Minoxidil in patients with chronic left heart failure: contrasting hemodynamic and clinical effects in a controlled trial

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ABSTRACT Minoxidil, a potent predominant arterial dilator, improves hemodynamics over the short term in patients with heart failure. In random double-blind fashion 17 patients with chronic left heart failure were given minoxidil (nine patients) or placebo (eight patients) in addition to digoxin and diuretics for 3 months. Cardiac index and heart rate increased and mean arterial pressure and systemic vascular resistance fell within 4 hr of minoxidil administration. Right heart and pulmonary arterial pressures were unchanged over the short term but rose after long-term minoxidil. After 3 months of minoxidil treatment, systemic vascular resistance was still reduced (11.7 ± 6.3[SD] vs 17.1 ± 3.1 U at baseline; p < .05). Hemodynamics were similar at baseline and remained unchanged during placebo treatment. Mean left ventricular ejection fraction rose from 29.6 ± 17.7% to 42.7 ± 22.3% (p < .05) after 3 months of minoxidil treatment (this result was influenced largely by responses in two patients), and remained unchanged (at 25.1 ± 16.6%) after 3 months of placebo. Exercise duration and maximal oxygen uptake during exercise were unchanged during minoxidil or placebo treatment. Total clinical events, including increased need for diuretics, angina, ventricular arrhythmias, worsening heart failure, and death were all more frequent during minoxidil vs placebo administration (21 vs seven total events; p < .01). Thus, despite improving hemodynamics and left ventricular function, long-term minoxidil administration was associated with a poorer clinical course in patients with chronic left ventricular failure. Furthermore, this experience demonstrates that improvement of left ventricular function alone cannot be reliably interpreted as proof of clinical efficacy of therapeutic interventions in patients with heart failure.


Minoxidil is a potent, orally effective, direct-acting arterial dilator that improves left ventricular performance over the short term in patients with congestive heart failure.1 Long-term beneficial effects of minoxidil have been reported in uncontrolled trials in heart failure, but the effects of hydralazine, a similar drug, were no different than those of placebo in controlled studies.2–4 This study was designed to assess the effects of long-term minoxidil administration in patients with chronic left ventricular failure in a controlled trial. The study was undertaken despite the well-known sympathetic stimulation and fluid retention produced by minoxidil in hypertensive patients because other vasodilators that have similar effects in hypertensive patients have not usually produced these effects in patients with heart failure.4–6

Methods

Seventeen patients with chronic congestive heart failure who had been symptomatic for at least 3 months despite treatment with digitalis and diuretics were selected for study. The diagnosis of congestive heart failure was based on a history of symptoms on exertion and the presence of a ventricular gallop sound, jugular venous distention, pulmonary rales, or otherwise unexplained peripheral edema. In addition, all patients were required to have at least one of the following during the month preceding enrollment into the study: (1) cardiothoracic ratio on standard chest x-ray of greater than 0.55, (2) left ventricular ejection fraction less than 40% by radionuclide angiography, (3) echocardiographic left ventricular end-diastolic dimension greater than 2.7 cm/m2, or (4) resting cardiac index by carbon dioxide rebreathing below 2.5 liters/min/m2.

The cause of congestive heart failure was coronary artery
disease or idiopathic dilated cardiomyopathy in all patients. Coronary artery disease was diagnosed by a history of documented acute myocardial infarction or on coronary arteriographic examination. Idiopathic dilated cardiomyopathy was diagnosed when no other cause of heart failure was demonstrable. Patients were excluded if they had primary valvular heart disease, obstructive cardiomyopathy, acute myocardial infarction within 3 months, hypertension requiring treatment, primary pulmonary disease, angina pectoris, or were unable to exercise for any reason other than dyspnea or fatigue. Patients meeting the above criteria gave written informed consent, and the study protocol was approved by the human investigation committees of the institutions involved.

On the first clinic visit dosages of digitalis and diuretics were adjusted as needed and any vasodilators were discontinued. After a 2 week stabilization period each patient was reevaluated and an electrocardiogram, chest x-ray, and M mode echocardiogram were obtained and radionuclide left ventricular ejection fraction was determined. Patients in whom there were no changes in medications or clinical findings and whose weights varied less than 3% during this period entered the randomization phase of the study. On the day of randomization diuretics were withheld and maintenance doses of digoxin were given. Heart rate and rhythm as determined by the electrocardiogram, blood pressure (standard cuff technique), and cardiac output (carbon dioxide rebreathing) were measured at rest and during exercise. We have previously validated the carbon dioxide rebreathing method for cardiac output measurement in congestive heart failure. Exercise was performed on an upright bicycle beginning at 150 kilopond-meters (kpm)/min and increasing by 150 kpm every 4 min until symptomatic maximum of dyspnea or fatigue. Expired air was collected for on-line measurement of oxygen consumption, carbon dioxide production, and respiratory quotient. A rise in the respiratory quotient of at least 0.15 during exercise was required to indicate achievement of anaerobic threshold. In consenting patients a Swan-Ganz catheter was inserted to measure pulmonary arterial pressures and cardiac output by thermodilution. In these patients cardiac output was also determined by carbon dioxide rebreathing.

After completion of all baseline hemodynamic and exercise measurements, patients were given, in random double-blind fashion, the first dose of test drug. Nine patients received 20 mg (two 10 mg tablets) of minoxidil by mouth, and eight patients received two placebo tablets. All measurements were made again 4 hr later.

Upon completion of the randomization day studies, patients were maintained on 20 mg bid minoxidil or two tablets bid placebo in addition to digitalis and diuretics. During a 3 month follow-up period patients were seen monthly in the clinic and maintained on constant doses of test drug and digoxin; dosage of diuretic was adjusted as necessary. M mode echocardiograms and radionuclide left ventriculograms were obtained after 1 and 3 months. At the end of the 3 month follow-up period all resting and exercise measurements were repeated by the same protocol as at baseline.

Derived hemodynamic variables were calculated as follows: mean arterial blood pressure was calculated as one-third of the pulse pressure plus diastolic blood pressure, systemic vascular resistance was calculated as mean arterial blood pressure divided by cardiac output, and pulmonary vascular resistance was calculated as pulmonary arterial mean pressure minus pulmonary wedge pressure divided by cardiac output. Statistical analysis was performed with Student’s t test for paired data to compare within-group responses and for unpaired data to compare responses between groups. An analysis of variance was done for all sequentially observed variables and t tests were performed only if F values were significant.

Results
Baseline characteristics of the patient population at randomization are shown in table 1. Two patients in each group had been receiving vasodilators. Two patients given minoxidil (patients 3 and 6) were in atrial fibrillation while all other patients were in normal sinus rhythm. There were no statistically significant differences between the groups at baseline, although the placebo group tended to have more severe symptoms, greater cardiac dimensions, and lower left ventricular ejection fractions. One patient in each group had a resting ejection fraction above 60% for unknown reasons, but both had elevated pulmonary wedge pressures (20 and 17 mm Hg) and decreased exercise capacity. The placebo group as a whole might have had more severe congestive heart failure. Nine patients agreed to Swan-Ganz catheterization and simultaneous measurements of cardiac output by thermodilution and carbon dioxide rebreathing were made in 14 instances. Cardiac output determined by thermodilution averaged 6.53 ± 2.83 (SD) vs 6.59 ± 3.00 liters/min by carbon dioxide rebreathing. Because of the close correlation between results of the two methods (r = .87, p < .001), subsequent cardiac outputs reported will be those determined by carbon dioxide rebreathing.

Hemodynamic measurements at baseline and 4 hr and 3 months after test drug administration are summarized in figure 1. There were no significant differences between minoxidil- and placebo-treated groups at control. Four hours after the initial doses of minoxidil mean arterial blood pressure fell significantly from 91.7 ± 14.2 to 85.0 ± 10.3 mm Hg; systemic vascular resistance also fell significantly from 17.1 ± 3.1 to 14.6 ± 4.4 U and cardiac index rose from 2.75 ± 0.64 to 3.22 ± 1.21 liters/min/m². The insignificant rise in cardiac index was largely due to a significant increase in heart rate since stroke volume was unchanged. Because of the considerable overlap in heart rate and blood pressure changes between treatment groups, the double blind was maintained.

After 3 months of minoxidil treatment, hemodynamic measurements 4 hr after a single dose showed persistent and significant reduction in systemic vascular resistance. Other hemodynamic changes also persisted but were not statistically significant. There were no significant hemodynamic changes any time after placebo administration. Pulmonary wedge pressure averaged 16.1 ± 7.5 mm Hg in nine patients (six minoxidil, three placebo), with no differences between groups at baseline. Pulmonary wedge pressure did not change 4 hr after minoxidil or placebo, but after 3 months of treatment it had risen by 6.8 ± 4.2 mm Hg.
during minoxidil (p < .05) and was unchanged during placebo. Right atrial pressure also rose significantly during minoxidil treatment, by 3.3 ± 1.3 mm Hg (p < .05). Pulmonary vascular resistance remained unchanged.

Left ventricular ejection fraction was similarly depressed in both groups of patients at baseline but rose from 29.6 ± 17.7% to 43.7 ± 26.6% (p < .05) after 1 month of minoxidil treatment and remained increased to 42.7 ± 22.3% (p < .05) after 3 months of the drug (figure 2). The effects of minoxidil on ejection fraction are exaggerated by the results in two patients whose ejection fractions increased more than 15%. The ejection fraction increased in all but one of the other five patients, but the average change was only 4.8 ± 9.8% at 3 months, which was not statistically significant in this small subgroup. Left ventricular ejection fraction was unchanged during placebo administration. Left ventricular dimensions as determined by echocardiography and New York Heart Association clinical classification remained unchanged in both groups of patients throughout the treatment period. Body weight increased by 5.6 ± 6.1 pounds (p < .05) in the minoxidil group after 1 month of treatment despite an increase in diuretic dosage. Weight changes were insignificant in the placebo group but overlapped with the minoxidil group to help protect the double blind.

Changes in exercise capacity are shown in figure 3. Control values were not significantly different between treatment groups. Exercise duration changed insignificantly during minoxidil and placebo. Maximal oxygen consumption also changed insignificantly from 15.9 ± 6.7 to 16.6 ± 4.4 ml/min/kg in minoxidil-treated patients and from 13.7 ± 5.1 to 15.0 ± 7.0 ml/min/kg in the placebo-treated group. There were no changes in exercise capacity 4 hr after initial doses of test drugs and no significant changes in hemodynamics during exercise after either minoxidil or placebo at any time.

A total of 21 clinical events occurred during minoxidil treatment compared with seven during a comparable number of patient-weeks of placebo treatment (p < .01; table 2). All types of events were more frequent during minoxidil therapy and all patients on minoxidil required an increase in diuretic dosage, which is con-

| TABLE 1 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Baseline characteristics of patient population | | | | | | |
| Patient No. | Age (yr) | Weight (kg) | Cause of CHF | Duration of symptoms (mo) | Clinical class (NYHA) | CTR (%) | LVDD (mm) | LVEF (%) |
| Minoxidil | | | | | | | | |
| 1 | 49 | 103 | PMD | 14 | 2 | 51 | 52 | 71 |
| 2 | 53 | 64 | PMD | 6 | 2 | 49 | 56 | 35 |
| 3 | 49 | 90 | PMD | 17 | 2 | 58 | 71 | 16 |
| 4 | 66 | 56 | PMD | 8 | 3 | 45 | 53 | 10 |
| 5 | 66 | 100 | IHD | 12 | 3 | 61 | 61 | 31 |
| 6 | 50 | 119 | PMD | 72 | 3 | 61 | 67 | 21 |
| 7 | 51 | 89 | IHD | 9 | 3 | 42 | 57 | 35 |
| 8 | 48 | 68 | IHD | 6 | 2 | 50 | 58 | 27 |
| 9 | 54 | 85 | IHD | 24 | 3 | 50 | 66 | 20 |
| Mean | 54.0 | 86.0 | — | 18.7 | 2.6 | 51.9 | 60.1 | 29.6 |
| SD | 7.1 | 20.3 | — | 20.8 | 0.5 | 6.8 | 6.6 | 17.7 |
| Placebo | | | | | | | | |
| 10 | 61 | 88 | PMD | 12 | 2 | 51 | 62 | 61 |
| 11 | 48 | 87 | IHD | 60 | 3 | 64 | 70 | 17 |
| 12 | 58 | 65 | IHD | 12 | 3 | 56 | 100 | 9 |
| 13 | 44 | 80 | PMD | 74 | 2 | 60 | 67 | 11 |
| 14 | 62 | 88 | IHD | 12 | 3 | 55 | 73 | 22 |
| 15 | 53 | 82 | IHD | 18 | 3 | 54 | 66 | 25 |
| 16 | 63 | 64 | PMD | 14 | 3 | 57 | 57 | 25 |
| 17 | 60 | 106 | PMD | 22 | 3 | 51 | 72 | 15 |
| Mean | 56.1 | 82.5 | — | 28.0 | 2.8 | 56.0 | 70.9 | 23.1 |
| SD | 7.0 | 13.6 | — | 24.6 | 0.5 | 4.4 | 12.9 | 16.4 |

No differences between treatment groups are statistically significant.

CHF = congestive heart failure; CTR = cardiothoracic ratio; IHD = ischemic heart failure; NYHA = New York Heart Association criteria; LVDD = left ventricular diastolic dimension by echocardiography; LVEF = left ventricular ejection fraction by radionuclide angiography; PMD = primary myocardial disease.
sistent with the previously described increases in body weight, pulmonary wedge pressure, and right atrial pressure. Of the two deaths that occurred during minoxidil treatment, one was sudden and unexpected during the third week after randomization in a patient who experienced worsening symptoms during the preceding 2 weeks. The other death occurred within the first week after randomization in a patient whose symptoms progressively worsened, leading to hospitalization and ultimately to death. One other patient taking minoxidil withdrew prematurely after 10 weeks in the study because of increasing symptoms of congestive heart failure and the onset of new chest pain. One patient in the placebo-treated group also withdrew prematurely because of new angina pectoris. The ventricular arrhythmias that were noted during minoxidil included multiple premature ventricular contractions in one patient and a bout of symptomatic sustained ventricular tachycardia in another. Both were treated successfully with antiarrhythmic drugs and did not withdraw from the study.

Because of the increased frequency of clinical events without apparent benefit on symptomatic status during minoxidil treatment, the trial was terminated prematurely. It was not terminated sooner because these differences in undesirable effects were not significant. The original intent was to randomize 24 patients, 12 to each group, but this was not done for ethical reasons.

Discussion

Our results typify the current status of long-term vasodilator therapy for chronic congestive heart failure. We observed beneficial immediate and long-term hemodynamic effects of minoxidil along with improved left ventricular performance. Despite these improvements, minoxidil had no effect on exercise capacity, and patients actually did worse clinically on minoxidil than on placebo. In general vasodilators have been shown to improve hemodynamics and many have also been shown to improve exercise capacity, but their overall clinical effects remain to be estab-

FIGURE 1. Immediate and long-term hemodynamic effects of minoxidil in patients with chronic left ventricular failure. Values are mean ± SD. C = control value; 4 hr = value 4 hr after first dose of test drug; 3 mo = value after 3 months of treatment measured 4 hr after a dose of test drug.

FIGURE 2. Effects of minoxidil on left ventricular performance in patients with chronic left ventricular failure. Shaded areas are mean ± SEM. C = control values; 1 mo = values after 1 month of treatment; 3 mo = values after 3 months of treatment.
short-term hemodynamic effects of minoxidil and have also demonstrated a sustained vasodilator response during long-term minoxidil administration. We also demonstrated a sustained significant increase in left ventricular ejection fraction during minoxidil administration. The magnitude of increase in ejection fraction produced by minoxidil may be greater than that produced by other vasodilators.\textsuperscript{13, 14} Minoxidil may have direct inotropic effects.\textsuperscript{15} In addition, the observed increase in heart rate in our patients suggests reflex sympathetic stimulation, and the increased pulmonary wedge pressure during minoxidil treatment may indicate a positive inotropic effect resulting from increased preload. Minoxidil administration has also been associated with a rise in pulmonary arterial pressure in hypertensive patients.\textsuperscript{16}

Although hemodynamics and left ventricular function were improved by minoxidil, exercise capacity was not, which is consistent with previous observations that resting hemodynamics and left ventricular function do not correlate with exercise capacity in patients with heart failure.\textsuperscript{12} However, resting hemodynamics and left ventricular performance are related to long-term survival, whereas exercise capacity may not be in these patients.\textsuperscript{17-19}

The failure of minoxidil to increase exercise capacity is of considerable interest. Many other vasodilators do improve exercise ability in patients with heart failure, including nitrates, prazosin, and captopril.\textsuperscript{20-22} Among the vasodilators tested, only hydralazine, which like minoxidil is a predominant arterial dilator, has failed to improve exercise capacity any more than it is improved by placebo in patients with heart failure.\textsuperscript{1} Thus, it appears that only vasodilators with venodilating ability can increase exercise capacity in patients with chronic left ventricular failure, suggesting an important role of the pulmonary circulatory bed and right ventricle in determining functional capacity in chronic left ventricular failure.\textsuperscript{23, 24}

In conclusion, minoxidil produces sustained improvements in hemodynamics and left ventricular performance in patients with chronic left ventricular failure. Despite these improvements, minoxidil does not affect exercise performance, symptomatic status, or clinical complications that, if anything, are increased during minoxidil treatment. Based on these results, minoxidil should not be a vasodilator of primary interest in treating patients with chronic left ventricular failure.

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