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Long-Term Response to Calcium Channel Blockers in Idiopathic Pulmonary Arterial Hypertension

Olivier Sitbon, MD; Marc Humbert, MD, PhD; Xavier Jaïs, MD; Vincent Ioos, MD; Abdul M. Hamid, MD; Steeve Provencher, MD; Gilles Garcia, MD; Florence Parent, MD; Philippe Hervé, MD; Gérald Simonneau, MD

Background—Characteristics of patients with idiopathic pulmonary arterial hypertension (IPAH) who benefit from long-term calcium channel blockers (CCB) are unknown.

Methods and Results—Acute pulmonary vasodilator testing with epoprostenol or nitric oxide was performed in 557 IPAH patients. Acute responders, defined by a fall in both mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) >20%, received long-term oral CCB. Patients who benefit from long-term CCB were defined as those being in New York Heart Association (NYHA) functional class I or II after at least 1 year on CCB monotherapy. Among the 70 patients who displayed acute pulmonary vasoreactivity (12.6%; 95% CI, 9.8% to 15.3%) and received CCB therapy, only 38 showed long-term improvement (6.8%; 95% CI, 4.7% to 8.9%). Long-term CCB responders had less severe disease at baseline than patients who failed. During acute vasodilator testing, long-term CCB responders displayed a more pronounced fall in mean PAP (−39±11% versus −26±7%; P<0.0001), reaching an absolute value of mean PAP lower than that measured in patients who failed (33±8 versus 46±10 mm Hg; P<0.0001). After 7.0±4.1 years, all but 1 long-term CCB responders were alive in NYHA class I or II, with a sustained hemodynamic improvement. In the group of patients who failed on CCB, the 5-year survival rate was 48%.

Conclusions—Long-term CCB responders represent <10% of IPAH patients evaluated in a pulmonary vascular referral center. During acute vasodilator testing, these patients showed significantly lower levels of both mean PAP and PVR, which reached near-normal values. (Circulation. 2005;111:3105-3111.)

Key Words: calcium channel blockers ▪ follow-up studies ▪ hypertension, pulmonary ▪ nitric oxide ▪ pulmonary circulation

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and ultimately death. A diagnosis of idiopathic PAH (IPAH) is made when no known risk factor is documented. Despite recent improvements, all current treatments of IPAH do not achieve a cure of this devastating condition. As of 2004, 2 classes of drugs have been approved for IPAH treatment: prostacyclin derivatives and endothelin-receptor antagonists. In addition, uncontrolled studies have suggested that long-term administration of high-dose calcium channel blockers (CCB) prolongs survival in responsive patients. In 1992, Rich and colleagues reported that 17 of 64 IPAH patients were CCB responders and that they had a dramatic improvement in survival compared with nonresponders. In this pioneer study, responders were identified by performing an acute vasodilator challenge with CCB during right heart catheterization. However, the occurrence of life-threatening hemodynamic compromise by acute vasodilator challenge with CCB is well documented, and it is now widely accepted that these agents should not be used as first-line vasodilators for acute testing. Rather, short-acting agents such as intravenous prostacyclin, adenosine, or inhaled nitric oxide (NO) should be used. Chronic treatment with oral CCB should then be considered for patients who respond to this challenge. Although reduction of both mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) by at least 20% from baseline has been suggested for the initiation of oral CCB therapy, this definition does not discriminate between patients who will have a sustained benefit and those who will fail to improve. Long-term responders have a sustained benefit, defined as achieving New York Heart Association (NYHA) functional class I or II with near-normal hemodynamics after at least 1 year of follow-up. The goal of the present retrospective study was to define the proportion of long-term responders in a large cohort of patients with IPAH and to define clinical and hemodynamic characteristics that may help to identify these individuals.
Methods

Patient Sample
We retrospectively studied the medical records of all consecutive adult patients hospitalized in our institution from June 1984 through September 2001 with a diagnosis of IPAH. This research was authorized by our institutional review board. Pulmonary hypertension was defined by a resting mean PAP >25 mm Hg during right heart catheterization, with a mean pulmonary wedge pressure (PWP) <15 mm Hg. The diagnostic criteria for IPAH were based on the diagnostic classification of pulmonary hypertension that was proposed at the 2003 Pulmonary Arterial Hypertension World Symposium. Exclusion criteria were as follows: (1) PAH associated with anorexigen, connective tissue diseases, congenital heart diseases, portal hypertension, or HIV infection; (2) chronic thromboembolic pulmonary hypertension; and (3) other chronic respiratory diseases.

Baseline Evaluation
Baseline evaluation included medical history, NYHA functional class, physical examination, and routine blood tests. Since 1993, exercise capacity was assessed with an unencouraged 6-minute walk test as previously described. A complete baseline hemodynamic evaluation was performed in all patients with the use of standard techniques for right-side heart catheterization and after all vasodilating agents had been discontinued for at least 48 hours. Baseline hemodynamic measurements included mean right atrial pressure, mean PAP, mean PWP, cardiac output determined by the thermodilution technique, and mixed venous oxygen saturation (SvO2). Cardiac index was calculated as cardiac output divided by body surface area. PVR was calculated as (mean PAP−mean PWP)/H11002.

Acute Pulmonary Vasodilator Testing
Acute vasodilator testing was performed in all patients during the first hemodynamic evaluation. Acute pulmonary vasodilator responsiveness was assessed by a short-term vasodilator challenge with intravenous infusion of epoprostenol until 1994, then inhaled NO thereafter, as previously described. A significant acute response to NO and/or epoprostenol was defined as a fall in both mean PAP and PVR of at least 20% relative to baseline value.

Chronic Treatment With CCB
Chronic oral CCB therapy was initiated only in patients who displayed significant acute pulmonary vasoreactivity as defined above. The drug used was diltiazem or nifedipine (or amloidipine in 2 patients), the choice depending on the patient’s heart rate at rest (>100 or <100 bpm), as previously described. Patients were initiated with oral doses of nifedipine (10 mg) or diltiazem (60 mg) 3 times a day, then daily doses were upwardly titrated to nifedipine 20 mg TID or diltiazem 120 mg TID if patients did not exhibit severe side effects such as hypotension or bradycardia. Further upward titration was done after 3 months on CCB if patients displayed additional acute vasoreactivity during repeated right heart catheterization.

Clinical evaluation, including NYHA functional class and 6-minute walk test, was done every 3 to 6 months. Repeated right-side heart catheterization was performed after 3 months and 1 year of treatment with CCB and thereafter once yearly.

Long-term CCB responders were defined as patients in NYHA functional class I or II with a sustained hemodynamic improvement after at least 1 year on CCB without addition of epoprostenol, prostacyclin analogues, or endothelin receptor antagonists. Acute responders to NO and/or epoprostenol who failed to improve with long-term CCB therapy constituted the CCB failure group.

Statistical Analysis
Data were stored in a PC-based data spreadsheet. Analysis was performed with the use of Statview 5.0 (SAS Institute Inc) statistical package. All values are expressed as mean±SD. Student t test and χ2 test for independence were used to compare differences between mean values and between rates measured at baseline for acute responders and acute nonresponders, as appropriate. Similarly, differences in mean baseline values between long-term CCB responders and CCB failure groups were assessed by the same statistical analysis. One-way ANOVA with repeated measures was performed for functional and hemodynamic values obtained at baseline, during vasodilator testing, and after long-term treatment with CCB. Multiple comparisons were made when the F value was statistically significant. In regard to the retrospective nature of the study, all statistical tests were only exploratory. In addition, the high number of statistical tests given the small sample of patients could dramatically inflate type I error. Therefore, a more stringent significance criterion than the traditional 0.05 has been adopted: a probability value <0.005 was taken as statistically significant.

Survival was determined starting from 1 year onward on CCB therapy because long-term responders cannot be called responders until they have survived on therapy for 1 year. Patients who underwent lung transplantation were censored at the time of transplantation. The Kaplan-Meier method was used to estimate the proportion of patients surviving at each time point.

Logistic regression analysis was used to examine the following variables individually for a possible association with long-term CCB therapy success: age at diagnosis, age at CCB initiation, sex ratio, time between first symptoms and diagnosis of PAH, history of syncope and right heart failure, presence of Raynaud’s phenomenon, antinuclear antibody titer, baseline (ie, before CCB initiation) NYHA functional class, 6-minute walk distance, and hemodynamic parameters (at rest and during vasodilator testing). For continuous variables, we chose to separate patients into 2 groups on both sides of the median value. Results are expressed as odds ratios with 95% CIs. Multiple logistic regression was used to identify the variables that were associated with treatment success. Each variable with a significant association (P<0.05) and additional variables that were not significant but had potential clinical importance were introduced into a forward, stepwise, logistic regression model. Results of the 6-minute walk test were not included in the multiple logistic regression because there were too many missing values.

Results

Study Group
Five hundred fifty-seven patients met the criteria of IPAH and were included in the analysis. The clinical characteristics and baseline hemodynamic parameters of these 557 patients are listed in Table 1. Mean age, sex distribution (female-to-male ratio 2:1), disease duration, and extent of functional impairment were characteristic of IPAH, as well as severity of hemodynamic features, with marked elevations of mean PAP (61±14 mm Hg) and PVR (14.8±6.5 Wood units) and low cardiac output (3.9±1.2 L·min⁻¹).

Acute Response to Vasodilators
One hundred fifty-six patients were tested acutely with intravenous epoprostenol and 401 with inhaled NO. Four hundred eighty-seven patients (87.4%; 95% CI, 84.7% to 90.2%) did not respond to acute vasodilator challenge and did not receive CCB therapy. In the 70 remaining patients (12.6%; 95% CI, 9.8% to 15.3%) who responded acutely to NO or epoprostenol, mean PAP and PVR decreased significantly by a mean of 33±11% (range, 20% to 59%) and 45±15% (range, 24% to 77%), respectively. In all these patients, mean PAP decreased by ≥10 mm Hg from baseline during acute testing. The mean change in mean PAP was similar in acute responder patients tested with inhaled NO (decrease by 33±12% from baseline) and in those tested with intravenous epoprostenol (32±11%). By contrast, PVR...
TABLE 1. Clinical Characteristics, Baseline Hemodynamics, and Exercise Capacity of the Studied Patient Sample

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Acute Responders</th>
<th>Non-Acute Responders</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis, y</strong></td>
<td>45±15</td>
<td>44±16</td>
<td>45±15</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Male:female, %</strong></td>
<td>36.65</td>
<td>34.66</td>
<td>35.65</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Onset of symptoms, mo</strong></td>
<td>20±31</td>
<td>29±38</td>
<td>19±29</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Raynaud’s phenomenon, %</strong></td>
<td>14</td>
<td>16</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Antinuclear antibody titer &gt;1/80, %</strong></td>
<td>13</td>
<td>16</td>
<td>10</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>History of syncope, %</strong></td>
<td>37</td>
<td>54</td>
<td>36</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td><strong>History of right heart failure, %</strong></td>
<td>33</td>
<td>19</td>
<td>35</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td><strong>NYHA class I-II:III-IV, %</strong></td>
<td>19:81</td>
<td>47:53</td>
<td>15:85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Six-minute walk distance, m</strong></td>
<td>287±139 (n=351)</td>
<td>346±130 (n=43)</td>
<td>279±139 (n=308)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Baseline hemodynamics**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Acute Responders</th>
<th>Non-Acute Responders</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean RAP, mm Hg</strong></td>
<td>10±5</td>
<td>7±4</td>
<td>11±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Mean PAP, mm Hg</strong></td>
<td>61±14</td>
<td>57±12</td>
<td>62±14</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Mean PWP, mm Hg</strong></td>
<td>9±3</td>
<td>8±3</td>
<td>9±3</td>
<td>0.020</td>
</tr>
<tr>
<td><strong>Cardiac output, L·min⁻¹</strong></td>
<td>3.9±1.2</td>
<td>4.5±1.4</td>
<td>3.7±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PVR, Wood units</strong></td>
<td>14.8±6.5</td>
<td>12.2±5.3</td>
<td>15.3±6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>SvO₂, %</strong></td>
<td>59±10</td>
<td>66±9</td>
<td>58±10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

RAP indicates right atrial pressure.
*Comparison between acute responders and nonresponders (Student t or \( \chi^2 \) test, as appropriate).

decreased to a greater extent with intravenous epoprostenol (decrease by 54±11%) than with inhaled NO (−44±15%). Finally, in the 70 patients who displayed acute pulmonary vasoreactivity, long-term treatment with oral CCB was initiated with either diltiazem (n=53), nifedipine (n=15), or amlodipine (n=2).

**Long-Term Response to Oral CCB Treatment**

According to the criteria previously established, among patients who were considered acute responders, 38 improved after 1 year on CCB therapy (long-term CCB responders group), and 32 failed to improve (CCB failure group). Long-term CCB responders represented 54% of acute responders and 6.8% (95% CI, 4.7% to 8.9%) of the patient sample. These patients had a less severe disease than patients from the CCB failure group, as indicated by a greater proportion of patients in NYHA functional class II, a longer distance walked, and less severe hemodynamic parameters (Table 2). By contrast, patients who failed to respond to long-term CCB (CCB failure group) did not differ from nonresponders to acute vasodilator testing in terms of clinical and hemodynamic characteristics. In regard to initial acute vasodilator response, long-term CCB responders had a more pronounced fall in mean PAP and PVR than patients who failed, with a mean decrease by 39% and 50% in mean PAP and PVR, respectively (Table 3). In addition, levels of both mean PAP and PVR reached during acute vasodilator testing were lower in long-term CCB responders (mean PAP, 33±8 versus 46±10 mm Hg, \( P<0.0001 \); PVR, 5.2±2.7 versus 8.6±3.3 Wood units, \( P<0.0001 \)). Therefore, in long-term CCB responders, mean PAP reached during acute vasodilator testing was <40 mm Hg in 33 of 38 patients (Figure 1). By contrast, in patients who failed on CCB, mean PAP remained >40 mm Hg during acute testing in 22 of 32 patients (Figure 1).

Long-term CCB responders and CCB failure groups did not differ in terms of treatment regimen: in the long-term CCB responders group, the mean daily dose of diltiazem (n=27) was 482±151 mg (range, 180 to 720 mg), that of nifedipine (n=9) was 102±27 mg (range, 60 to 120 mg), and 2 patients received amlodipine at a daily dose of 20 mg. In the CCB failure group, 26 patients were treated with diltiazem at a mean daily dose of 431±174 mg (range, 180 to 720 mg) and 6 with nifedipine at a mean daily dose of 144±68 mg (range, 60 to 240 mg).

In long-term CCB responders, all but 1 were alive 1 to 18 years (7.0±4.1 years) after initiation of CCB therapy. One patient died from breast cancer after 2 years on CCB, although her pulmonary hypertension had markedly improved. The last clinical and hemodynamic evaluation was performed after 5.3±3.8 years (range, 1.0 to 15.9 years) of CCB therapy. At the time of last evaluation, 22 patients were in NYHA functional class I and 16 in class II. Their mean 6-minute walk distance was 467±101 m, and all displayed a sustained improvement in hemodynamics, with mean right atrial pressure of 5±3 mm Hg, mean PAP of 35±7 mm Hg, mean PWP of 8±3 mm Hg, mean cardiac output of 6.6±1.8 L·min⁻¹, and mean PVR of 4.4±1.7 Wood units (Table 4).

In the CCB failure group, the mean follow-up of patients was 30±28 months (range, 1 to 100 months). Twelve patients had died (7 on CCB, 4 after intravenous epoprostenol transition, 1 after inhaled iloprost transition), 7 had undergone lung or heart/lung transplantation (6 on CCB, 1 after epoprostenol transition), 3 were lost to follow-up (on CCB), and 10 remained alive. Among survivors, 6 patients were transitioned to oral endothelin receptor antagonist bosentan, 1
was transitioned to intravenous epoprostenol (and successfully underwent lung transplantation), and 3 remained on background therapy. Overall survival of this group of patients was 71%, 66%, 62%, and 48% at 1, 2, 3, and 5 years, respectively. Analysis of survival started from 1 year onward on CCB (Figure 2) demonstrated a significant difference in mortality between the long-term CCB responders and CCB failure groups ($P=0.0007$ by Cox-Mantel log-rank test).

### Predictors of Long-Term Response to CCB

Table 5 summarizes results of univariate analysis used to find predictors of long-term favorable response to CCB. Although it is clear that because of the small sample size the precision of the estimates is poor and the power to detect moderate effects is low, Table 5 is provided to provide the available information on this sample that nevertheless has clinical relevance.

In the multivariate analysis, only baseline SvO$_2$ and PVR levels reached during acute vasodilator testing were associated with long-term CCB therapy success.

### Discussion

Two classes of drugs (ie, prostanoids and endothelin receptor antagonists) are currently approved for the long-term treatment of PAH. However, a large number of patients receive...
other agents such as CCB on the basis of reports of dramatic clinical and hemodynamic improvements with acute and chronic use.\textsuperscript{9} Unfortunately, oral CCB may disserve PAH patients if they are not appropriate candidates. In these patients, CCB can decrease cardiac output and systemic vascular resistance without improvement in PAP and PVR. Therefore, outcome may be worsened in the absence of appropriate treatment. Only a subset of patients currently receiving CCB benefits from their chronic use, emphasizing the need for a better way to define true CCB responders. Guidelines have highlighted the fact that true CCB responders should be detected with an acute vasodilator challenge during right heart catheterization.\textsuperscript{10} However, there was no consensus about how to define an acute responder to vasodilators. In the present study we attempted to evaluate parameters that may help to characterize individuals who may have a favorable outcome with long-term oral CCB therapy.

Our study suggests that only a minority of patients with IPAH benefit from long-term treatment with oral CCB. We did not find any clinical characteristics or baseline hemodynamic feature that would enable physicians to distinguish patients who would respond acutely to vasodilators from those who would not. This finding is in agreement with studies already published in that field.\textsuperscript{7,9,16,18} However, acute responders have less severe disease, as demonstrated by a higher proportion of patients in NYHA functional class I or II (47\% compared with 15\% in nonresponders), a better 6-minute walk test, and a lower PVR (Table 1). Interestingly, we found a higher proportion of syncope in the history of acute responders, probably because these patients have less severe disease and are able to perform more vigorous activities. Finally, acute responders had a significantly longer duration of symptoms before diagnosis, in addition to a less severe disease. Similar findings have been observed when prostacyclin alone has been used to test vasoreactivity.\textsuperscript{18} In this latter study, patients who displayed a major response to short-term prostacyclin infusion (ie, a decrease in PVR \textgreek{50}\% ) had a significantly longer duration of symptoms (ie, time between onset of symptoms and first catheterization) than other patients.\textsuperscript{18} This is not consistent with the hypothesis that a favorable acute response to vasodilators is related to a less advanced stage of the disease but may rather indicate a spontaneously slower evolution and possibly a different disease. Although lung biopsies could provide major infor-

### Table 4. Hemodynamic Effects of Long-Term CCB Therapy in Long-Term CCB Responders Group (n=38)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Long-term Evaluation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RAP, mm Hg</td>
<td>7±4</td>
<td>5±3†</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>54±10</td>
<td>35±7‡</td>
</tr>
<tr>
<td>Cardiac index, L \cdot min\textsuperscript{-1} \cdot m\textsuperscript{-2}</td>
<td>2.8±0.6</td>
<td>3.7±0.9‡</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>10.3±4.6</td>
<td>4.4±1.7‡</td>
</tr>
<tr>
<td>SVO\textsubscript{2}, %</td>
<td>69±8</td>
<td>75±5‡</td>
</tr>
</tbody>
</table>

Values are mean±SD. RAP indicates right atrial pressure.

*Long-term evaluation: 65±46 months (range, 18–191 months).
†P=0.012, ‡P<0.0001, comparison with baseline values (ANOVA).

![Figure 1](image1.png)

**Figure 1.** Mean PAP (mPAP) reached during acute vasodilator testing with inhaled NO or intravenous epoprostenol in the 38 long-term CCB responders (left) and in the 32 patients who failed to respond to long-term therapy with CCB (right). In long-term CCB responders, mean PAP during acute vasodilator testing was <40 mm Hg in 33 of 38 patients. In patients who failed on CCB, mean PAP remained >40 mm Hg during acute testing in 22 of 32 patients.

![Figure 2](image2.png)

**Figure 2.** Kaplan-Meier estimates in the 57 of 70 acute responder patients who survived after 1 year onward on CCB. The number of patients included in the long-term CCB failure subgroup was only 19 of 32, with the 13 remaining patients being dead (n=6), transplanted (n=4), or lost to follow-up (n=3, considered “dead” in the analysis) within the first year. The difference between the group of long-term CCB responders (solid line) and that of patients who failed on CCB (dashed line) was highly significant (P=0.0007 by Cox-Mantel log-rank test).
mation on the nature of histological changes or the severity of vascular changes in these patients, such information was not available in the present study. Only 1 patient had undergone video-assisted thoracoscopic lung biopsy because she experienced recurrent spontaneous pneumothorax requiring pleurodesis. In this patient, histological examination of the pulmonary arteries revealed only medial and intimal hypertrophy, but no complex plexiform lesion was seen. Additional clinical observations suggest that only a vasoconstrictive process without fixed vascular changes may be involved in these highly vasoreactive patients: in 1 of our patients, withdrawal of CCB after 2 years of successful treatment led to rapid hemodynamic deterioration within 24 hours. Interestingly, this patient maintained a major acute vasodilator response during inhalation of NO, and reintroduction of chronic diltiazem therapy gave excellent pulmonary vasodilator response during inhalation of NO, and reintroduction of chronic diltiazem therapy gave excellent long-term results.

It is widely accepted that the initial response to acute pulmonary vasodilator testing accurately identifies PAH patients who are likely to respond to chronic oral treatment with CCB. However, no definite criteria have been uniformly accepted for a beneficial response to acute pulmonary vasodilator testing. When applying criteria used by Rich and coworkers,9 (decrease in both PAP and PVR of ≥20% relative from baseline values), we found only 70 among 557 patients (12.6%; 95% CI, 9.8% to 15.3%) displaying an acute vasodilator response leading to initiation of long-term CCB. Among these acute responders, only 38 patients (ie, 54% of acute responders and 6.8% of overall studied patient sample; 95% CI, 4.7% to 8.9%) have a sustained long-term benefit with oral calcium antagonists as monotherapy. The number of patients who showed a benefit from CCB in this large series is much lower than that previously described, at 26.6% (95% CI, 15.7% to 37.4%) in the study published by Rich and coworkers.9 In a series of 16 consecutive patients with IPAH, only 3 showed a positive hemodynamic effect during acute vasodilator trial, and only 1 of these patients experienced a substantial clinical improvement after long-term treatment with high-dose nifedipine.19 In this small series, a treatment benefit was detectable in only 1 of 16 patients, with a rate (6.3%; 95% CI, 0.0% to 18.1%) similar to that shown in our series.

To improve specificity of the acute pulmonary vasodilator testing, recent guidelines based on experts opinions have recently proposed that long-term CCB responders could be identified by a drop of mean PAP of >10 mm Hg, leading to a mean PAP <40 mm Hg and a normal cardiac output.20 However, 6 of 38 long-term CCB responders did not meet this new criterion, although their long-term outcome was excellent (Table 6). An important practical aspect of our study for clinical practice consists of the absolute necessity to monitor patients clinically and hemodynamically when chronic CCB therapy is chosen, irrespective of the criteria used to define vasodilator response. In daily practice we still sometimes consider CCB therapy in patients who do not entirely meet current guidelines for use of CCB.20 However, this is always done with extreme caution, and these patients are always reevaluated clinically and hemodynamically to assess efficacy.

Limitations of the Study
The main limitation of the present study is due to its retrospective nature. In addition, patients were evaluated in a single referral center, and some patients with a good response to CCB may have been treated empirically and never referred. Thus, the rate of long-term responders to CCB might be underestimated. In the present study we used inhaled NO or intravenous epoprostenol to test pulmonary vasoreactivity acutely.10,16 The acute predictors of long-term response to CCB have been found when these short-term agents are used to test vasoreactivity and may not be applicable when other vasodilators such as intravenous adenosine12 or inhaled ilo-

### TABLE 5. Odds Ratios for Variables Associated With Treatment Success on Long-Term CCB for Acute Responders (Univariate Analysis)

<table>
<thead>
<tr>
<th>Variables achieved during acute vasodilator testing</th>
<th>Dichotomy/Median</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PAP, mm Hg</td>
<td>&lt;37</td>
<td>6.13</td>
<td>2.11–17.86</td>
<td>0.0009</td>
</tr>
<tr>
<td>Fall in mean PAP, %</td>
<td>&gt;31</td>
<td>7.35</td>
<td>2.54–21.28</td>
<td>0.0002</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>&lt;6.7</td>
<td>7.35</td>
<td>2.54–21.28</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fall in PVR, %</td>
<td>&gt;45</td>
<td>3.27</td>
<td>1.22–8.77</td>
<td>0.018</td>
</tr>
</tbody>
</table>

RHF indicates right heart failure; RAP, right atrial pressure.
prost\textsuperscript{21} are used for acute testing. Furthermore, only patients showing an acute response to NO or epoprostenol have been initiated with oral CCB therapy. Therefore, it is not possible to evaluate the effect of CCB in patients who did not display acute pulmonary vasodilatation because they never received this therapy. Finally, only IPAH was analyzed in this report. However, a preliminary analysis of acute vasoreactivity testing in PAH associated with various conditions such as connective tissue diseases, HIV infection, portal hypertension, and left-to-right congenital shunts indicates that acute response to NO and/or epoprostenol is less common than in IPAH.\textsuperscript{22}

In conclusion, routine administration of CCB as first-line therapy in IPAH patients is ill advised. Our study demonstrates that long-term treatment with oral CCB is effective in a minority of patients with IPAH. These patients can be detected by acute pulmonary vasoreactivity testing with a short-acting agent such as inhaled NO or intravenous epoprostenol. During acute vasodilator challenge, these patients display a marked decrease in both PAP and PVR, reaching nearly normal values.

\section*{References}