Short- and Long-term Hemodynamic Effects of Oral Nifedipine in Patients with Pulmonary Hypertension Secondary to COPD and Lung Fibrosis*  
Deleterious Effects in Patients with Restrictive Disease  
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Study Objective: The present study was undertaken to evaluate at rest the short- and long-term effects of oral nifedipine (N) in patients with pulmonary hypertension (PH).

Design and Setting: A prospective study with ten consecutive cases during two years in a setting of a district acute hospital.

Patients or Participants: Seven patients with advanced COPD and three with severe lung fibrosis (LF) during a period of stable condition. Three patients with COPD were eligible for the long-term investigation.

Interventions: Right heart catheterization with a 7F Swan-Ganz triple-lumen thermodilution catheter and radial cannulation with a 3F arterial catheter.

Measurements and Results: Measurement of CO, MAP, RAP, PAP, FWP, HR, and ABG and calculation of CI, TSR, PAR, and Do0 before and after 20 mg of N sublingually at rest. For the group as a whole, N induced a reduction in MAP and TSR, with a significant increase in CI and Do0. There were no significant changes in PAP, PAR (magnitude of the reduction: −10 percent), HR, and PaO2. The individual analysis of the driving pressures (PAP − FWP) in function of the cardiac output demonstrated that a real vasodilating effect in the pulmonary circulation occurred in only three COPD patients (magnitude of the PAR reduction: −43 percent), while in the three patients with LF, N induced a deleterious increase in PAP and PAR. After long-term treatment (10 mg of N daily every 4 h; average 12 months) in the former, despite a persistent beneficial hemodynamic effect (magnitude of the PAR reduction: −36 percent), there was the usually expected clinical worsening.

Conclusions: N in small doses may be able in some patients with severe COPD to induce a beneficial short- and long-term hemodynamic effect on the pulmonary circulation when PH is present. On the other hand, N should not be used in patients with PH and advanced LF.

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Despite the multifactorial etiology of secondary pulmonary hypertension (PH) and cor pulmonale, the hypoxic vasoconstriction with the subsequent arteriolar muscularization and the factors associated with the underlying parenchymal disease are considered to be the primary causes of this disorder in patients with COPD and in those with a restrictive lung disease.14 In patients with COPD, the degree of PH greatly influences prognosis; indirect evidence suggests that the same could be true for patients with lung fibrosis (LF), despite the fact that the various native diseases strongly play an important role in the different progression of the parenchymal lesions. Long-term oxygen therapy appears to improve survival in some hypoxemic patients with COPD; this treatment may delay the progression of the PH despite the possible absence of a significant decrease in pulmonary arterial pressure and an unpredictable effect on cardiac output, which, as we know, is considered to be an important prognostic factor in these patients.12

Vasoconstriction is mediated by the transmembrane influx of calcium in the smooth muscle cell, and drugs that inhibit this process (calcium channel blockers) may provide a specific approach to the treatment of PH. Nifedipine (N), a slow channel calcium antagonist, has been shown to inhibit hypoxic pulmonary vasoconstriction in animal15,16 as well as in clinical studies.17-24 Only a few investigators have carried out long-term studies, but, for the most part, with disappointing results.18,23,24 Reports of results with N in patients with severe restrictive disease are rare; on the other hand, other investigators have dealt with the

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treatment of PH in LF with other vasodilators (hydralazine), supporting beneficial results only in those patients showing a predominance of inflammation over fibrosis.26

To investigate further the role of N as a potentially useful pulmonary vasodilator, we studied the hemodynamic response at rest of this drug in ten clinically stable patients, seven with COPD and three with advanced LF. We also investigated the long-term hemodynamic effects on those who showed a positive response (i.e., a real pulmonary vasodilatation).

Materials and Methods

Selection of Patients

We evaluated ten patients who were clinically suspected of having PH secondary to advanced COPD (seven patients) and LF (three patients). These were studied during a period of stable condition. They had no history of systemic hypertension or cardiac, valvular, or ischemic disease. All had experienced at least one previous episode of right heart failure and two had been mechanically ventilated on one occasion. All patients with COPD had an FEV1 <60 percent predicted and no significant changes after bronchodilators; the three patients with LF had a distinct infiltrative lung disorder diagnosed histologically and a functional correlate of severe restricted disease (TLC <50 percent predicted); the diagnoses were cryptogenic fibrosing alveolitis, advanced sarcoidosis, and a rheumatic lung disease.

All patients with COPD were treated with low-flow oxygen therapy with a home O2-concentrator and a regimen of diuretics, digitalis, steroids, β-adrenergic drugs, and methyIxanthines; all patients with lung LF received steroids, digitalis, diuretics, and oxygen therapy.

Table 1 shows the characteristics of study patients.

The study was approved by the local ethics committee and informed consent was obtained from each patient.

Protocol

Treatment with all medicines was stopped at least 24 h prior to the study, except oxygen and inhaled β-adrenergics, which were withheld at least 3 h prior to the test. Then the patients underwent catheterization with a 7F Swan-Ganz triple-lumen thermodilution catheter and a radial artery catheter. The pressures were monitored (P23 Statham Transducer). Transducers were referenced 5 cm below the sternal angle in the supine position and at the parasternal level of the fourth intercostal space when the patient poorly tolerated the supine and chose a semireclining position. Values were averaged for four respiratory cycles. Cardiac output was measured in triplicate by thermodilution. Arterial and mixed venous blood gas analyses were performed on heparinized samples using a blood gas analyzer (AVL). The protocol was begun when pressures, heart rate, and respiratory rate were stable.

MAP was measured continuously. Baseline variables included RAP, PAP, PWP, CO, and HR; derived variables were calculated according to the usual formulas and included cardiac index (CI), total systemic resistance (TSR), pulmonary arteriolar resistance (PAR), and oxygen delivery (Do2).

Patients then received 20 mg of N sublingually and measurements were obtained from 30 to 60 min later because the maximal fall of PAP after N seems to occur at that time.17 Only the hemodynamic profile with the lowest PAP value was considered for the overall results.

In those patients showing a positive hemodynamic response on the driving pressure-cardiac output diagram of the pulmonary circulation, we repeated a further (average 12 months) study after continuous N therapy in small doses (10 mg every 4 h during the daytime). On that occasion, the hemodynamic measurements were obtained in the early morning, about 7 h after the last doses of N. During the follow-up period, the usual treatment was maintained, including the low-flow oxygen therapy.

Statistical analysis were performed using Student's t test for paired data; p<0.05 was considered significant.

Results

Characterization of Patients

A total of ten patients (six men and four women) underwent the vasodilator test. Seven patients were severely obstructive (mean FEV1 = 19 ± SD 9.8 percent of predicted value) and three severely restrictive (mean TLC = 41 ± SD 10.1 percent of predicted value). The mean age was 60.7 years. All were hypoxemic (mean resting PaO2 = 6.9 ± 1 SEM 0.3 kPa); mean resting PaCO2 was 5.79 ± 0.19 kPa (Table 1).

Hemodynamic and Hemogasometric Response to N

For the group as a whole, N produced a significant decrease in MAP (96 ± 1 SEM 5.5 vs 83 ± 1 SEM 2 mm Hg; p<0.0025) and TSR (1,635 ± 217 vs 1,009 ± 181 dynes·s·cm⁻²; p<0.0025); concomitantly, there was a rise in CI (3 ± 0.1 vs 3.9 ± 0.2 L/min/sq m; p<0.005) and in Do2 (925 ± 55 vs 1,103 ± 30 ml/min; p<0.01). There was a moderate and not significant decrease in PAR (−10 percent) and no significant change was found in the PAP, which showed, in the group as a whole, a slight tendency to rise. PaO2 and HR did not change significantly (Fig 1).

No significant differences were observed after N in RAP, PWP, PaCO2, FVC, and calculated oxygen consumption (VO2) (Table 2).

Individual Analysis of Hemodynamics

To better evaluate the individual response induced by N at the level of pulmonary circulation, we built a

Table 1—Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Patient No./</th>
<th>Age, yr</th>
<th>Diagnosis</th>
<th>FEV1, %</th>
<th>FVC/FVC, %</th>
<th>TLC, %, pred</th>
<th>Resting air, ABC (kPa)</th>
</tr>
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<tbody>
<tr>
<td>1/53/M</td>
<td>64/F</td>
<td>Fibrosis</td>
<td>40</td>
<td>7.7</td>
<td>5.3</td>
<td></td>
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<tr>
<td>2/55/F</td>
<td>55/F</td>
<td>COPD</td>
<td>14</td>
<td>7.0</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>3/64/F</td>
<td>64/F</td>
<td>Fibrosis</td>
<td>45</td>
<td>8.5</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>4/55/F</td>
<td>55/F</td>
<td>Fibrosis</td>
<td>38</td>
<td>5.5</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>5/70/M</td>
<td>COPD</td>
<td>14</td>
<td>5.9</td>
<td>6.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/55/M</td>
<td>COPD</td>
<td>18</td>
<td>6.1</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/65/F</td>
<td>COPD</td>
<td>22</td>
<td>8.2</td>
<td>5.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/64/M</td>
<td>COPD</td>
<td>28</td>
<td>7.1</td>
<td>5.1</td>
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<td></td>
</tr>
<tr>
<td>9/55/M</td>
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<td>20</td>
<td>6.4</td>
<td>7.0</td>
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<td></td>
</tr>
<tr>
<td>10/68/M</td>
<td>COPD</td>
<td>25</td>
<td>7.2</td>
<td>5.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ABC = arterial blood gases; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; TLC = total lung capacity; pred = predicted.
driving pressure (PAP - PWP)-flow (CO) diagram with isoresistance lines passing through the origin; this allows a better interpretation of the induced fluctuations in PAR in a state where the CO changes.

Three different responses were observed (Fig 2): three patients with COPD demonstrated a decrease of PAP - PWP with a concomitant increase in CO and a shift through lower isoresistance lines (the magnitude of the PAR reduction from the baseline was −43 percent); four patients with COPD showed a shift on equal isoresistance lines while CO and driving pressure increased; finally, the three patients with lung fibrosis showed a shift toward higher isoresistance lines, concomitant with a rise in PAP - PWP while the CO increased only slightly or even decreased.

**Hemodynamic Response during Long-term Treatment with N**

The later hemodynamic response to oral N after a maintenance treatment in the three patients with COPD who demonstrated a positive response to the drug during the initial test is shown in Figure 3: PAP and PAR remained lower while CI and Do decreased higher than the baseline values; the magnitude of the PAR reduction from the baseline was −36 percent.

Despite this, there was a progressive clinical worsening and all the patients died two to four months after the second hemodynamic study (one patient from a sudden death at home, the remaining two from a refractory chronic respiratory failure).

During the maintenance period, no side effects ascribed to N were observed in these three patients.
Table 2—Hemodynamic and Hemogasometric Data before and after Nifedipine*

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nifedipine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x ± 1 SEM</td>
<td>x ± 1 SEM</td>
<td>Value</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>3 ± 0.7</td>
<td>2.7 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>PWP, mm Hg</td>
<td>8.7 ± 1.3</td>
<td>8 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>29 ± 1.9</td>
<td>31 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>96 ± 5.5</td>
<td>83 ± 4.6</td>
<td>&lt;0.0025</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>92 ± 5.6</td>
<td>98 ± 6.0</td>
<td>NS</td>
</tr>
<tr>
<td>CI, L/min/sq m</td>
<td>3 ± 0.1</td>
<td>3.9 ± 0.3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PAR, dynes·cm⁻¹⁻¹</td>
<td>351 ± 35</td>
<td>316 ± 38</td>
<td>NS</td>
</tr>
<tr>
<td>TSR, dynes·cm⁻¹⁻¹</td>
<td>1,635 ± 217</td>
<td>1,009 ± 160</td>
<td>&lt;0.0025</td>
</tr>
<tr>
<td>VO₂, ml/min</td>
<td>187 ± 12</td>
<td>230 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td>DO₂, ml/min</td>
<td>925 ± 56</td>
<td>1,103 ± 41</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PaO₂, kPa</td>
<td>6.9 ± 0.3</td>
<td>6.7 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO₂, kPa</td>
<td>5.5 ± 0.2</td>
<td>5.6 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>PVO₂, kPa</td>
<td>4.7 ± 0.2</td>
<td>5.0 ± 0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*RAP = mean right atrial pressure; PWP = mean pulmonary wedge pressure; PAP = mean pulmonary arterial pressure; MAP = mean arterial pressure; HR = heart rate; CI = cardiac index; PAR = pulmonary arteriolar resistance; TSR = total systemic resistance; VO₂ = oxygen uptake (calculated); DO₂ = oxygen delivery; PVO₂ = partial oxygen tension in arterial blood; PaCO₂ = partial carbon dioxide tension in arterial blood; PaO₂ = partial oxygen tension in mixed venous blood.

**Discussion**

Our study partially confirms previous observations that nifedipine is able to reduce acutely pulmonary arterial pressure and pulmonary vascular resistances through an active vasodilatation process in patients with severe COPD. To attribute changes in pulmonary hemodynamics to active vasodilatation in three of our patients with COPD, it is important to exclude any effect induced by the drug on lung mechanics and, furthermore, a phenomenon of recruitment of unperfused or insufficiently perfused pulmonary vessels.

Although nifedipine, under some circumstances, can induce changes in the bronchomotor tone of obstructive patients when at rest, bronchodilator effects are known to be absent or modest. Moreover, the analysis of our wedge pressure tracings did not disclose changes in the amplitude of intrathoracic pressure swings after administration of nifedipine.

As pulmonary pressure, we used the driving pressure to avoid the effects of the drug on the pulmonary circulation through hemodynamic changes at the left atrial level. The concomitant fall in pulmonary arterial pressure and pulmonary driving pressure, associated with an increase in cardiac output, rule out a vessel recruitment phenomenon and involve a true effect related to changes in pulmonary vascular tone (Fig 2).

On the other hand, the four remaining patients with COPD showed a shift on equal isoresistance lines while increasing their driving pressures: this acute reaction is consistent with a recruitment phenomenon produced by the increase in cardiac output secondary to the known hemodynamic changes of nifedipine at systemic level.

As pointed out in many previous studies, our investigation underlines once again that the nifedipine response in patients with stable COPD remains unpredictable; until now, therefore, right heart catheterization has been mandatory to define exactly the hemodynamic response. It is difficult to explain precisely why, in the presence of apparently related functional hemodynamic and hemogasometric situations, a given patient with COPD reacts in a different way from another; in patients with apparently small but variable degrees of pathophysiologic derangements, different prolonged periods of hypoxia seem to produce different biochemical and structural obliterative changes which, in turn, determine the responsiveness or the unresponsiveness to any pharmacologic intervention.

Our study provides evidence that nifedipine, given in small doses (10 mg) daily every 4 h, exerted a persistent vasodilating effect during an 8- to 14-month observation period in our three patients with COPD who showed a positive hemodynamic response during the first trial. This observation as well as others suggests that in some patients with COPD with pulmonary hypertension there is possibility of continuous release of hypoxic vasoconstriction despite the anatomic restriction of the vascular bed.

Only one study clearly established that low-flow oxygen therapy can induce a greater hemodynamic benefit when added to nifedipine; others, on the contrary, showed no additional benefit or even deleterious effects, as demonstrated by Agostoni and
coworkers; they concluded that nifedipine, given in high dosage in the long term was poorly tolerated and inhibited the oxygen capability to reduce pulmonary pressure. Because of this, we therefore decided to treat our three patients with COPD who were receiving low-flow oxygen therapy during the night with small doses of nifedipine (10 mg) given every 4 h during the daytime.

As pointed out in other studies, despite the persistent beneficial hemodynamic long-term response, there was the same decline in the clinical state as in the other patients with COPD without vasodilating treatment. This is in agreement with the concept that the lung function indices are good predictors of pulmonary deaths. In fact, our seven patients with COPD had initially a very severe obstruction and all were hypoxemic (Table 1); it is well known that the FEV, relates firstly with the clinically documented disease, secondly with the prediction of the longitudinal decline in lung function, and finally with the mortality rate.

Even in the event of a rapid clinical decline, we cannot exclude some potential benefits of nifedipine; however, on the whole, the small number of patients does not allow us to draw specific conclusions about some important end points like quality of life and exercise capacity.

After the first investigation, the mean survival period was 15 months in the treated group and 17 months in the four remaining patients with COPD without nifedipine. The mean survival period was 27 months in our small group of patients with restrictive lung disease. It is clearly speculative to arrive at conclusions about the differences in survival between the patients with COPD and those with a restrictive disease. First, the groups are small and definite results cannot be demonstrated. Second, the primary causes of the pulmonary hypertension in patients with an advanced restrictive disease are partially different from those related to a chronic obstructive disease; thus, it is quite possible that the degree of pulmonary hypertension secondary to a lung fibrosis has a different influence on the prognosis than in patients with COPD. Finally, the prognosis in patients with a fibrosis is clearly dependent on the different evolution of the native lung disease.

In the three patients with a restrictive lung disease, nifedipine induced deleterious effects: mean pulmonary artery pressure, pulmonary arteriolar resistances, and driving pressure rose after the test. In two of them, this was probably the consequence of an augmented flow through a restricted pulmonary vascular bed. In the third patient, however, the cardiac output failed to increase and even decreased; concomitantly, this patient reacted with a further reduction of an already low mean arterial pressure and with a marked decrease in heart rate, and his PaO, fell with nifedipine from 63 to 55 mm Hg. To explain this, a hypothesis may be offered: a diversion of blood flow from normal lung units to units with a low V̇A/Q distribution is known to be a possible deleterious effect of nifedipine or other vasodilators; the resulting arterial oxygen desaturation is usually counterbalanced by a significant increase in cardiac output which, in turn, enhances the mixed venous oxygenation.

![Figure 3. Late hemodynamic response after a mean maintenance treatment period of 12 months with 10 mg of nifedipine three times a day in the three patients with COPD who demonstrated a positive response to 20 mg of sublingual nifedipine during the initial test. PAP = mean pulmonary arterial pressure; PAR = pulmonary arteriolar resistance; CI = cardiac index; and CaO₂ × CO = oxygen delivery.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21654/ on 04/28/2017)
The same can be true if an increase in total minute-ventilation or a decrease in oxygen uptake will contribute to prevent a deterioration in arterial PaO₂. This patient did not show any increase in ventilation nor any significant decrease in calculated VO₂. As a consequence, his hypoxic vasoconstriction deteriorated, raising, in turn, the right ventricular afterload. An increase in impedance to right ventricular ejection could ultimately have worsened the right and left ventricular performances. On the other hand, nifedipine is known to have a direct cardiodepressant effect at cellular level, thus inducing a decrease in myocardial contractility; finally, as reported in patients with a primary pulmonary hypertension, an excessive systemic vasodilation may lead to a critical reduction in coronary flow to a hypertrophied right ventricle, inducing a right ventricular myocardial dysfunction through a phenomenon of depressed contractility.

There has been little experience with vasodilators in treating pulmonary hypertension secondary to lung fibrosis. Lupi-Herrera and colleagues have studied a small group of patients with a mild to moderate interstitial disease treated with hydralazines. They found that the drug exerted a beneficial vasodilation with minimal side effects; their results are in agreement with the proven fact that the patients most likely to benefit from vasodilators are those with early stages of the disease and, therefore, with a still active pulmonary vasoconstriction. On the contrary, our patients had a severe interstitial lung disease with lung biopsy specimens showing a predominance of fibrosis over inflammation; this fibrosis seems to preclude a response to vasodilators and exposes the patients to potential serious side effects and even death.

To summarize, despite the limited number of cases, our report underlines once again the heterogeneity of the hemodynamic response with vasodilators in patients with COPD and lung fibrosis with secondary pulmonary hypertension.

Nifedipine in small doses may well be capable of inducing, without side effects, a beneficial short- and long-term vascular response in some patients with COPD, even with an advanced disease; on the other hand, caution is needed in treating with nifedipine those patients with an advanced lung fibrosis.

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