THERAPY AND PREVENTION
PULMONARY HYPERTENSION

The effect of vasodilator therapy on the clinical outcome of patients with primary pulmonary hypertension

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ABSTRACT The short- and long-term hemodynamic effects of vasodilators in patients with primary pulmonary hypertension have been studied, but whether they affect survival is unknown. We measured the short-term response to nifedipine and hydralazine in 23 patients with primary pulmonary hypertension and followed their clinical course over 2 years. A favorable drug response, defined as a fall in the pulmonary vascular resistance of 20% or greater, occurred in 18 patients (78%). Half of the patients who exhibited a favorable short-term response were treated with long-term vasodilator therapy. Their clinical course was compared with that of responders who were not treated and with that of the nonresponders. Of the responders who were treated, two improved, four had no change, and three died; of the responders who were not treated, one improved, three had no change, and five died. Using stepwise Cox regression, we evaluated age, sex, functional class on entry, pulmonary arterial pressure, pulmonary vascular resistance, and short-term drug response as predictors of survival and found only functional class and a favorable short-term drug response to be significant predictors (p < .01); however, there was no difference in survival between the responders who were treated and those who were not. We conclude that the ability to respond to short-term nifedipine or hydralazine therapy predicts longer survival for patients with primary pulmonary hypertension, but placing patients with a favorable short-term response on long-term vasodilator therapy does not affect the overall outcome. Circulation 71, No. 6, 1191–1196, 1985.

THERE HAVE BEEN several studies on the use of vasodilator drugs for primary pulmonary hypertension in the last decade. These reports have focused on short- and long-term effects and have demonstrated both beneficial and adverse drug responses.1–6

It has been difficult to determine the therapeutic value of these drugs in primary pulmonary hypertension because of the lack of controlled clinical studies with adequate numbers of patients. Moreover, since these drugs rarely lower the pulmonary arterial pressure, there has been disagreement as to whether the hemodynamic changes that occur are beneficial to the patient.7

We evaluated 23 patients with primary pulmonary hypertension receiving short-term vasodilator therapy and subsequently followed their clinical course. Decisions to treat the patients with long-term therapy were based on the short-term drug responses, with half of the responders receiving and the other half not receiving treatment. We then reviewed the effects that the vasodilators had on clinical outcome to determine whether treating patients with primary pulmonary hypertension with vasodilator drugs had any effect on their clinical course or survival.

Methods

Subjects. We studied 23 consecutive patients (16 female, seven male, ages 11 to 61 years, mean 38 ± 15) referred to the University of Illinois at Chicago (15 patients) and the University of California at San Francisco (eight patients) with unexplained pulmonary hypertension between January 1982 and July 1983. After a thorough work-up to exclude secondary causes of pulmonary hypertension (described elsewhere),8 the patients were diagnosed as having primary pulmonary hypertension. All the patients were followed prospectively after their hospital discharge.

Hemodynamic studies. All patients underwent cardiac catheterization to assess their hemodynamic status. A No. 7F Swan-Ganz catheter was placed into the pulmonary artery to monitor pulmonary arterial pressure, and a small Teflon catheter was placed in the radial or femoral artery to monitor systemic pressure. Cardiac output was determined by the thermodilution

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technique. Mean arterial pressures were determined by electronic integration and vascular resistances were determined by standard formulas for systemic and pulmonary vascular resistance.

**Short-term drug testing.** All patients were tested for the short-term effects of nifedipine, and 16 were treated with hydralazine. The University of Illinois protocol was as follows: Nifedipine was given as a 20 mg oral dose, with pressures and cardiac outputs determined after 90 min. Hydralazine was given as a 0.03 mg/kg iv dose, with pressures and cardiac outputs determined after 30 min. The University of California at San Francisco protocol was as follows: Nifedipine was administered as a 10 to 30 mg oral dose, with pressure and outputs determined after 90 min, and hydralazine was given as a 50 mg oral dose, with pressures and cardiac outputs measured after 90 min. At both institutions adequate intervals (6 to 12 hr) were maintained between drug tests to allow for drug clearance and for the hemodynamic values to return to baseline. Patients receiving both drugs received hydralazine first. The studies received approval from their respective institutional review boards, and informed consent was obtained from the patients.

**Long-term drug therapy.** Decisions to treat patients with long-term therapy were based on the results of the short-term drug tests. Patients who did not exhibit a favorable short-term response to drug testing were not treated. All patients who were treated with a vasodilator demonstrated a short-term fall in pulmonary vascular resistance, but not all patients with favorable short-term responses were treated with long-term therapy. The decision to treat and the selection of a specific drug in patients responding to more than one of the drugs tested were arbitrary and were sometimes made by the referring physician. For every patient, longitudinal follow-up was done at a minimum of 6 month intervals, and for the patients who died the exact date and cause of death were determined. Patient follow-up was closed as of January 1, 1984, with the vital status of each patient determined as of that date. The minimum follow-up period for patients who did not die was 100 days.

**Other therapy.** All patients were allowed to continue on digitalis and diuretic therapy. Five patients (Nos. 1, 2, 4, 5, and 10) were also placed on long-term therapy with anticoagulants. No other form of long-term treatment was used.

**Data review.** In addition to standard demographic variables and hemodynamic parameters, patients were also categorized in the following ways:

1. Functional class: Their functional class, both at the time of their initial hemodynamic study and at the end of the follow-up period, were determined according to New York Heart Association criteria.
2. Short-term drug response: A favorable short-term drug response was defined as a fall in pulmonary vascular resistance of 20% or more. Patients with a favorable response to either nifedipine or hydralazine (or both) were categorized as responders.
3. Long-term treatment: Patients were also categorized as those who received long-term treatment with vasodilators and those who did not.

In five patients, a decision was made to administer vasodilators on a long-term basis, but the patients were unable to tolerate the drugs because of side effects and had to be withdrawn from the study. These included ankle edema from nifedipine, nausea and headache, but not systemic hypotension or syncope. These five patients, none of whom were on vasodilator therapy for more than 30 days, were considered as patients who were not treated over the long term.

One patient was tested with hydralazine, nifedipine, and captopril and received long-term therapy with captopril, although he manifested similar short-term responses to captopril and nifedipine. This patient was considered to have been treated with long-term vasodilator therapy.

Twelve of the patients died before the end of the follow-up period. In 11 of these 12, the reported cause of death was either progressive right heart failure or sudden death, with both attributed to the progression of their underlying disease. One patient died shortly after an attempted lung-heart transplant. He underwent transplant because, in spite of being treated with vasodilators, he continued to deteriorate clinically.

**Statistical methods.** Stepwise Cox regression was used to examine the relationship between survival and each of the following variables taken at the initial evaluation: age, sex, functional class upon entry into the study, mean pulmonary arterial pressure, pulmonary vascular resistance, stroke volume, short-term drug response, and long-term drug treatment.

In addition, Kaplan-Meier product limit estimation was used to describe the survival experience of the study group and of subgroups of interest.

To examine the relationship between clinical course and the independent variables listed above, we used multiple stepwise linear regression with change in functional status as the dependent variable.

Comparisons between the baseline hemodynamic values of the patients (responders) who received long-term treatment with those who did not were made with Student's t test for unpaired data.

**Results**

The demographic characteristics of the study group are shown in table 1. Sixteen female patients were studied, 11 of whom died. Of the seven male patients, one died during the study. The average age of the study group was 38.4 ± 15 years (range 11 to 61), 36.4 in the female group and 42.7 in the male group. Nine patients received long-term therapy, one with hydralazine, one with captopril, and seven with nifedipine.

The baseline hemodynamic values of the 23 patients and their short-term responses to nifedipine are shown in table 2. For the group, nifedipine caused a 22% fall in pulmonary vascular resistance, a 3.5% fall in pulmonary arterial pressure, and a 29% increase in cardiac output. Thirteen patients had a favorable short-term drug response.

The short-term drug responses to hydralazine in the 16 patients tested are shown in table 3. As compared with nifedipine, hydralazine caused a 20% fall in pulmonary vascular resistance, a 30% increase in cardiac output, and no change in pulmonary arterial pressure. Nine of the 16 patients tested had favorable short-term drug responses.

With stepwise Cox regression analysis, functional class upon entry and a favorable short-term drug response were found to be independent predictors of survival in the 23 patients who received nifedipine and in the subgroup of 16 patients who were tested with both drugs (p < .01). Age, sex, baseline pulmonary arterial pressure, pulmonary vascular resistance,
stroke volume, and cardiac output, were not found to be predictive of survival.

The patients' clinical courses were further analyzed with respect to simultaneous categorization according to the short-term drug response and long-term treatment. Group I comprised patients with an unfavorable short-term drug response who were not treated. Four of five patients in this group died, and one patient remained unchanged (figure 1). Group II comprised patients with a favorable short-term drug response but who were also untreated, and group III included patients with a favorable drug response who received long-term treatment. There was no significant difference between the baseline demographic or hemodynamic characteristics of the nine responders who received long-term therapy and the nine who did not.

The clinical outcome of patients in group II are shown in figure 2 and that of patients in group III are shown in figure 3. Cox regression analysis with functional class, short-term drug response, and long-term drug treatment as independent variables showed that functional class and short-term drug response were significantly related to survival but long-term treatment with a vasodilator was not (table 4). Furthermore, using multiple linear regression with clinical course (i.e., change in functional class) as a dependent variable, we found no relationship between long-term drug treatment and clinical outcome (figure 4).

Since a favorable short-term drug response did reflect improved survival, we analyzed the quantitative percent change in pulmonary vascular resistance after nifedipine and hydralazine with outcome (i.e., alive or dead) and with survival in days. We are unable to correlate the degree of short-term reduction in pulmonary vascular resistance with either. Table 1 illustrates the relationship between the change in pulmonary resistance after nifedipine with the clinical course.

**Discussion**

Vasodilator drugs were initially developed as therapeutic agents for patients with essential hypertension. Their effectiveness in that regard is unquestioned by their ability to reduce elevated blood pressure to normal levels, to reverse end-organ damage to the heart and kidneys with long-term therapy, and to improve survival in treated patients. They have also received recent attention in their ability to reduce systemic vascular resistance and increase the cardiac output in pa-

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### TABLE 1

**Characteristics of the study group**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/sex</th>
<th>Functional class on entry</th>
<th>Follow-up (days)</th>
<th>% Fall in pulmonary resistance after nifedipine</th>
<th>Long-term treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41/F</td>
<td>3</td>
<td>647</td>
<td>(increased 25%)</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>32/F</td>
<td>3</td>
<td>338</td>
<td>12</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>48/M</td>
<td>3</td>
<td>618</td>
<td>35</td>
<td>Unchanged</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>33/M</td>
<td>2</td>
<td>586</td>
<td>0</td>
<td>Unchanged</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>57/M</td>
<td>3</td>
<td>586</td>
<td>0</td>
<td>Unchanged</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>55/F</td>
<td>3</td>
<td>534</td>
<td>31</td>
<td>NIF Unchanged</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>53/F</td>
<td>4</td>
<td>173</td>
<td>41</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>41/F</td>
<td>4</td>
<td>513</td>
<td>24</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>50/F</td>
<td>3</td>
<td>93</td>
<td>17</td>
<td>Died</td>
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</tr>
<tr>
<td>10</td>
<td>60/F</td>
<td>3</td>
<td>434</td>
<td>22</td>
<td>NIF Unchanged</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>45/M</td>
<td>2</td>
<td>395</td>
<td>13</td>
<td>Unchanged</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>30/F</td>
<td>4</td>
<td>27</td>
<td>42</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>61/F</td>
<td>4</td>
<td>100</td>
<td>23</td>
<td>NIF Unchanged</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>11/F</td>
<td>3</td>
<td>2</td>
<td>37</td>
<td>NIF Died</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>21/F</td>
<td>3</td>
<td>74</td>
<td>14</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>25/F</td>
<td>4</td>
<td>8</td>
<td>(increased 22%)</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>17/F</td>
<td>4</td>
<td>62</td>
<td>30</td>
<td>NIF Died</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>40/M</td>
<td>3</td>
<td>498</td>
<td>25</td>
<td>CAP Improved</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>33/F</td>
<td>3</td>
<td>441</td>
<td>22</td>
<td>NIF Improved</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>34/F</td>
<td>4</td>
<td>226</td>
<td>(increased 4%)</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>21/M</td>
<td>4</td>
<td>365</td>
<td>34</td>
<td>NIF Died</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>19/F</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>55/M</td>
<td>3</td>
<td>251</td>
<td>31</td>
<td>HYD Unchanged</td>
<td></td>
</tr>
</tbody>
</table>

CAP = captopril; HYD = hydralazine; NIF = nifedipine.
patients with congestive heart failure. Although this generally results in improved functional performance of the patients receiving such therapy, it remains unproved as to whether vasodilator drugs improve survival in patients with congestive heart failure.

There have been attempts to treat patients with primary pulmonary hypertension with vasodilators for decades, although it has been in the last several years that they have been widely tested. The mechanism of action and effectiveness of vasodilators in these patients has been questioned. Although they do lower the pulmonary vascular resistance, as a rule they do not significantly affect the pulmonary arterial pressure. Improvement in clinical class has been reported by some investigators, but adverse effects have been shown to be common by others.

Vasodilators have not been evaluated in patients with primary pulmonary hypertension by randomized clinical trials. This is understandable, given the conflicting reports about short-term benefit and the lack of data regarding their effects for more than 6 months. In some investigators, improvement in clinical class has been reported by some investigators, but adverse effects have been shown to be common by others.

![FIGURE 1. Clinical outcome of the patients who did not respond favorably to nifedipine or hydralazine (group I). Inability to respond favorably predicted a poor outcome.

In this study we evaluated 23 patients with primary pulmonary hypertension and made decisions to treat them on the basis of their short-term drug response. Five failed to respond and thus were not treated. Eighteen patients did have favorable short-term drug responses.
Half of them received long-term vasodilator therapy, and the other half, although they had similar short-term drug responses, did not. Although the decision for long-term therapy was not made by random selection, the patients in the treated and untreated groups were comparable in their demographic and hemodynamic variables.

We found that functional class on entry was a strong predictor of survival. This is consistent with previous observations on the survival of patients with primary pulmonary hypertension. We also found that a short-term fall in pulmonary vascular resistance of greater than 20% after nifedipine and/or hydralazine also predicted longer survival, although placing patients on long-term therapy did not affect outcome. The reason for this finding is not entirely clear. It is possible that the short-term drug effects were unable to be sustained in the drug responders. It is also possible that the ability to lower the pulmonary vascular resistance in response to short-term use of a vasodilator drug reflects the existence of residual vasodilatory reserve within the pulmonary vascular bed, which allows the patient to adapt to circulatory demands even if only in a limited fashion.

It has been suggested that the relative change in resistance between the pulmonary and systemic circulation may be a better reflection of drug effect. For this reason we also analyzed the data with a favorable short-term drug response defined as a percent fall in pulmonary resistance that exceeded the fall in systemic resistance. By this categorization, a favorable response was neither predictive of survival nor correlated with clinical course.

The results of this study must be interpreted in proper perspective. It was neither a randomized nor blinded trial. Although the numbers are relatively large for a study of primary pulmonary hypertension, the statistical power of these conclusions would be enhanced by a larger series of patients. In addition, even though the patients were referred consecutively to our institutions, they may reflect a selection bias in that they were considered quite ill by their referring physicians and in need of aggressive treatment. The mean survival of the patients in this study was 412 days (limited to a maxi-

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**FIGURE 2.** Clinical outcome of the patients who responded favorably to short-term testing who were not treated with long-term therapy (group II).

**FIGURE 3.** Clinical outcome of the patients who responded favorably to short-term testing and who were treated with long-term therapy (group III). There was no difference in the baseline hemodynamics or clinical course between these patients and the responders who were not treated (group II).

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**TABLE 4**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional class</td>
<td>2.07</td>
<td>0.68</td>
<td>.002</td>
</tr>
<tr>
<td>Short-term drug response</td>
<td>2.74</td>
<td>1.00</td>
<td>.006</td>
</tr>
<tr>
<td>Long-term drug treatment</td>
<td>0.05</td>
<td>0.77</td>
<td>.953</td>
</tr>
</tbody>
</table>
maximum follow-up of 647 days), which is shorter than the 2 to 3 year mean survival that has been reported in the past. Finally, inclusion of patients who stopped therapy within the first 30 days in the untreated group could also bias the results, but exclusion of these patients would have made long-term therapy appear even less effective.

It is of interest that although the ability to respond to short-term use of nifedipine and hydralazine predicted longer survival, this was unrelated to the magnitude of the fall in pulmonary vascular resistance. As shown in table 1, some of the patients with the greatest reduction in pulmonary resistance to nifedipine died, whereas others with only modest responses survived. This illustrates that achievement of a substantial reduction in pulmonary resistance with short-term use of vasodilator drugs in patients with primary pulmonary hypertension should not lul] into a false sense of security by the magnitude of the acute drug response.

A few case reports describing long-term (more than 1 year) beneficial effects of vasodilator therapy for primary pulmonary hypertension have appeared in the literature (one with diazoxide and two with nifedipine). Interestingly, in each case there was a dramatic and sustained reduction in pulmonary arterial pressure associated with an increased cardiac output, with the mean pulmonary arterial pressure after treatment between 17 to 27 mm Hg (an average fall of 50%). We had no such reductions in pulmonary pressure in our series, even with our “best cases.” This raises the question as to whether one must reduce the pulmonary arterial pressure to near-normal levels with therapy before long-term clinical benefit will be realized in patients with primary pulmonary hypertension.

We conclude that functional class upon initial evaluation may be the simplest predictor of the clinical course in patients with primary pulmonary hypertension. The ability to reduce their pulmonary vascular resistance greater than 20% with nifedipine and/or hydralazine is also a predictor of longer survival. However, treating patients who respond with a reduction in pulmonary resistance, unaccompanied by a dramatic fall in pulmonary pressure, does not appear to result in an improved functional class or survival. For these reasons, we believe that more data documenting long-term beneficial effects in these patients need to be forthcoming before a randomized, controlled clinical trial of vasodilators for primary pulmonary hypertension would be warranted.

References

9. The Criteria Committee of the New York Heart Association: Nomenclature and criteria for diagnosis of diseases of the heart and great vessels, ed 8, Boston, 1979, Little Brown and Co., p 290
12. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 213:1143, 1970
17. Gatewood RP, Yu PN: Primary pulmonary hypertension. Prog Cardiol 8:305, 1979
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