (l/min per m²)</th>
<th>Stroke volume index (ml/m²)</th>
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<tr>
<td></td>
<td>Pi  H  Pr</td>
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<td>9</td>
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<td>72 75 75</td>
<td>87 90 68</td>
<td>1.1 1.6 2.1</td>
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<tr>
<td>Mean</td>
<td>294 303 281</td>
<td>96 99 98</td>
<td>89 87 81</td>
<td>1.9 2.3 2.4</td>
<td>22 23 25</td>
</tr>
<tr>
<td>SE</td>
<td>24 20 24</td>
<td>7 6 6</td>
<td>4 4 4</td>
<td>0.1 0.1 0.1</td>
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<tr>
<td>p NS</td>
<td>NS NS NS</td>
<td></td>
<td></td>
<td>NS &lt; 0.05</td>
<td>NS &lt; 0.05</td>
</tr>
</tbody>
</table>

SE, Standard error of mean; NS, p < 0.05.

Pi, placebo; H, hydralazine; Pr, prazosin.

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**Fig.** The effects of placebo (Pi), hydralazine (H), and prazosin (Pr), on the heart rate, mean arterial pressure, cardiac index, arteriovenous (A-V) oxygen content at rest and during steady state exercise.
Vasodilator drugs and exercise

Mean arterial pressure was calculated from the diastolic pressure plus one-third of the pulse pressure. Arteriovenous oxygen content difference was calculated from the oxygen uptake divided by the cardiac output. Systemic vascular resistance (dynes s cm\(^{-5}\)) was calculated from mean arterial pressure divided by the cardiac output multiplied by 80.

Statistical analysis between groups was performed using Student's paired t test.

**METHOD OF STUDY**

The patients attended the hospital at the same time on three mornings within the same week. The order of the oral treatment was selected by a random double blind design. In order to avoid first dose effects, one capsule was given on the evening before each study, which contained the same drug as administered on the morning of the study. Each capsule contained either prazosin 1 mg, hydralazine 25 mg, or placebo.

The exercise study started two hours after the administration of three capsules (that is hydralazine 75 mg or prazosin 3 mg or placebo). Exercise was performed seated on a bicycle ergometer (Elema Schonander). Starting at a workload of 200 kpm/min, work was increased by 50 kpm every one minute until terminated by fatigue or dyspnoea. One exercise study was stopped prematurely because of frequent ventricular extrasystoles; this was excluded from the analysis.

After resting for 30 minutes, the patient exercised for four minutes to a steady state of oxygen consumption at a workload of approximately 60 per cent of the highest load previously attained and the same workload was used in the subsequent two studies. Haemodynamic and ventilatory measurements were made during the final minute of exercise on each occasion.

**Results**

**RESTING MEASUREMENTS**

The effects of hydralazine and prazosin are compared with placebo for the resting patient seated on the bicycle ergometer (Table 1 and Fig.). Cardiac index increased significantly after prazosin from 1.9±0.1 to 2.4±0.1 l/min per m\(^2\) (p<0.05), but after hydralazine the increase did not achieve statistical significance. Systemic vascular resistance was reduced from 2217±271 to 1782±140 dynes s cm\(^{-5}\) after hydralazine (p<0.05) and to 1461±214 dynes s cm\(^{-5}\) after prazosin (p<0.01). The arteriovenous oxygen content difference decreased in both treatment groups (9.1±0.7 ml/100 ml versus hydralazine 7.1±0.4 ml/100 ml (p<0.05) and prazosin 6.9±0.9 ml/100 ml (p<0.005)).

**PROGRESSIVE EXERCISE**

The values in Table 2 represent the individual maxima attained on each treatment at the peak

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**Table 2 Observations at maximal exercise**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Maximal oxygen uptake (ml/kg per min)</th>
<th>Peak heart rate (b/min)</th>
<th>Peak ventilation (l/min)</th>
<th>Duration of exercise (min)</th>
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<tr>
<td>SE</td>
<td>0.6</td>
<td>0.5</td>
<td>1.2</td>
<td>7</td>
</tr>
</tbody>
</table>

PI, placebo; H, hydralazine; Pr, prazosin.
workload achieved. Neither hydralazine nor prazosin had any significant effect on the duration of exercise, maximal oxygen uptake, peak heart rate, peak ventilation, or peak blood pressure.

**SUBMAXIMAL STEADY STATE EXERCISE**

Measurements taken during the fourth minute of steady state exercise, after hydralazine and prazosin, are shown in Table 3. No significant change in heart rate, arterial blood pressure, cardiac index, systemic vascular resistance, arteriovenous oxygen content difference, or lactate production was observed after either vasodilator drug.

**Discussion**

The patients in the present study all had a severe limitation of their effort tolerance and only achieved a maximal oxygen consumption of 13.8 ml/min per kg. This probably resulted from the restricted rise in cardiac output as well as the rise in the pulmonary venous pressures. Vasodilator drugs, if effective during exertion, might be expected to improve the factors that limit exercise performance. Hydralazine, an arteriolar vasodilator when given to resting supine patients with cardiac failure, increases the cardiac output, yet has only a modest effect on pulmonary venous pressures.\(^2\) In contrast, prazosin acts both on the arteriolar resistance and the venous capacitance vessels: at rest, there is an increase in cardiac output and a fall in left ventricular filling pressures.\(^9\) Prazosin might therefore be expected to improve exercise capacity more than hydralazine by virtue of its double site of action. On the other hand, venodilatation may reduce the venous return during exertion and further limit a rise in cardiac output.

Although the predicted beneficial effects of both hydralazine and prazosin occurred at rest, there was no improvement in either maximal effort capacity or cardiac output during submaximal steady state exercise.

The failure of vasodilator drugs to improve the exercise performance of patients with cardiac failure may be the result of an interaction of several mechanisms. In the exercising patient with cardiac failure, the normal reduction of peripheral vascular resistance, and thus afterload, is restricted by increased sympathetic activity\(^10\) as well as an increased stiffness of the walls of the muscular arterioles.\(^11\) In the present study using the doses of drugs administered and the exercise loads studied, there was no augmentation of the fall in systemic vascular resistance towards normal levels by either agent.

The oxygen delivery to exercising muscles is an important factor limiting exercise capacity in both health and disease.\(^12\) In cardiac failure, the inadequate increase in cardiac output,\(^13\) and a limited ability of the resistance vessels in skeletal muscle to dilate,\(^11\) will decrease the oxygen delivery to the active muscle and reduce exercise capacity. Arteriolar vasodilator drugs act predominantly on visceral and skin vessels as well as dilating the arterioles in resting muscle, yet they would be expected to have no effect on the resistance vessels in the muscle of the exercising limb, which are already maximally dilated. Thus, any potentially beneficial increase in cardiac output may be diverted away from the exercising muscle, and could potentially decrease exercise capacity.

The reduction of both left and right ventricular filling pressures with drugs which dilate the systemic and pulmonary venous capacitance vessels, though decreasing pulmonary congestion, may interfere with the reflex venoconstriction which normally increases venous return and maintains the cardiac output during exercise. The present group of
patients had a severely limited exercise capacity despite maximal treatment with diuretics. Further reduction of the effective circulating volume by venodilatation may augment the effect of a diuresis by reducing exercise performance further.\textsuperscript{14}

The results of the present study are similar to those observed after nitrates\textsuperscript{18} and hydralazine plus nitrates.\textsuperscript{8} In both studies, no differences were observed at maximal effort, though during sub-maximal exertion cardiac output was slightly higher after the drugs. After the short-term oral administration of prazosin, Rubin \textit{et al.}\textsuperscript{5} observed no haemodynamic change at rest yet an increased stroke volume and decreased filling pressures during supine exercise. The apparently differing results may be explained both by the supine posture, and a sympatholytic effect which persists after tachyphylaxis to the vasodilator effect of prazosin has developed.\textsuperscript{18} The adrenergic blockade may enhance the limited decrease in vascular resistance by overcoming the sympathetic hyperactivity which occurs during exercise in patients with heart failure.\textsuperscript{10} The improvement of exercise capacity in patients with chronic rheumatic heart disease after nitrates\textsuperscript{4} is probably the result of a reduction in valvular regurgitation, an improvement that persists during exercise.

Finally, it is interesting that though the acute administration of a vasodilator drug has little effect on the peak exercise performance of the patient with cardiac failure, the long-term administration of nitrates,\textsuperscript{17} prazosin,\textsuperscript{18} and trimazosin\textsuperscript{19} does improve exercise capacity. The differences between the effects of a first dose of a vasodilator and those observed after a long period of administration are unclear. An improvement in renal perfusion will increase the response of the kidneys to diuretics and mobilise extravascular fluid. The removal of perivascular oedema will improve the dilator capacity of the muscular arterioles\textsuperscript{11} and may then allow the vasodilator drug to augment the limited fall in systemic vascular resistance during exercise. A comparison of the hemodynamic response to exercise after the acute administration and long-term treatment with a vasodilator drug is now desirable to establish why the differences exist.

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Requests for reprints to Dr D H Fitchett, Cardiovascular Research Unit, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, PQ, Canada H3A 1AI.
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