β-Adrenergic stimulation of the failing ventricle: a double-blind, randomized trial of sustained oral therapy with prenalterol


ABSTRACT Eleven patients with severe left ventricular impairment (mean ejection fraction 24%) and moderate impairment of exercise tolerance underwent a double-blind, placebo-controlled, crossover trial of the orally administered β-agonist prenalterol. Exercise hemodynamics and tolerance were measured during bicycle and treadmill exercise after 2 weeks of therapy with placebo or prenalterol. Cardiac index, ejection fraction, and stroke work index were not improved and exercise duration and peak oxygen consumption were not significantly different during the two treatments. During prenalterol treatment heart rate during exercise was consistently reduced. These results show that prolonged therapy with prenalterol does not improve hemodynamics or exercise tolerance and is associated with a diminished heart rate response to exercise.


SHORT-TERM administration of orally active β-adrenergic agonists improves hemodynamics in patients with heart failure both at rest and during exercise. However, doubts exist as to the ability of the impaired ventricle, already exposed to increased sympathomimetic activity, to respond to additional long-term adrenergic stimulation. There have been no well-controlled trials of prolonged β-agonist therapy in patients with heart failure. This study was designed to examine the effects of 2 weeks of oral therapy with the β-agonist prenalterol on left ventricular function, exercise hemodynamics, and exercise tolerance in ambulant patients with moderately severe left ventricular impairment.

Methods

Patient selection. Eleven patients with chronic left ventricular failure (>3 months duration) due to congestive cardiomyopathy (six patients) or previous myocardial infarction (five patients) were studied. Their mean age was 51 years (range 27 to 59). Clinical details are shown in table 1. Mean radionuclide left ventricular ejection fraction before entry into the study was 24% (range 16% to 32%). All patients were New York Heart Association functional class II or III and on treadmill exercise testing had an estimated peak oxygen consumption equal to or less than 60% of that predicted for a healthy subject of similar age. In all patients exercise was limited by dyspnea, fatigue, or both. No patient suffered chest pain or had evidence of exercise-induced myocardial ischemia and all were in sinus rhythm.

Study protocol. All patients were studied as outpatients and gave written informed consent. After a 2 week stabilization period, patients entered a dose-ranging phase in which prenalterol was given in an initial dosage of 50 mg every 12 hr. After 4 days patients were reassessed and in the absence of adverse findings or side effects, the dosage was increased to 100 mg every 12 hr. The patients were again reassessed on day 8. Eight patients were able to tolerate the drug at the higher dosage. The remaining three patients tolerated only 50 mg bd due to sinus tachycardia (one patient), increasing frequency of ventricular ectopic beats (one patient), and unpleasant palpitations (one patient).

A 1 week washout period then followed, after which patients were randomly assigned to receive either placebo or active drug at the appropriate dosage. After 2 weeks of oral therapy patients had a further 1 week washout period and then received the alternative treatment. Patients were studied on the last day of each treatment phase. Digoxin was stopped in all patients before the stabilization period, but diuretics and vasodilators (three patients) were continued (table 1). On both study days, blood levels were measured 2 hr after ingestion of prenalterol or placebo. The mean plasma concentration of prenalterol was 231 nmol/liter (range 81 to 438).

Exercise and hemodynamic assessment. On the morning of each study day, diuretics and vasodilators were withheld and ingestion of drug was supervised. A radial arterial cannula and a No. 7F Swan-Ganz thermodilution catheter were inserted percutaneously in 10 of the 11 patients. One patient underwent exercise testing and radionuclide studies without invasive
hemodynamic monitoring. Exercise testing was performed on a bicycle ergometer after a 1 hr rest period (2 hr after ingestion of drug). A treadmill hemodynamic exercise test was performed after another 2 hr rest.

**Bicycle exercise.** Rest and exercise measurements were performed in an air-conditioned laboratory with the patient positioned semiupright on an exercise table (Atomic Products, New York) set at 45 degrees to the horizontal and equipped with an electronically braked bicycle ergometer (Siemens-Elema 380B). During exercise, heart rate, electrocardiogram from lead CM5, phasic and mean (by electronic damping) radial arterial pressures, pulmonary arterial pressure, and right atrial pressure were recorded continuously. Pulmonary arterial wedge pressure was recorded during the last 30 sec of each exercise level. When a satisfactory wedge pressure could not be obtained, the pulmonary arterial diastolic pressure was used for comparison between the two studies. The zero reference point for pressures (Bell and Howell 4-327-1 transducers) was set at the fourth intercostal space in the midaxillary line and recorded on an Electronics for Medicine VR-12 recorder. Exercise was limited by symptoms, with the workload commencing at 15 W and increasing by 15 W every 3 min.

A 12-lead electrocardiogram was recorded every minute. Cardiac output was measured by thermodilution with ice-cold 5% dextrose and was calculated with an Instrumentation Laboratory Computer (Model 701). Five measurements were made at rest. During exercise, at least three measurements were made in the last 1.5 min of each 3 min exercise level. Stroke volume, stroke work index, and systemic vascular resistance were calculated with standard formulas.11

Radial and pulmonary arterial blood samples were collected at rest and at the end of each exercise level for measurement of oxygen saturation. The radial arterial sample was also used for measuring hemoglobin at rest and during exercise. The arteriovenous oxygen content difference was calculated as 1.39 \times (the difference between radial arterial and pulmonary arterial oxygen saturations) \times hemoglobin level.12 Oxygen consumption was calculated as the cardiac output \times arteriovenous oxygen content difference.

**Radionuclide ventriculography.** Multiple-gated equilibrium radionuclide ventriculography was performed after labeling of red cells in vivo with technetium-99m. Imaging was performed with patients in a modified left anterior oblique position by an Ohio nuclear gamma camera (Sigma 420) equipped with a 30 degree slant hole and high-sensitivity collimator and interfaced to a PDP-11 computer. Counts were collected for 6 min at rest with simultaneous recordings of intravascular pressures and cardiac output. During exercise, counts were collected in the last 2 min of each 3 min stage. The composite cardiac cycle was divided into 24 frames for analysis by a variable region of interest. Left ventricular ejection fraction was calculated from the background-corrected time-activity curve.

Stroke volume was determined from the thermodilution cardiac output and expressed as stroke volume index. End-diastolic volume was calculated by dividing the thermodilution stroke volume index by the radionuclide ejection fraction and was expressed as the end-diastolic volume index. End-systolic volume index was calculated as end-diastolic volume index minus the stroke volume index.

This method of measuring absolute left ventricular volumes has been validated in 10 patients. Thermodilution cardiac output and radionuclide ejection fraction were measured with patients in the supine position and the derived end-diastolic volumes (thermodilution stroke volume/radionuclide ejection fraction) were correlated with their corresponding end-diastolic volumes calculated from single-plane cineangiographic studies by the area-length method of Kennedy et al.13 Derived end-diastolic volume was equal to 1.1 angiographic end-diastolic volume + 13 ml \( r = .94, p < .01 \). The reproducibility of derived end-diastolic volumes at rest and on exercise was tested 2 days apart.
The mean difference in observations made at rest was 5 ± 19% (± SD) (n = 13) and that in observations made during exercise was 6 ± 13% (n = 13).

**Treadmill exercise.** Treadmill exercise (Avionics Delmar C16) was performed according to a modified Naughton protocol and the work level was increased every 3 min. Hemodynamic parameters were measured continuously by means of pressure transducers positioned on the handrail of the treadmill, with the same reference point as for bicycle exercise. Exercise was limited by symptoms as determined from hemodynamic measurements and blood gas analyses made at each work level.

**Statistical analysis.** Results are expressed as mean ± 1 SD. Hemodynamic measurements at rest and exercise with patients on active treatment were compared with the results of the placebo rest and exercise studies by a three-way analysis of variance.

When there was significant interaction between drug therapy and exercise level, active treatment and placebo studies were compiled separately at rest and during exercise by a t statistic derived from the pooled error mean square. The t value required for two planned comparisons was applied according to the Bonferroni method, with p < .05 defined as significant.

**Results**

**Resting hemodynamics.** Resting hemodynamic values obtained before bicycle and treadmill exercise tests are shown in figures 1 and 2. The resting left ventricular ejection fraction was similar during the peneralterol and placebo phases. Cardiac index at rest, with patients in
TABLE 2
Comparison of hemodynamics at rest and during maximum exercise

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**HR (bpm)** | MAP (mm Hg) | CI (l/min/m²) | RAP (mm Hg) | SVR (dyne-sec-cm⁻²) | SVI (ml/m²) |

Data expressed as mean ± SD.

Pren = prenalterol; Plac = placebo; Ex = maximum exercise level; HR = heart rate; MAP = mean arterial pressure; CI = cardiac index; SVR = systemic vascular resistance; SWI = stroke work index; SVI = stroke volume index; EF = ejection fraction; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; PAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; RAP = right atrial pressure; AVO₂D = arteriovenous oxygen content difference.

Statistical comparisons (prenalterol vs placebo): *p < .05; **p < .01.

both the semiupright and upright postures, was the same with both treatments. Pulmonary wedge pressure was unchanged with patients in the semiupright posture but was slightly reduced during prenalterol treatment before treadmill exercise. There were no differences in heart rate, mean arterial pressure, stroke work index, and systemic vascular resistance between the two treatment phases (table 2).

Exercise capacity (figure 3). Exercise was stopped in all patients because of dyspnea, leg fatigue, or both. Leg fatigue was the predominant symptom on bicycle exercise. Durations of exercise were similar during the prenalterol and placebo phases: bicycle (15.88 ± 7.1 vs 14.78 ± 5.1 min; p = NS) and treadmill (24.49 ± 6.9 vs 22.49 ± 6.39 min; p = NS).

Peak oxygen consumption achieved during tread-
mill exercise was not changed during prenalterol treatment (19.9 ± 6.0 vs 22.0 ± 6.8 ml/min/kg; p = NS). Peak oxygen consumption achieved during bicycle exercise was also similar during the prenalterol and placebo phases (17.4 ± 6.4 vs 16.8 ± 6.1 ml/min/kg) but both were significantly less than that achieved on the treadmill (p < .01). Maximum peripheral oxygen extraction measured by the arteriovenous oxygen content difference did not differ between treatments either on treadmill (15.3 ± 3.4 vs 15.6 ± 1.9 ml/100 ml) or bicycle (13.7 ± 2.3 vs 13.9 ± 2.7 ml/100 ml).

Exercise hemodynamics. Hemodynamic values obtained at the maximum workload achieved during bicycle exercise are shown in figure 4. Maximum exercise ejection fraction, cardiac index, and stroke work index were similar during the prenalterol and placebo phases. During prenalterol treatment there was a significant reduction in heart rate at maximum workload and this was associated with an increase in both end-diastolic (188 ± 51 vs 153 ± 54 ml/m²; p < .01) and end-systolic volumes (117 ± 48 vs 148 ± 45 ml/m²; p < .05) and a small increase in stroke volume (figure 5). There was no significant difference between treatments in pulmonary arterial wedge pressure, right atrial pressure, mean arterial pressure, and systemic vascular resistance (table 2).

Hemodynamic values obtained at the maximum treadmill exercise level are compared in figure 6. Cardiac index at maximum workload tended to be lower during active treatment and was associated with a sig-
significant reduction in maximal heart rate (133 ± 18 vs 147 ± 19; p < .05). Stroke work index was the same during both phases. Pulmonary arterial wedge pressure was slightly lower at maximal workload during prenalterol treatment, but mean arterial and right atrial pressures and systemic vascular resistance were unchanged (table 2). In contrast to that observed during bicycle exercise with patients in the semiupright posture, the lower maximum heart rate was not associated with an increase in stroke volume index.

Discussion

In this double-blind, placebo-controlled, crossover trial in patients with cardiac failure, 2 weeks of oral
\( \beta \)-adrenergic receptor stimulation with prenalterol did not improve left ventricular function, exercise hemodynamics, or exercise tolerance. These negative results emphasize the importance of assessing these agents with such a protocol and of studying prolonged therapy.

The plasma levels of prenalterol obtained in this study are similar to those observed with infusions of 50 to 100 \( \mu \)g/kg body weight,\textsuperscript{18} which in short-term studies have produced marked improvement in rest and exercise hemodynamics and left ventricular function in patients with heart failure.\textsuperscript{1-5, 15-19} In normal subjects, sustained-release prenalterol tablets have been reported to produce the same short-term hemodynamic effects as intravenous administration.\textsuperscript{10} There have been few trials of sustained oral therapy. In a single-blind study assessing 1 to 2 weeks of oral therapy with prenalterol, Hjalmarson et al.\textsuperscript{17} found significant improvement in echocardiographic estimates of left ventricular contractility and most patients had improvement of symptoms. Significant reductions in exercise heart rates on active treatment were also noted.

In contrast, we found that left ventricular performance was not improved either at rest or during exercise. Resting ejection fraction, cardiac index, and stroke work index were not improved with patients in either the upright or the semiprone posture. Pulmonary arterial wedge pressure was slightly reduced by prenalterol during treadmill exercise but this was not observed during bicycle exercise, which emphasizes the varying hemodynamic responses seen when patients exercise in different postures. Despite the presence of severe left ventricular dysfunction and poor exercise tolerance, two patients appeared to have uncharacteristically low filling pressures, which may have prevented an improvement in hemodynamics. Inclusion of these patients is unlikely to have obscured the effect of the drug on the group results, since both showed a small increase in cardiac index with prenalterol.

Cardiac index at high work levels tended to be lower on the treadmill during prenalterol treatment because of the reduction in heart rate. During bicycle exercise neither ejection fraction nor stroke work index were improved, but in contrast to observations made during treadmill exercise, the reduction in heart rate at high workloads was accompanied by an increase in left ventricular volumes and cardiac index was unchanged. The difference between the two forms of exercise may be explained by the higher left ventricular filling pressures during bicycle exercise. Although the increase in end-diastolic volume at peak exercise was probably related to the reduction in heart rate,\textsuperscript{20, 21} the increase in end-systolic volume in the absence of an increase in arterial pressure suggests that myocardial contractility may have been depressed. A similar increase in left ventricular volumes during exercise has been reported in patients with left ventricular dysfunction who were treated with \( \beta \)-adrenergic blocking drugs,\textsuperscript{22} but heart rate decreased and volumes increased at rest, an effect not seen with prenalterol. In this study the apparent decrease in left ventricular function at peak exercise with prenalterol was not seen in the ejection fraction response and confirms that ejection fraction is an insensitive measure of left ventricular dysfunction in patients with heart failure and large left ventricular volumes.\textsuperscript{23}

Our findings are consistent with those of Colucci et al.,\textsuperscript{5} who found that short-term hemodynamic benefits with the \( \beta_2 \)-agonist pirbuterol were not maintained after 30 days of therapy.

Not unexpectedly, the changes observed in exercise hemodynamics were not associated with improved exercise capacity. Treadmill exercise was performed because it provides a better assessment of exercise tolerance and maximal oxygen consumption, particularly in the patient with cardiac failure who develops early leg fatigue on the bicycle ergometer. Although treadmill exercise time tended to be prolonged during prenalterol therapy, peak oxygen consumption was unchanged. This disparity emphasizes the importance of measuring oxygen consumption as an objective indicator of aerobic capacity.

The predominant hemodynamic effect of prenalterol in our study was inhibition of exercise-induced tachycardia. In animal experiments prenalterol has had about 70\% of the intrinsic activity of isoproterenol on \( \beta \)-adrenoceptors and could be classified as a partial agonist with \( \beta \)-antagonist effect.\textsuperscript{18} In short-term studies a \( \beta \)-agonist effect with reduction in heart rate has not been seen, and a significant increase in exercise heart rate was reported when high doses of the drug were used.\textsuperscript{1, 15} A study by Hjalmarson et al.\textsuperscript{17} is the only one to report a reduction in exercise heart rate after 2 weeks of oral treatment with a dosage lower than that in the present study.

The difference between short- and long-term exposure to prenalterol may be explained by the readjustment of autonomically mediated reflex changes with prolonged exposure. Patients with cardiac dysfunction have an impairment of autonomic heart rate control,\textsuperscript{24} probably caused in part by a reduction in the number and sensitivity of \( \beta \)-receptors,\textsuperscript{6, 7} associated with long-term elevation of endogenous catecholamines. It is
possible that further sustained β-adrenergic receptor stimulation could bring about additional downgrading of β-receptors in the failing myocardium and further impair the largely adrenergically mediated tachycardia seen at peak exercise. Colucci et al.6 demonstrated that long-term β-adrenergic therapy in patients with heart failure produced a reduction in the β-adrenergic receptor density of the lymphocytes, but doubts have been expressed about the validity of extending these observations to receptors in cardiac tissues.25 Bristow et al.7 found that β-adrenergic receptor density was reduced by 50% in the failing ventricles of transplant recipients when compared with that in donor hearts. In animal experiments26-4 days of continuous adrenergic stimulation produced evidence of β-adrenoceptor down-regulation, with a parallel shift to the right of the concentration-response curves to isoproterenol and complete suppression of response to prenalterol. In the present study, after 2 weeks of prenalterol therapy, patients with heart failure had diminution of the adrenergically mediated heart rate response of exercise and an apparent decrease in left ventricular contractility, which may be explained by a downgrading of cardiac adrenergic receptors or a partial β-antagonist effect not seen with short-term administration.

In contrast to results of short-term studies, our findings showed that oral β-adrenergic stimulation with prenalterol in patients with heart failure did not improve exercise hemodynamics or exercise tolerance. The diminution of heart rate response to exercise after 2 weeks of therapy appeared to be caused by a reduced response to endogenous adrenergic stimulation.

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