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The Effects of Minoxidil on Pulmonary and Systemic Hemodynamics in Hypertensive Man

PAUL E. KLOTMAN, M.D., CLARENCE E. GRIM, M.D., MYRON H. WEINBERGER, M.D., AND WALTER E. JUDSON, M.D.

SUMMARY Pulmonary hypertension has been described as a possible complication of the antihypertensive vasodilator, minoxidil. A prospective study was undertaken in seven severely hypertensive patients refractory to multiple drug therapy. Treatment was initiated with fixed doses of hydrochlorothiazide (100 mg/day) and propranolol (160 mg/day) for a control period. Mean systemic arterial pressure, cardiac output, and pulmonary artery pressure were then compared before and after the addition of acute (5 day) and chronic (2 month) therapy with minoxidil.

DIRECT-ACTING VASODILATORS are frequently used in the treatment of arterial hypertension. Hydralazine has been the only antihypertensive oral vasodilator available and two disadvantages have been associated with its use: inadequate potency in severely hypertensive patients and the development of a lupus erythematosus-like syndrome at doses greater than 200 mg/d. In contrast, the vasodilator minoxidil (6-amino-1, 2-dihydro-1-hydroxy-2-imino piperidino-pyrimidine) has been demonstrated to be more potent and more efficacious than hydralazine and has not been associated with the development of positive LE preps and antinuclear antibodies. Treatment with vasodilators has been associated with tachycardia due to reflex β-adrenergic stimulation, and with sodium retention, and increased plasma renin activity. In addition to these side effects common to vasodilators, minoxidil has been implicated in the development of pulmonary hypertension. Since vasodilators are useful not only in the treatment of hypertension but also in the management of refractory congestive heart failure, angina, and even cardiogenic shock, it is important to evaluate the hemodynamic effects of such agents on the pulmonary as well as systemic circulation. The present study was designed to compare mean pulmonary artery and capillary wedge pressures, cardiac output, and pulmonary artery resistance before and after acute (5 day) and chronic (2 month) minoxidil administration in severely hypertensive humans.

Mean arterial blood pressure decreased from a control value of 135 mm Hg to a value of 104 mm Hg acutely and 108 mm Hg chronically. Significant increases in mean cardiac output occurred with minoxidil therapy (from 4.2 L/min control to 5.4 L/min acutely and 5.1 L/min chronically) despite concomitant propranolol treatment. Mean pulmonary arterial pressure did not increase either acutely or chronically. The data suggest that in patients with normal pulmonary hemodynamics prior to treatment, pulmonary hypertension does not develop during two months of minoxidil therapy.

Methods
Patient Characteristics

Seven patients were studied at the Clinical Research Center of the Indiana University Hospital. The studies were approved by the Indiana University Human Use Committee and informed consent was obtained from each patient. Participation in the present study was not a precondition for treatment with minoxidil. The only criterion for entrance to the study was severe hypertension (as evidenced by outpatient diastolic pressures > 115 mm Hg) not controlled by maximally tolerated doses of several antihypertensive drugs (as indicated in table 1).

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From the Specialized Center of Research in Hypertension, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana. Supported in part by USPHS grants HL 14159 (Specialized Center of Research-SCOR-in Hypertension) and RR 00750 (Clinical Research Center). A preliminary report of these studies was made at the Midwest Student Medical Research Committee and the National Student Research Forum, 1976.

Dr. Klotman's present address is Duke University Medical Center, Department of Medicine, Durham, North Carolina.

Address for reprint: Myron H. Weinberger, M.D., Department of Medicine, Indiana University School of Medicine, 1100 West Michigan Street, Indianapolis, Indiana 46202.

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Table 1. Demographic and Historical Characteristics of Patients Studied

<table>
<thead>
<tr>
<th>Pt/Age/Race/Sex</th>
<th>Etiology</th>
<th>Duration (yr)</th>
<th>CVA or TIA</th>
<th>CHF</th>
<th>Previous Meds</th>
<th>M (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/50/W/M</td>
<td>E</td>
<td>1.5</td>
<td>+</td>
<td>—</td>
<td>TD-P-H</td>
<td>20</td>
</tr>
<tr>
<td>2/55/B/F</td>
<td>E</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>TD-P-H-Al-G</td>
<td>20</td>
</tr>
<tr>
<td>3/37/B/M</td>
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<td>20</td>
<td>—</td>
<td>—</td>
<td>TD-P-H</td>
<td>40</td>
</tr>
<tr>
<td>4/52/W/F</td>
<td>RV</td>
<td>1.5</td>
<td>—</td>
<td>—</td>
<td>TD-P-H-Al-C</td>
<td>4</td>
</tr>
<tr>
<td>5/47/W/F</td>
<td>RV</td>
<td>2</td>
<td>+</td>
<td>—</td>
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</tr>
<tr>
<td>6/32/B/M</td>
<td>E</td>
<td>14</td>
<td>—</td>
<td>—</td>
<td>TD-P-H-Al-G-R</td>
<td>40</td>
</tr>
<tr>
<td>7/56/W/M</td>
<td>E</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>TD-P-H</td>
<td>30</td>
</tr>
</tbody>
</table>

Abbreviations: CVA = previous cerebral vascular accident; TIA = previous transient ischemic attack; CHF = history of congestive heart failure; M = minoxidil; E = essential hypertension; RV = renovascular hypertension; TD = thiazide diuretic; P = propranolol; H = hydralazine; Al = aldomet; G = guanethidine; C = clonidine; R = reserpine.

The mean age was 47. Five patients were thought to have essential hypertension by exclusion of secondary forms. Two patients were thought to have renovascular hypertension based on renal arteriography (table 2) and laterizing renal vein renin ratios, but were not cured by renal artery bypass surgery. The known duration of hypertension in four patients was less than or equal to two years and in three patients was 14–20 years.

Target organ assessment was performed in all patients at the initiation of the study and the results are indicated in table 2. Five patients demonstrated grade II K-W retinopathy with retinal hemorrhages seen in only two patients. Electrocardiographic abnormalities were seen in six patients and cardiomegaly on chest X-ray in four. The endogenous creatinine clearance ranged from 54–106 ml/min (mean = 77 ml/min) prior to the initiation of minoxidil therapy. Five of the seven patients were studied at all of the specified protocol periods.

Protocol of Study

Patients entered the study period following at least a two week interval during which antihypertensive medications were limited to hydralazine, propranolol, and hydrochlorothiazide. While in the hospital, dietary intake was controlled at 2 g sodium, 3 g potassium, 100 g protein, and 1800 cal/day. On day 1 of the study, those patients who were receiving hydralazine had the medication discontinued. Fixed doses of hydrochlorothiazide (50 mg every 12 hours) and propranolol (40 mg every 6 hours) were then initiated to minimize the sodium retention and reflex tachycardia anticipated during subsequent minoxidil therapy.

The protocol was divided into three distinct periods of study. Patients were initially admitted for ten days which included a five day equilibration period, during which the patients received only hydrochlorothiazide and propranolol (control), followed by five days during which the effective minoxidil dose was established (acute study). After the first hospitalization, patients were discharged on the same effective dose of minoxidil, propranolol, and hydrochlorothiazide. Two months later, the patients were readmitted for a five day period (chronic study).

Catheterization

Hemodynamic data were obtained in the cardiac laboratory on the fifth day of each study period (control, acute, and chronic). The patients received their antihypertensive medications as previously described on the morning of catheterization. A #7 French, triple-lumen Swan-Ganz catheter was inserted into an antecubital vein and placed in the right pulmonary artery under fluoroscopy. Cannulation of the right femoral artery was performed immediately thereafter with catheter placement in the distal abdominal aorta. The patients were allowed to equilibrate for 5–15 min until mean arterial pressure stabilized. Mean pressures were obtained from the abdominal aorta (ABP), right atrium (RAP), pulmonary artery (PAP) and pulmonary capillary wedge position (PCWP) with Statham strain gauges (P23 GB). Cardiac output was determined by either the Fick or indicator dilution technique (Lexington Instruments automated cardiac output computer and clinical densitometer, model RLD). Indocyanine green was injected into the pulmonary artery with arterial blood sampling from the distal abdominal aorta. The method used for cardiac output measurements for the control, acute, and

Table 2. Diagnostic Data from Patients Studied

<table>
<thead>
<tr>
<th>Pt</th>
<th>Fundus Grade (K-W)</th>
<th>ECG</th>
<th>Cardiomegaly on CXR</th>
<th>Creat ml/min</th>
<th>IVP</th>
<th>Renal Arteriogram</th>
<th>Renal Scan</th>
<th>Abdominal Bruise</th>
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<tbody>
<tr>
<td>1</td>
<td>II</td>
<td>LVH</td>
<td>+</td>
<td>64</td>
<td>N</td>
<td>N</td>
<td>1 Right</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>II</td>
<td>LVH</td>
<td>+</td>
<td>106</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>II</td>
<td>LVH</td>
<td>+</td>
<td>72</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>—</td>
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<tr>
<td>4</td>
<td>III</td>
<td>Inf MI</td>
<td>NSST-TA</td>
<td>—</td>
<td>80</td>
<td>H C</td>
<td>RAS on R</td>
<td>ND</td>
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<tr>
<td>5</td>
<td>II</td>
<td>N</td>
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<td>75</td>
<td>N</td>
<td>Bilat RAS</td>
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<tr>
<td>6</td>
<td>II</td>
<td>LVH</td>
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<td>54</td>
<td>L Kidney</td>
<td>N</td>
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<td>—</td>
</tr>
<tr>
<td>7</td>
<td>III</td>
<td>NSST-TA</td>
<td>—</td>
<td>90</td>
<td>N</td>
<td>N</td>
<td>ND</td>
<td>—</td>
</tr>
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</table>

Abbreviations: CXR = chest X-ray; Creat = creatinine clearance; IVP = hypertensive intravenous pyelogram; LVH = left ventricular hypertrophy; NSST-TA = non-specific ST segment and T wave changes; Inf MI = inferior myocardial infarction; RAS = renal artery stenosis; N = normal; ND = not done; HC = hyperconcentration.
Table 3. Hemodynamic Data

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>C</th>
<th>AB</th>
<th>RA</th>
<th>PA</th>
<th>PCW</th>
<th>HR</th>
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<tbody>
<tr>
<td></td>
<td>C</td>
<td>5d</td>
<td>2m</td>
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<td>5d</td>
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<tr>
<td>1</td>
<td>140</td>
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<td>5</td>
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<td>Mean</td>
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<td>104</td>
<td>108</td>
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<tr>
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<td>0.6</td>
<td>1.0</td>
<td>1.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

\[ P^* = \text{Treatment vs control. Only significant values are tabulated.} \]

Abbreviations: AB = abdominal aorta; RA = right atrium; PA = pulmonary artery; PCW = pulmonary capillary wedge; HR = heart rate; CO = cardiac output; SV = stroke volume; Pe = peripheral; PAr = pulmonary arteriolar; TP = total pulmonary; C = control; 5d = 5 days of minoxidil therapy; 2m = 2 months of minoxidil therapy; SE = standard error.

P* \(<0.025<0.025\)

Chronic studies was the same for any given patient. In each study, pressures and cardiac output measurements were obtained sequentially in four sets of measurements. Each entry into table 3, therefore, represents the mean of these four different measurements.

Minoxidil Therapy

Immediately after cardiac catheterization, patients were begun on oral minoxidil (Upjohn) at an initial dose of 1 mg. Every 6 hours thereafter, the dose was increased by 1 mg increments until the blood pressure was controlled at less than 140/90 or a maximum total daily dose of 40 mg was reached. Final doses ranged from 4-40 mg/day. The side effects encountered were limited to hypertrichosis and mild sodium retention without edema. The hypertrichosis was not severe enough to cause the discontinuation of the drug in any of the patients.

Calculation of Resistance

The formulae for calculation of resistances (in dynes/sec cm²) are indicated below:

Peripheral vascular resistance = \( \frac{ABP \text{ (mm Hg)} - RAP \text{ (mm Hg)}}{\text{Cardiac output (ml/sec)}} \times 1332 \text{ dynes/cm}^2 \) (1)

Pulmonary arteriolar resistance = \( \frac{PAP - PCWP}{\text{Cardiac Output}} \times 1332 \) (2)

Total pulmonary vascular resistance = \( \frac{PAP}{\text{Cardiac Output}} \times 1332 \) (3)

Statistical Analysis

Since no assumption was made for a normal distribution, \( P \) values were determined by the Wilcoxon rank sum test, a nonparametric analysis. Linear functions of the graphed data were determined by least squares linear regression. Only statistically significant differences (\( P \leq 0.05 \)) are indicated in the figures.

Results

The observations during the study for one of the patients (5) are indicated in figure 1. As demonstrated, arterial pressure was brought into the normal range within two days of the initiation of minoxidil therapy. No significant orthostatic hypotension was seen in any of the patients studied. Mild sodium retention without overt edema occurred in all patients but none of the patients gained more than 1.5 kg over the two month period of study. Potassium balance and study design are shown in the figure. Although not shown in figure 1, serum sodium, potassium and creatinine concentrations and creatinine clearance did not change significantly in any of the patients studied.

Mean pressures (±SE) of all patients are demonstrated for the three periods of study in figure 2. Mean intra-arterial pressure demonstrated a significant decline into the normal range after five days of therapy. This effect was sustained at the chronic study. Mean pulmonary capillary wedge pressure and mean pulmonary artery pressure did not change significantly following five days and two months of minoxidil therapy. Similarly, mean right atrial pressure, indicated in table 3, did not change.

Cardiac output, heart rate, and stroke volume data are depicted in figure 3. Significant increases in mean cardiac output were observed in both the acute (29%) and chronic (22%) study. A significant increase in heart rate was observed acutely even with concurrent propranolol therapy. However, at the chronic study, heart rate was not significantly greater than control. Stroke volume was significantly increased compared to the control value both acutely and chronically. The mean increase in heart rate was 10% acutely and 3% chronically, whereas the mean increase in stroke volume was 16% acutely and 19% chronically. Therefore, changes in stroke volume had a greater effect on cardiac output than did changes in heart rate.

The significant decreases in both peripheral vascular and pulmonary arteriolar resistance in response to five days and two months of minoxidil therapy are displayed in table 3. As demonstrated in figure 4, the change in peripheral vascular resistance from control was significantly greater than the change in pulmonary arteriolar resistance from control, both in the five day and two month studies. The changes of both peripheral vascular and pulmonary arteriolar resistance were significantly correlated with their initial control levels (\( r = -0.890 \) and \(-0.838 \), respectively) as shown in figure 5. The higher the control peripheral or pulmonary resistance, the greater was the decrease observed in response.
to five days of minoxidil therapy. This relationship was not seen at the two month study.

Discussion

The experimental vasodilator minoxidil offers considerable promise in the treatment of severe, refractory hypertension. Minoxidil is a direct-acting vasodilator whose action is not inhibited by β-adrenergic, cholinergic, or histaminergic blockers. It does not abolish reflex sympathetic activity and unlike the parenteral vasodilators nitroprusside and phentolamine, it does not increase venous capacitance. Because venous return and reflex sympathetic activity are not significantly altered, orthostatic hypotension is not a major complication. Reports of an association between minoxidil therapy and pulmonary hypertension, however, raise significant questions about the effects of vasodilators on pulmonary hemodynamics in the management of chronic disease.

The efficacy of minoxidil in reducing severely elevated blood pressure has been confirmed in the present study. All of the patients had been severely hypertensive and refractory to maximally tolerated doses of several antihypertensive drugs but were well controlled with the combination of minoxidil, propranolol, and hydrochlorothiazide. Although our patients were not selected for the absence of a history of congestive heart failure, they all demonstrated low-normal pulmonary capillary wedge and pulmonary artery pressures.

Figure 1. Study design and responses of one patient (5). Changes in supine and upright blood pressure, body weight, and sodium and potassium balance are shown for the three study periods (control, acute, and chronic). Cardiac catheterization was performed at the times indicated by arrows. Diet and medications are also indicated.
An increase in cardiac output in response to minoxidil has been observed by several authors. This was noted in the present study as well, even though patients were treated concurrently with propranolol. Furthermore, the relatively greater increase in stroke volume when compared to heart rate during minoxidil treatment appeared to account for this increase in cardiac output. By significantly lowering arterial blood pressure and therefore afterload, minoxidil would enhance ventricular efficiency and increase both stroke volume and cardiac output without an increase in cardiac work.

Minoxidil exerts a greater effect on peripheral vascular resistance than pulmonary arteriolar resistance. It is not surprising that the decrease in peripheral resistance was proportionately greater than that of pulmonary arteriolar resistance, as indicated in figure 4. One might anticipate this differential response because of the greater number of muscular resistance arterioles in the peripheral system as compared to the capacitance system of the pulmonary vascular bed. Since the effect of minoxidil would be expected to be greatest on the active resistance vessels, the greatest dilatory response or decrease in resistance would be expected to occur in those vessels with the highest initial resistance.

The relationship depicted in figure 5 substantiates this hypothesis both in the peripheral and pulmonary vascular beds. However, the fact that this relationship was not observed at the 2 month study may well reflect an auto-regulatory response.

In the normal pulmonary circuit, increases in flow do not increase pressure because of the tremendous capacitance of the pulmonary system. The present study has shown that the decrease in resistance induced by minoxidil in the peripheral system is greater than the comparable decrease in the pulmonary system (fig. 4). Furthermore, cardiac output increases in response to minoxidil therapy (fig. 3). In a hypertensive patient treated with minoxidil, a reduction in peripheral resistance occurs that is sufficient to produce normal arterial pressure despite this increase in cardiac output. However, should the pulmonary resistance decrease less than cardiac output increases, an increase in pulmonary arterial pressure might result in response to minoxidil. Indeed, Tarazi has reported this phenomenon in four patients studied during minoxidil therapy without propranolol. Two of these patients were subsequently treated with propranolol and a decrease in cardiac output and pulmonary artery pressure occurred. In the present study, all patients were treated with propranolol at the initiation of minoxidil therapy and although an increase in mean cardiac output of 29% was noted, pulmonary artery pressure remained normal.

From the hemodynamic data obtained in the present study,
In addition, patients with intravascular volume overload as a result of congestive heart failure and impaired renal sodium excretion might also be at risk for the development of pulmonary hypertension, should the pulmonary vascular capacity be reached. Further increases in cardiac output would not be accommodated by the pulmonary vascular bed and PAP would increase accordingly.

No evidence exists to suggest that this is a specific complication peculiar to minoxidil therapy. Rather, these hemodynamic phenomena can be anticipated with the use of any vasodilator producing an increase in cardiac output. Of the patients previously reported in the literature with pulmonary hypertension noted after the initiation of minoxidil therapy, congestive heart failure and substantial renal impairment were frequent findings. The patients in the present study, however, had neither a history of congestive heart failure nor critically impaired renal function, and these patients were able to tolerate the increase in cardiac output as a result of minoxidil therapy with no change in the pulmonary pressure.

In summary, the present study has demonstrated the potency and efficacy of minoxidil in the treatment of refractory hypertension. The observed increase in cardiac output with minoxidil therapy in the face of concomitant propranolol treatment is primarily due to an increase in stroke volume. Minoxidil reduced both peripheral and pulmonary resistance, but a relatively greater effect was noted in the systemic circuit.

This study has shown that if the reflex increase in heart
rate is blocked by propranolol and the increase in stroke volume is minimized by diuretic administration, the potential development of pulmonary hypertension due to large increases in cardiac output can be prevented in patients with initially normal pulmonary hemodynamics. However, in patients with pre-existing pulmonary hypertension, chronic congestive heart failure, or significant renal impairment, careful evaluation for evidence of increasing pulmonary artery pressure as a result of enhanced cardiac output is warranted.

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References


\[ y = -0.3 x + 27.61 \]
\[ r = -0.890 \]

\[ y = -0.22 x + 14.48 \]
\[ r = -0.838 \]
The effects of minoxidil on pulmonary and systemic hemodynamics in hypertensive man.
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