Effects of Minoxidil on Hemodynamics in Patients with Congestive Heart Failure

JOSEPH A. FRANCIOSA, M.D., AND JAY N. COHN, M.D.

SUMMARY Vasodilators used in chronic congestive heart failure are not optimal in that nitrates are predominant venodilators, prazosin is associated with tolerance development, and hydralazine produces chronic toxicity. Therefore, we studied the acute hemodynamic effects of a single dose of minoxidil in 18 patients with chronic left ventricular failure caused by ischemic or primary cardiomyopathy. Peak effects were observed 5 hours after single oral doses of minoxidil, averaging 15.3 ± 1.4 mg (SEM). Heart rate rose slightly, from 85.4 ± 2.9 to 90.9 ± 3.2 beats/min, after minoxidil (p < 0.02) and mean arterial pressure fell slightly, from 88.0 ± 2.3 to 84.9 ± 2.5 mm Hg (p < 0.05). Cardiac index increased from 2.34 ± 0.14 to 2.95 ± 0.29 l/min/m² after minoxidil (p < 0.02) and systemic vascular resistance fell from 19.6 ± 1.5 to 15.0 ± 1.3 units (p < 0.01). Minoxidil did not affect right atrial, pulmonary arterial and pulmonary wedge pressures. Hemodynamic effects of minoxidil persisted for at least 8 hours after a single dose. Minoxidil appears to be an effective arterial dilating agent in patients with heart failure and resembles hydralazine in its actions. Because of its potency, prolonged duration of action and relatively low toxicity, minoxidil may be a useful vasodilator for heart failure. However, its long-term effect must be further evaluated.

NONE OF THE VASODILATORS available for use in heart failure is optimal.1−2 The effects of nitrates on cardiac output are less consistent and smaller in magnitude than those of other impedance reducing agents.3−4 Prazosin may be associated with early development of tolerance to its resting hemodynamic effects, whereas hydralazine has little effect on ventricular filling pressure in patients with heart failure.5−9 Although combining hydralazine with nitrates can mimic the hemodynamic effects of a nitroprusside infusion, a major limitation to the long-term use of hydralazine is its propensity to produce a “lupus-like” reaction.10,11 To avoid this toxic effect, the dose of hydralazine is usually limited, so patients may receive suboptimal therapy.

Minoxidil, which has recently become available, is a potent, orally effective vasodilator with predominant arterial dilating activity, thus rendering it similar to hydralazine.12 Unlike hydralazine, minoxidil has not produced any major toxicity during long-term administration to hypertensive patients.13 It is an effective antihypertensive agent, and has been used in isolated cases of left ventricular failure with good results.14−18 Because currently available vasodilators are less than optimal and because minoxidil has not been systematically evaluated in patients with heart failure, the present study was performed to define the acute hemodynamic effects of a single dose of minoxidil in patients with chronic left ventricular failure.

Methods

Studies were performed in 18 male patients with clinical and radiographic evidence of chronic left ventricular failure due to ischemic or primary cardiomyopathy. The former was diagnosed on the basis of previous acute myocardial infarction documented by serial electrocardiographic and serum enzyme changes, or by coronary arteriographic demonstration of significant coronary arterial occlusive disease. Primary cardiomyopathy was diagnosed if no other cause of left ventricular failure was demonstrable. All patients had objective evidence of left ventricular dysfunction as measured by chest x-ray, M-mode echocardiography or radionuclide angiography. Patients with primary valvular heart disease, primary pulmonary disease or acute myocardial infarction within the last 3 months were excluded. Patients with relative mitral insufficiency were included if left ventricular ejection fraction was 45% or less.

All studies were performed in a special procedure room adjacent to the coronary care unit. On the day of study, all diuretics and vasodilators were withheld for at least 24 hours before study; patients who were taking maintenance digitalis therapy were given their daily dose of this medication.

After patients gave written informed consent, a triple-lumen thermistor equipped Swan-Ganz catheter (Edwards Laboratories) was inserted percutaneously via an antecubital or femoral vein and advanced into the pulmonary artery. In two patients, a #7 Cournand catheter was inserted after unsuccessful attempts to insert a Swan-Ganz catheter. In all patients, a brachial artery was cannulated with a short Teflon catheter advanced over an 18-gauge thin walled needle. All catheters and cannulae were connected to P23D Statham pressure transducers positioned at the level of the midaxillary line with the patient supine. All pressures were recorded in this position on a Hewlett-Packard multichannel direct-writing recorder.

Pulmonary wedge pressure was taken as occluded or diastolic pulmonary arterial pressure, and these were not interchanged. Cardiac output was measured...
by thermodilution (16 patients) or indicator dilution using indocyanine green (two patients without Swan-Ganz catheters). These two methods correlate very closely, and the variation on successive determinations by either method is less than 10% in our laboratory.\textsuperscript{15, 18} Thermodilution outputs were done in triplicate and dye-dilution curves in duplicate. Heart rate and rhythm were recorded continuously electrocardiographically.

After allowing at least 30 minutes to elapse from the time of completion of all invasive procedures, control measurements were made twice at 20-minute intervals. These included heart rate, systemic arterial pressure, right atrial pressure, pulmonary arterial pressure, pulmonary wedge pressure and cardiac output. To qualify for continuation in the study, patients had to have systolic blood pressure 100 mm Hg or higher and either pulmonary wedge pressure above 14 mm Hg or cardiac index below 2.5 l/min/m\textsuperscript{2}.

In qualifying patients, oral minoxidil (Loniten, The Upjohn Company) was then administered and hemodynamics were measured at ½, 1, 1½, 2, 3, 4, 5, 6, 7 and 8 hours after drug. The effective dose of minoxidil was established in the first several patients. Pairs of patients were given the same dose of minoxidil, which was progressively increased until both patients in each pair had at least a 30% rise in cardiac output without undesirable effects after minoxidil administration. When this response was observed, eight more patients were given that dose. Ten patients were studied after receiving the same effective dose of minoxidil.

In addition to the hemodynamic responses, blood specimens were drawn at control and at peak hemodynamic effects after minoxidil for measurement of plasma renin activity (method of Sealey et al.\textsuperscript{19}) and plasma catecholamines (by radioenzymatic assay, Cat-A-kit, Upjohn Company).\textsuperscript{20, 21} Systemic arterial blood samples were also drawn for blood gas determination before and at peak minoxidil effect.

Systemic vascular resistance was calculated as the ratio of mean systemic arterial pressure to cardiac output and was expressed in units. Right atrial pressures were not available in all patients and therefore were not used in this calculation. Pulmonary vascular resistance was calculated as mean pulmonary arterial pressure minus pulmonary wedge pressure divided by cardiac output, and was also expressed in units. Statistical analysis was performed using the \( t \) test to compare postdrug values to controls. These latter were taken as an average of the two sets of control measurements.

**Results**

The baseline characteristics of the patient population are summarized in table 1. Ischemic cardiomyopathy was diagnosed in 10 patients and

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Clinical class*</th>
<th>Cardiotoracic ratio (%)</th>
<th>Ejection fraction (%)</th>
<th>LVDD (cm)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>IHD</td>
<td>III</td>
<td>64</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>IHD</td>
<td>IV</td>
<td>65</td>
<td>28</td>
<td>6.7</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>IHD</td>
<td>III</td>
<td>55</td>
<td>15</td>
<td>5.7</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>PMD</td>
<td>III</td>
<td>51</td>
<td>28</td>
<td>6.2</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>IHD</td>
<td>III</td>
<td>59</td>
<td>24</td>
<td>5.6</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>IHD</td>
<td>III</td>
<td>61</td>
<td>41</td>
<td>6.9</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>PMD</td>
<td>III</td>
<td>55</td>
<td>37</td>
<td>7.0</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>PMD</td>
<td>III</td>
<td>58</td>
<td>34</td>
<td>6.9</td>
</tr>
<tr>
<td>9</td>
<td>55</td>
<td>IHD</td>
<td>III</td>
<td>57</td>
<td>16</td>
<td>6.1</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>PMD</td>
<td>IV</td>
<td>62</td>
<td>22</td>
<td>7.4</td>
</tr>
<tr>
<td>11</td>
<td>57</td>
<td>IHD</td>
<td>III</td>
<td>67</td>
<td>34</td>
<td>6.9</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>IHD</td>
<td>III</td>
<td>63</td>
<td>39</td>
<td>6.8</td>
</tr>
<tr>
<td>13</td>
<td>54</td>
<td>PMD</td>
<td>II</td>
<td>48</td>
<td>29</td>
<td>6.5</td>
</tr>
<tr>
<td>14</td>
<td>52</td>
<td>PMD</td>
<td>III</td>
<td>52</td>
<td>47</td>
<td>5.3</td>
</tr>
<tr>
<td>15</td>
<td>53</td>
<td>IHD</td>
<td>III</td>
<td>49</td>
<td>21</td>
<td>7.4</td>
</tr>
<tr>
<td>16</td>
<td>59</td>
<td>PMD</td>
<td>III</td>
<td>58</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>61</td>
<td>IHD</td>
<td>IV</td>
<td>55</td>
<td>45</td>
<td>5.5</td>
</tr>
<tr>
<td>18</td>
<td>61</td>
<td>PMD</td>
<td>III</td>
<td>66</td>
<td>42</td>
<td>7.3</td>
</tr>
</tbody>
</table>

| Mean SEM | 56.6 ± 1.9 | —          | —                | 58.1 ± 1.4             | 31.4 ± 2.5        | 6.5        |

*New York Heart Association criteria.
†M-mode echocardiography.
Abbreviations: IHD = ischemic cardiomyopathy; LVDD = left ventricular end-diastolic dimension; PMD = primary cardiomyopathy.
primary cardiomyopathy in the other eight. Murmurs of relative mitral insufficiency were present in eight patients (nos. 2, 6, 7, 8, 12, 15, 17 and 18); atrial fibrillation was present in four patients (nos. 5, 8, 14 and 17), and the others all had normal sinus rhythm. All patients had been taking digitalis and diuretics and four (nos. 1, 12, 15 and 17) had also been receiving vasodilators (hydralazine and/or nitrates) for their heart failure. The patient group as a whole had increased cardiac dimensions by both chest x-ray and echocardiogram, while ejection fraction was below 50% in every patient in whom it was measured. Thus, all patients had objective evidence of left ventricular dysfunction; heart failure had been present from 3 months to 5 years (average duration 21.5 ± 3.8 months (SEM)).

Although all doses of minoxidil increased cardiac output at some point after minoxidil administration, the 5- and 7.5-mg doses did not produce an increase of more than 30% in any patient. A dose of 20 mg was the first to raise cardiac output by more than 30% in both patients of a pair, and this dose was used in the eight subsequent patients studied.

The time course of hemodynamic changes after minoxidil administration is shown in figure 1. Cardiac index was significantly increased by 1 hour, with the increase peaking at 5 hours and persisting through 8 hours. Mean systemic arterial pressure was maximally reduced also between 4 and 6 hours, but returned to control by 8 hours.

Based on this time course of cardiac output changes, peak hemodynamic effects of minoxidil were analyzed at 5 hours (table 2). Heart rate rose slightly but significantly, and mean systemic arterial pressure fell slightly but significantly. The product of heart rate and systolic pressure was unchanged (4.8 ± 3.6%). Cardiac index at peak effect was significantly increased; stroke volume was also higher, while systemic vascular resistance decreased significantly. Pulmonary wedge pressure did not change after minoxidil. The three patients in whom cardiac index did not increase at 5 hours, all had increases in cardiac index at other times after minoxidil. When patient 14, whose cardiac index more than doubled at 5 hours after minoxidil, was excluded from analysis, the rise in cardiac index was still significant in the other 17 patients (0.42 ± 0.14 l/min/m², p < 0.01). Right atrial and mean pulmonary arterial pressures were not significantly changed by minoxidil (9.2 ± 1.3 vs 9.9 ± 1.3 mm Hg and 34.8 ± 3.3 vs 36.1 ± 2.0 mm Hg, respectively). Pulmonary vascular resistance was insignificantly reduced, from 2.9 ± 0.4 to 2.7 ± 0.3 units. Systemic arterial oxygen tension averaged 74.2 ± 4.5 mm Hg before and 72.5 ± 3.5 mm Hg after minoxidil.

Only 10 of the 18 patients received 20 mg of minoxidil, while the others received lower doses, so results in the 10 who received the 20-mg dose were analyzed separately. Their hemodynamic responses were like those of the group as a whole; that is, a significant rise in cardiac index and fall in systemic vascular

**Figure 1.** Time course of hemodynamic changes after minoxidil administration in patients with left ventricular failure. Values are mean ± SEM.
resistance and no change in pulmonary wedge pressure. When these 10 patients were compared to the eight receiving smaller doses of minoxidil, the magnitude of responses was not significantly different between the two groups, although the rise in cardiac index achieved significance only in the group receiving 20 mg of minoxidil.

Since an increase in cardiac index was the major response to minoxidil, the data were analyzed to assess factors that might have influenced this response. There were no significant correlations between changes in cardiac index and baseline pulmonary wedge pressure, cardiac index, systemic vascular resistance, left ventricular end-diastolic dimension, carthoanacric ratio or left ventricular ejection fraction. Also, mitral regurgitation did not affect the change in cardiac index, which rose by 0.56 ± 0.20 l/min/m² in patients with this lesion, and by 0.65 ± 0.36 l/min/m² in those without it. The rise in cardiac index was also not different between patients with ischemic (0.59 ± 0.18 l/min/m²) or primary cardiomyopathy (0.65 ± 0.48 l/min/m²).

The effects of minoxidil on plasma renin activity and catecholamine levels are shown in figure 2. All of these variables were elevated at baseline, and only plasma renin activity increased significantly after minoxidil, while catecholamines were unchanged. There were no significant correlations between baseline plasma renin activity or catecholamines and baseline hemodynamics. These measurements also failed to correlate with any hemodynamic responses to minoxidil.

**Discussion**

Minoxidil is a direct-acting vascular smooth-muscle relaxant with a predominant arterial site of action; it has been extensively evaluated as an antihypertensive agent and is extremely potent, more so than hydralazine, which acts similarly. 

Minoxidil has been used to treat isolated cases of heart failure, and it has significantly increased cardiac output. The present study extends these earlier isolated observations to a series of patients with chronic normotensive left ventricular failure in which the principal effect of minoxidil was to raise cardiac output and stroke volume, while lowering systemic vascular resistance. Heart rate increased only slightly and blood pressure was minimally reduced. Pulmonary wedge, pulmonary arterial and right atrial pressures were unchanged.
These hemodynamic changes are consistent with an arterial dilating effect unaccompanied by venodilation. The hemodynamic effects were demonstrable to varying degrees, with single doses of minoxidil ranging from 5-15 mg, but a single dose of 20 mg was needed to obtain more uniform hemodynamic effects. The presence of continued significant hemodynamic effects at 8 hours after a single dose is consistent with the previously reported prolonged duration of antihypertensive effect of minoxidil.22, 23

The clinical pharmacology of minoxidil has been well documented in hypertensive patients in whom both systolic and diastolic blood pressures are reduced, even in patients refractory to other agents, including hydralazine.12-15, 22, 23 Cardiac output also rises after minoxidil administration in hypertensive patients without heart failure, but this increase may result from significant tachycardia as well as increased stroke volume.12, 24, 25 Pulmonary arterial and wedge pressures are likewise unaffected by minoxidil in these patients, and earlier reports of pulmonary hypertension have not been substantiated, as more recent studies have demonstrated reduced pulmonary vascular resistance due to increased flow after minoxidil.26, 27 Pharmacodynamic studies demonstrate almost complete absorption of minoxidil after oral administration, with detectable blood levels evident by 0.5-1 hour and a plasma half-life of 4 hours.22, 23 However, antihypertensive activity peaks at 4-8 hours and lasts more than 24 hours, consistent with the time course of hemodynamic changes observed in the present patients with heart failure. This discrepancy between blood levels and prolonged hemodynamic effects might be explained by tissue binding in arterial walls.23, 28 Thus, minoxidil is suited to once- or twice-daily administration.

Long-term use of minoxidil in hypertensive patients has not been associated with serious toxicity.13-15, 24, 26, 29 The most common disturbing effect has been hypertrichosis. Another side effect of long-term minoxidil administration in hypertensive patients is sodium and fluid retention, which would be undesirable in patients with heart failure. Most patients with advanced heart failure take diuretics; they may be mandatory when minoxidil is required. The increase in heart rate after minoxidil in the present study was small, and appears to be considerably less than that in patients without heart failure.25

Minoxidil increases plasma renin activity and catecholamine levels in hypertensive patients.12, 13 Prolonged stimulation of the renin-angiotensin system or catecholamines in patients with heart failure could offset the initial acute hemodynamic benefits. However, hemodynamic improvement could also lead to a withdrawal of sympathetic tone in patients with heart failure, which might explain the lack of a significant rise in plasma catecholamine levels after minoxidil.

The present study shows that minoxidil is an orally effective arterial dilator in patients with chronic left ventricular failure. It produces hemodynamic improvement primarily by raising cardiac output and is thus similar to hydralazine in this setting. Hydralazine is associated with chronic toxicity, and minoxidil may be more potent and less toxic, so minoxidil may be preferable to hydralazine and deserves further evaluation in patients with chronic left ventricular failure. Switching from hydralazine to minoxidil should not be done routinely, however, until the long-term safety of minoxidil is established in heart failure. In the meantime, minoxidil should be considered only as an alternative to hydralazine when this latter agent has produced toxicity or when its effects are suboptimal and further increase in dose is considered unsafe.40

Acknowledgement

The authors are indebted to Mary Wilen and Susan Ziesche, R.N., for their skilled technical assistance and to Ethel McGee for her help in preparing the manuscript. We also thank Dr. William B. Martin of the Upjohn Company, Kalamazoo, Michigan, for generously providing supplies of minoxidil.

References

16. Chatterjee K, Drew D, Parmley WW, Klausner SC, Polansky J, Zacherle B: Combination vasodilator therapy for severe
Effects of minoxidil on hemodynamics in patients with congestive heart failure.
J A Franciosa and J N Cohn

Circulation. 1981;63:652-657
doi: 10.1161/01.CIR.63.3.652

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/63/3/652

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/