THE EFFECT OF HIGH DOSES OF CALCIUM-CHANNEL BLOCKERS ON SURVIVAL IN PRIMARY PULMONARY HYPERTENSION


Abstract Background. Primary pulmonary hypertension is a progressive, fatal disease of unknown cause. Vasodilator drugs have been used as a treatment, but their efficacy is uncertain.

Methods. We treated 64 patients with primary pulmonary hypertension with high doses of calcium-channel blockers. Patients who responded to treatment (defined as those whose pulmonary-artery pressure and pulmonary vascular resistance immediately fell by more than 20 percent after challenge) were treated for up to five years. Their survival was compared with that of the patients who did not respond and with patients enrolled in the National Institutes of Health (NIH) Registry on Primary Pulmonary Hypertension. Warfarin was given to 55 percent of the patients as concurrent therapy, on the basis of a lung scan showing nonuniformity of pulmonary blood flow (47 percent of patients who responded and 57 percent of those who did not respond).

Results. Seventeen patients (26 percent) responded to treatment, as indicated by a 39 percent fall in pulmonary-artery pressure and a 53 percent fall in the pulmonary-vascular resistance index (P<0.001). Nifedipine (mean [±SD] daily dose, 172±41 mg) was given to 13 patients, and diltiazem (mean daily dose, 720±208 mg) was given to 4 patients. After five years, 94 percent of the patients who responded (16 of 17) were alive, as compared with 55 percent of the patients who did not respond (26 of 47, P=0.003). The survival of the patients who responded was also significantly better than that of the NIH Registry cohort (P=0.002) and patients from the NIH Registry who were treated at the University of Illinois (P=0.001). The use of warfarin was associated with improved survival (P=0.025), particularly in the patients who did not respond.

Conclusions. This study suggests that high doses of calcium-channel blockers in patients with primary pulmonary hypertension who respond with reductions in pulmonary-artery pressure and pulmonary vascular resistance may improve survival over a five-year period. (N Engl J Med 1992;327:76-81.)

Primary pulmonary hypertension is an uncommon disease that is progressive and incurable.1,2 The recent National Institutes of Health (NIH) Registry on Primary Pulmonary Hypertension documented a median survival of 2.8 years after the diagnosis.3 In the 1980s interest in the treatment of primary pulmonary hypertension focused on vasodilator drugs and anticoagulant therapy.4,5 Although there are numerous descriptions of the short-term hemodynamic effects of many vasodilator drugs, reports documenting long-term effectiveness have been scarce. Anticoagulants have been recommended, but their long-term effectiveness also remains in question.6-8 In 1987 Rich and Brundage conducted a preliminary study of the use of high doses of calcium-channel–blocking drugs in patients with primary pulmonary hypertension9 and found that when the drugs were titrated to produce maximal physiologic effects, there were substantial reductions in pulmonary-artery pressure and pulmonary vascular resistance. When followed for one year, patients who had favorable responses had improvement in symptoms as well as regression of right ventricular hypertrophy, documented by electrocardiography and echocardiography. That initial experience has served as the basis for this prospective evaluation of calcium-channel blockers for patients with primary pulmonary hypertension.

Methods

Treatment Protocol

Patients who were enrolled were referred to the University of Illinois between July 1, 1985, and March 31, 1991, and fulfilled the diagnostic criteria for primary pulmonary hypertension.10 Informed consent for the study, approved by the University of Illinois Institutional Review Board, was obtained from patients fulfilling the criteria for primary pulmonary hypertension. The patients’ response to the regimen for calcium-channel blockers was then evaluated, as previously described in detail.9,11 In brief, a balloon flotation catheter was placed in the pulmonary artery and a short Teflon cannula in the femoral artery, after which the patients were monitored in the coronary care unit. All pressures and the cardiac output were recorded hourly, and the systemic and pulmonary resistances were calculated according to standard formulas. Patients were given oral doses of nifedipine (20 mg) or diltiazem (60 mg) if they had a resting tachycardia, and the doses were repeated every hour until a favorable response was achieved (defined as a more than 20 percent decrease in pulmonary-artery pressure and pulmonary vascular resistance), unless systemic hypotension or other intolerable side effects precluded further drug testing. The daily dose was then determined for the patients who responded to treatment by halving the initially effective dose and readministering it every six to eight hours. This dosing regimen remained constant throughout the follow-up period. The survival status of all patients evaluated from July 1983 through March 1991 was last determined in October 1991. Additional therapy for primary pulmonary hypertension and right ventricular failure was prescribed and administered by the attending physicians. Digoxin was prescribed for all patients taking calcium-channel blockers. Diuretics were recommended if the patient had any history of peripheral edema or if the right atrial pressure exceeded 8 mm Hg. Anticoagulant therapy was advised if the lung scan revealed nonuniformity of pulmonary blood flow.12 Forty-seven percent of the patients who responded and 57 percent of those who did not respond received anticoagulant therapy.

Comparison Groups

To assess the survival of the patients who were considered to have responded to the regimen of calcium-channel blockers, we compared them with the patients who did not respond and who were
evaluated at the University of Illinois from 1985 until 1991 and followed concurrently. We also compared them with the 22 patients who were referred to and followed prospectively at the University of Illinois from 1981 until 1987 as part of the study conducted by the NIH Registry on Primary Pulmonary Hypertension, as well as 166 other patients from the NIH registry who were seen during the same period. Mortality from all causes was used as the primary end point. Patients who responded were grouped according to an intention-to-treat basis.

**Statistical Analysis**

Differences between base-line and follow-up values for hemodynamic variables in the patients who responded to treatment were evaluated by paired Student’s t-test. Differences among the four groups of patients (patients who responded, patients who did not respond, the portion of the NIH registry cohort treated at the University of Illinois, and the NIH registry cohort) in base-line hemodynamic and other variables were evaluated by one-way analysis of variance. All P values are based on two-sided tests of significance.

Most values are expressed as means ±SD.

Kaplan–Meier curves were constructed for each of the four groups of patients, and median survival as well as the probability of survival at one year, three years, and five years was estimated. Differences in survival among the groups were examined with the log-rank test and by proportional-hazards regression analysis. The covariates assessed for possible inclusion in the regression analysis were age, sex, mean pulmonary-artery pressure, mean right atrial pressure, cardiac index, pulmonary vascular resistance, and treatment with warfarin. An algorithm developed by Mickey and Greenland was used to determine which of these covariates would be included in the regression. The effect of concurrent warfarin therapy on survival was examined in a similar manner by proportional-hazards regression analysis.

The data from the NIH registry were used to develop and validate an equation to predict survival at one, three, and five years on the basis of three hemodynamic variables: mean pulmonary-artery pressure, mean right atrial pressure, and cardiac index. Differences between the actual survival at one, three, and five years and that predicted on the basis of this equation were determined for the patients who responded, the patients who did not respond, and historical controls. One-way analysis of variance was used to test for differences among these groups with respect to the expected and observed lengths of survival.

**RESULTS**

**Short-Term Response to Calcium-Channel Blockers**

Of the 71 patients given a diagnosis of primary pulmonary hypertension between July 1, 1985, and March 31, 1991, 7 were not tested because they were considered to be too ill at the time of catheterization. They were not included in the analyses. (Similar patients were excluded from the NIH registry cohort.) Of the remaining 64 patients, 17 responded to drug testing with a 39 percent reduction in mean-pulmonary artery pressure, from 58.3±14.2 to 35.5±9.5 mm Hg (P<0.001), and a 53 percent reduction in the pulmonary-vascular-resistance index, from 23.6±11.0 to 11.6±6.4 units (P<0.001) (Table 1). This was significantly greater (P<0.001 for pulmonary pressure, and P = 0.04 for pulmonary resistance) than the response of the remaining 47 patients, who had only a slight decrease in mean pulmonary-artery pressure (from 60.7±15.4 to 56.8±14.3 mm Hg; 6.4 percent; P = 0.2) and the pulmonary-vascular-resistance index (from 26.5±13.3 to 22.1±12.7 units; 16.6 percent; P = 0.05).

Among the 17 patients who responded to treatment,
13 received a mean daily dose of 172±41 mg of nifedipine (range, 120 to 240) and 4 (Patients 1, 7, 11, and 12) received a mean daily dose of 720±208 mg of diltiazem (range, 540 to 900). Thirteen of the 47 patients who did not respond to treatment had more than 20 percent reductions in pulmonary vascular resistance without a reduction in pulmonary-artery pressure and were sent home while receiving calcium-channel blockers. The daily doses used, however, were considerably lower (60 mg of nifedipine in eight patients and 120 mg of diltiazem in five patients).

Long-Term Response to Calcium-Channel Blockers

All 17 patients who responded were asked to return annually for follow-up testing. Thirteen patients agreed to at least one follow-up catheterization study. One patient declined to return for financial reasons (Patient 17), one patient died before the annual visit (Patient 14), and at the time of the most recent follow-up two patients had been followed for less than 12 months. The patient who died did so after therapy was stopped abruptly, after being treated successfully with 240 mg of nifedipine per day for four months.

Clinical improvement was noted in all patients who returned for follow-up. Functional capacity was judged to be significantly improved as characterized by a change in the New York Heart Association functional class from 2.39±0.5 to 1.45±0.5 (P = 0.02). In addition, regression of right ventricular hypertrophy was documented by a leftward shift in the mean QRS axis (from 106±21 to 83±28 degrees, P = 0.05) and a reduction in the R-wave voltage in precordial lead V1 (from 4.3±2.7 to 2.2±2.2 mm, P = 0.05).

Serial hemodynamic studies also documented the sustained effectiveness of calcium-channel blockers (Table 1 and Fig. 1); the mean pulmonary-artery pressure and pulmonary vascular resistance at follow-up were similar to the values obtained after the initial drug challenge in all but two patients. In contrast, none of the patients who had only a reduction in pulmonary resistance were judged to have had improvements after three months on the basis of a reduction in the severity of dyspnea and fatigue.

Group Comparisons

To test whether the base-line demographic or hemodynamic characteristics of the patients who responded differed significantly from those of the patients who did not respond or the two historical control groups, we compared age, sex, and selected base-line hemodynamic variables in the four groups (Table 2). Mean pulmonary-artery pressure, right atrial pressure, and cardiac index were chosen because they have been shown in previous studies to be most closely associated with survival. There was no significant difference in any of these variables among the groups, although the patients who responded to treatment tended to have lower right atrial pressures and higher cardiac indexes than the other three groups of patients. There also tended to be a greater proportion of
cause they had less advanced disease, their prognosis at one, three, and five years was computed from a formula that incorporates mean pulmonary-artery pressure, right atrial pressure, and cardiac index. Using this equation, we projected that the three-year survival for the patients who responded would be 55 percent, a rate that was significantly less than the observed survival of 94 percent (P<0.001). The projected rates of survival for the patients who did not respond, the University of Illinois historical controls, and the NIH registry cohort were all similar to the actual rates (Table 3).

**Concurrent Therapy**

To test the possibility that concurrent therapy might confound the assessment of outcome, the 64 study patients were also analyzed with respect to the influence on survival of the concurrent administration of digoxin, diuretics, and warfarin. Digoxin and diuretics were given to more than 90 percent of the patients, and no significant influences were found. Warfarin was administered to 55 percent of the study group (47 percent of the patients who responded and 57 percent of the patients who did not respond). Survival was significantly better among those given anticoagulants than among those not given anticoagulants (P = 0.025) after the analysis was controlled for both base-line hemodynamic variables and the response to calcium-channel blockers (Fig. 3). The improvement

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**Table 2. Demographic and Hemodynamic Characteristics of the Four Groups of Patients.**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>PULMONARY-ARTERY PRESSURE</th>
<th>RIGHT ATRIAL PRESSURE</th>
<th>CARDIAC INDEX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yr</td>
<td>mm Hg</td>
<td>liters/min²</td>
</tr>
<tr>
<td>Responders (n = 17)</td>
<td>35±10</td>
<td>59±15</td>
<td>7±4</td>
</tr>
<tr>
<td>Nonresponders (n = 47)</td>
<td>36±12</td>
<td>61±15</td>
<td>10±7</td>
</tr>
<tr>
<td>UIC cohort (n = 22)</td>
<td>38±16</td>
<td>64±15</td>
<td>9±5</td>
</tr>
<tr>
<td>NIH registry cohort (n = 166)</td>
<td>36±15</td>
<td>60±18</td>
<td>10±6</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ±SD. There were no significant differences among groups.

†UIC cohort denotes the subgroup of patients enrolled in the NIH registry who were treated at the University of Illinois.

women than men in the subgroup of patients enrolled in the NIH registry and treated at the University of Illinois (4.1 to 1), as compared with the patients in the NIH registry cohort who were treated at other centers (1.7 to 1).

**Survival**

Of the 64 patients tested with calcium-channel blockers, 73 percent (17 patients who responded and 30 patients who did not respond) were followed one or more years, 34 percent (10 patients who responded and 12 patients who did not respond) three or more years, and 13 percent (2 patients who responded and 6 patients who did not respond) more than five years. As of October 1991, 42 were alive and 22 were dead. Sixteen of the 17 patients who responded (94 percent) were alive, as compared with only 26 of the 47 patients who did not respond to treatment (55 percent). Overall survival among patients who responded to treatment with the calcium-channel blockers was significantly better than that among the patients who did not respond (P = 0.003).

Survival data were tabulated for the 22 University of Illinois patients enrolled in the NIH Registry on Primary Pulmonary Hypertension from 1981 to 1985 and for the remainder of the NIH registry cohort. Kaplan–Meier estimates were made to examine survival in the four groups (Fig. 2). Patients who responded to treatment had significantly better survival rates than the patients who did not respond (P = 0.003), the patients enrolled in the NIH registry and treated at the University of Illinois — considered historical controls — (P = 0.001), or the remainder of the NIH registry cohort (P = 0.002). The survival rate among the patients who responded was 94 percent at one, three, and five years, as compared with a one-year survival of 68 percent, a three-year survival of 47 percent, and a five-year survival of 38 percent among the patients in the NIH registry cohort.

To test whether the patients who responded reflected a group with a greater likelihood of survival be-
in survival with anticoagulation was apparent primarily in the patients who did not respond to treatment with calcium-channel blockers, with a one-year survival of 91 percent, three-year survival of 62 percent, and five-year survival of 47 percent, as compared with rates of 52 percent, 31 percent, and 31 percent, respectively, in patients who did not respond who were not treated with anticoagulation.

**DISCUSSION**

Primary pulmonary hypertension has always been characterized as a progressive, incurable disease. Previous reports have often described mean survival as less than four years. The recent NIH Registry on Primary Pulmonary Hypertension has documented a median survival of 2.8 years in a large cohort followed prospectively for 7 years.

Over the past decade there has been considerable interest in the use of vasodilator agents in the treatment of patients with primary pulmonary hypertension. Observations that pulmonary-artery pressure and pulmonary vascular resistance could be lowered rapidly by a variety of vasodilator agents led to the speculation that vasoconstriction was a feature of the disease. However, despite numerous case reports describing marked reductions in pulmonary-artery pressure, pulmonary vascular resistance, or both after treatment with a variety of vasodilator drugs, the long-term effectiveness of these drugs had not been demonstrated.

Our initial observation that treatment with calcium-channel blockers titrated to produce maximal physiologic effects was associated with sustained improvement in clinical symptoms and regression of right ventricular hypertrophy led us to conduct this prospective study so that patients could be followed for five years. A response to treatment was defined as a reduction of more than 20 percent in pulmonary-artery pressure and pulmonary vascular resistance, since it had been previously shown that a reduction in pulmonary vascular resistance alone did not alter the clinical course or survival of patients treated with vasodilator agents.

The overall survival of the 64 patients entered in this study since 1985 was similar to the survival of those followed in the NIH Registry on Primary Pulmonary Hypertension. However, the subgroup of patients who responded to the calcium-channel blockers had markedly better survival during the five-year follow-up than the patients who did not respond, the NIH registry cohort, and the University of Illinois patients enrolled in the NIH registry. To address the possibility that the patients who responded to treatment had less advanced disease than the other three groups, we calculated the expected survival in this group with a formula derived from the data base of the NIH registry. When these corrections were made, it was still apparent that the patients who responded to treatment had a better-than-expected rate of survival.

Because all patients who responded initially were treated, it remains possible that the ability to respond to high doses of calcium-channel blockers identifies a subgroup of patients with primary pulmonary hypertension who have a better prognosis. This may relate to the nature of the histologic changes or to the severity of vascular changes at the time. Although the information obtained from open-lung biopsies could provide great insight into these possibilities, such information was not available in this study. In addition, the optimal dose of calcium-channel blockers for primary pulmonary hypertension remains unknown, since this study did not examine whether lower, traditional doses would have been equally effective in our patients.

The patients who responded to treatment had a better quality of life than the patients who did not respond, as reflected by the presence of fewer symptoms, better exercise tolerance, and evidence of the regression of right ventricular hypertrophy. It remains unknown, however, whether this response will persist indefinitely. In addition, we did not examine whether withdrawing the medication or reducing the dose influences long-term survival. It also remains unknown whether calcium-channel blockers taken in high doses for long periods might produce adverse effects.

![Figure 3. Kaplan-Meier Estimates of Survival, According to the Presence or Absence of a Response to Calcium-Channel Blockers and to the Use of Concurrent Therapy with Warfarin. Overall survival was significantly improved by warfarin therapy (P = 0.025).](image-url)
In two of the patients who responded, the level of hemodynamic improvement was not maintained after long-term treatment. They did not differ from the other patients with respect to any of the base-line variables, which suggests that even in the face of short-term drug effectiveness, other undefined factors may be involved in determining long-term effectiveness or survival. It is interesting, however, that in the other patients, in whom the hemodynamic effects were maintained for the first year, further reductions in pulmonary vascular resistance were noted at serial follow-up studies. The symptoms of the patients who had reductions in pulmonary vascular resistance but who did not have a short-term decrease in mean pulmonary-artery pressure did not appear to be reduced by long-term therapy. It should also be emphasized that calcium-channel blockers may worsen right ventricular function and need to be administered with caution.11

Our interest in the effects of anticoagulation in these patients resulted from the observation that long-term warfarin therapy might be associated with improved survival.6 In the light of the recent report that thrombosis occurs in the pulmonary vascular bed in patients with primary pulmonary hypertension,22 we thought that it was important to assess whether anticoagulation also affected the outcome. When the analysis was corrected for all other variables, the use of anticoagulation was associated with improved survival. This was noted primarily in the patients who did not respond, since the patients who responded had excellent survival rates regardless of whether they were treated concomitantly with warfarin. Since this study was not designed to test the influence of anticoagulation, the results need to be interpreted with caution. They may reflect a bias, in that anticoagulation was generally recommended when the perfusion lung scan was abnormal, and they might thus pertain to a subgroup of patients with a greater likelihood of survival in any case. Nevertheless, we recommend anticoagulant therapy for patients with primary pulmonary hypertension unless the presence of other underlying conditions increases the risk inordinately.

This study demonstrates that primary pulmonary hypertension may not be uniformly fatal as previously believed. Our data suggest that it is important to evaluate the response of all patients with primary pulmonary hypertension to calcium-channel blocking drugs given in appropriate doses. Patients who have a favorable response should continue drug therapy. In the patients who do not respond, long-term anticoagulation may be warranted. Current alternative strategies include the use of the investigational drug prostacyclin,23 often as a means of readying the patient for a heart–lung or lung transplantation. Recent reports of the transplantation of a single lung for the treatment of primary pulmonary hypertension suggest that patients who do not respond to therapy with calcium-channel blockers be considered for this procedure.24

References