Effects of Nifedipine on Ventilation/Perfusion Matching in Primary Pulmonary Hypertension*

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The effects of nifedipine on hemodynamics and pulmonary gas exchange were investigated in two patients with primary pulmonary hypertension. After 20 mg of the drug taken sublingually, pulmonary and systemic vascular resistances decreased, cardiac output increased, and blood oxygenation was improved. As assessed by the multiple inert gas elimination technique, nifedipine induced a deterioration in ventilation/perfusion (V/Q) relationships consisting in an increased perfusion of units with low V/Q. In spite of this negative effect on gas exchange, arterial Po2 increased as a consequence of increased mixed venous Po2 in relation to an augmented cardiac output, and in one patient there was a decrease in the secondary atrial shunt. Both patients were clinically improved by the nifedipine as a long-term treatment.

Patients with primary pulmonary hypertension have widened alveolar-arterial Po2 gradients and may become hypoxic in advanced stages of the disease, when cardiac output also falls.1 Studies using the multiple inert gas elimination technique have provided a better understanding of the mechanisms of abnormal gas exchange in these patients, and show in particular that a pharmacologic reduction in pulmonary vascular tone deteriorates ventilation/perfusion (V/Q) matching.2-3 This potentially deleterious effect of pulmonary vasodilation received little attention in most of the recent reports on vasodilator therapy in primary pulmonary hypertension.4-13

On the other hand, vasodilators tested until now in primary pulmonary hypertension with variable success are not specific for the pulmonary circulation and have also been occasionally associated with serious adverse effects.10-13

We observed favorable clinical results in two patients with primary pulmonary hypertension who were given nifedipine and have investigated the effects of this drug on hemodynamics as well as on pulmonary gas exchange.

CASE REPORTS

Case 1

A 61-year-old woman was admitted with a history of progressively severe exertional dyspnea and fatigue over the preceding ten years. She denied previous use of drugs and had never before had symptoms suggestive of cardiac or pulmonary disease. From three years before admission, exertional dyspnea had become invalidating (walking on level ground) and was accompanied by chest pain and palpitations and on four occasions by syncope. One year before admission, a right heart catheterization showed severe pulmonary hypertension, partially reversible after a prostaglandin E1 (PGE1) infusion, 0.02 μg/kg/min (Table 1).

Hydralazine, 50 mg given four times per day orally, did not affect the gradient between pulmonary artery pressures and wedge pressures, but induced a 45 percent reduction in pulmonary vascular resistances, and was therefore attempted as a long-term treatment. The patient, however, soon discontinued use of hydralazine because of side effects consisting of malaise, headache, nervousness, and frequent nausea. Physical examination on admission showed her to be healthy-looking, slightly cyanotic, with no distress at rest, 157 cm tall and weighing 60 kg. Blood pressure was 110/60 mm Hg, heart rate 68 beats/min, rectal temperature 36.8°C, and respiratory rate 18 breaths/min. There was jugular distention with visible A waves. The lungs were clear. The heart had a palpable S1 and a parasternal heave. A grade 2 pansystolic murmur, increased at inspiration, was heard along the left sternal border. The second heart sound had a loudly accentuated pulmonic component. There was no hepatomegaly, ascites, or peripheral edema. An ECG revealed a right axis deviation and a right ventricular hypertrophy. Chest roentgenogram showed enlarged pulmonary arteries, with attenuation of the peripheral vascular markings and an enlargement of the right ventricle. Results of plasma electrolyte and renal and liver function tests, complete blood count, and a coagulation profile were normal. There was no laboratory evidence of connective tissue disorder. A ventilation/perfusion lung scan showed no evidence of pulmonary thromboembolic disease. A pulmonary arteriogram disclosed no filling defect in the pulmonary vasculature. Lung function tests were normal, except for a reduction in diffusion capacity for carbon monoxide at 12.9 ml/min/mm Hg. M mode and two-dimensional echocardiography showed a normal-sized left ventricle, a dilated right ventricle with marked hypertrophy of ventricular walls, and a normal aortic and mitral valves. A prominent B point was noted on the tricuspid valve, the pulmonic valve E-F slope was reduced, and the A wave was absent; the pulmonic valve showed a midystolic notch, forming a "W" pattern. Contrast echocardiography was performed using intravenous (IV) injection of 5 percent dextrose in water and demonstrated a right-to-left atrial shunt.

Right heart catheterization was performed according to a procedure reported elsewhere.14 Hemodynamic and gasometric measurements were obtained in duplicate before and 60 minutes after nifedipine, 20 mg given sublingually. As shown in Table 1, the basal determinations were comparable to those of one year before (except for an increase in right atrial pressures), indicating slow progression.

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Table 1—Mean Values of Duplicate Hemodynamic and Blood Gases Determinations in Two Patients With Primary Pulmonary Hypertension Given PGE₁, Hydralazine, and Nifedipine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient 1, 1st Catheterization</th>
<th>Patient 2, 2nd Catheterization</th>
<th>Patient 2, Baseline</th>
<th>Patient 2, Nifedipine</th>
<th>Patient 2, Pulmonary Resistance, dyne.s.cm⁻²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH</td>
<td>7.46</td>
<td>7.45</td>
<td>7.46</td>
<td>7.48</td>
<td>7.48</td>
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<tr>
<td>Arterial Pao₂, mm Hg</td>
<td>46</td>
<td>56</td>
<td>63</td>
<td>42</td>
<td>49</td>
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<tr>
<td>Arterial Pco₂, mm Hg</td>
<td>27</td>
<td>29</td>
<td>25</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Mixed Venous Pco₂, mm Hg</td>
<td>27</td>
<td>35</td>
<td>37</td>
<td>25</td>
<td>30</td>
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<tr>
<td>O₂ Transport, m/min/m²</td>
<td>292</td>
<td>465</td>
<td>568</td>
<td>320</td>
<td>470</td>
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<tr>
<td>O₂ Consumption, m/min/m²</td>
<td>125</td>
<td>131</td>
<td>136</td>
<td>133</td>
<td>147</td>
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<tr>
<td>P(A-a) O₂, mm Hg</td>
<td>70</td>
<td>58</td>
<td>56</td>
<td>77</td>
<td>69</td>
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<tr>
<td>Venous admixture, (%)</td>
<td>34</td>
<td>28</td>
<td>22</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>1.9</td>
<td>2.8</td>
<td>3.3</td>
<td>2.0</td>
<td>2.8</td>
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<td>Heart rate, beat/min</td>
<td>75</td>
<td>74</td>
<td>92</td>
<td>75</td>
<td>95</td>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>76</td>
<td>70</td>
<td>75</td>
<td>78</td>
<td>58</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyne.s.cm⁻²</td>
<td>1733</td>
<td>1140</td>
<td>1018</td>
<td>1656</td>
<td>801</td>
</tr>
<tr>
<td>Mean right atrial pressure, mm Hg</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td>13</td>
<td>14</td>
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<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>74</td>
<td>53</td>
<td>72</td>
<td>75</td>
<td>62</td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure, mm Hg</td>
<td>8</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

*Calculated using the ideal alveolar gas equation, assuming a respiratory ratio equal to 0.8.

†Calculated as (capillary O₂ content-arterial O₂ content/capillary O₂ content-mixed venous O₂ content).

‡Ranges obtained from right heart catheterizations performed in 23 healthy volunteers.

The disease. Nifedipine induced pulmonary vasodilatation, increases in cardiac index and O₂ transport, and improvement in blood oxygenation. Between the two baseline and the two nifedipine measurements, arterial and mixed venous blood and mixed expired gas were sampled to determine W/Q distributions by the multiple inert gas elimination technique as described by Wagner and coworkers. The least-squares analysis with enforced smoothing was used to minimize the effects of random experimental error. The W/Q distributions were combined with the mixed venous blood gases, cardiac output, minute ventilation, and Pao₂ in a lung model described by West and Wagner to predict the arterial pressure of oxygen assuming complete alveolar-capillary equilibrium in each lung unit. Minute ventilation and respiratory rate were measured using a pneumotachograph of the Fleisch type connected with an electronic integrator (AUPREM 91 A). The W/Q distributions before and after nifedipine are shown in Figure 1. Before nifedipine, the majority of pulmonary blood flow was distributed to a mode around the units with a W/Q ratio of 2.6. The shape and position of this mode along the W/Q axis were comparable to those of normal subjects. There was an additional mode of blood flow to units with low W/Q ratios (11.9 percent of total blood flow to units with W/Q<0.2). Dead space was normal (32 percent of tidal volume). Shunt was 20 percent of total blood flow. It must be noted that the inert gas method does not allow differentiation between pulmonary and cardiac right-to-left shunt. After nifedipine, there was a deterioration in W/Q relationships, with an increased perfusion to units with low W/Q ratios (18.9 percent of total blood flow to units with W/Q<0.2). Shunt decreased to 10 percent. Dead space increased to 51 percent, probably in relation to the reduction in pulmonary pressure. Before as well as after nifedipine, the absence of diffusion abnormality was confirmed by the good agreement between measured and predicted arterial Pao₂.

After nine months of treatment with nifedipine, 20 mg orally four times a day, the patient felt much better and enjoyed a nearly normal life. Her exertional dyspnea markedly decreased, and she had no chest pain and no syncope. She was even able to dance again—her favorite pastime, which she had had to abandon eight years previously.

**Case 2**

This 38-year-old woman had been in good health until one year previously, when she had several syncopes at exertion. Thereafter, she suffered from progressively severe exertional dyspnea, fatigue, frequent palpitations, and an average of one syncope at exertion.

![Figure 1. W/Q distributions before and after nifedipine, 20 mg sublingually, in patient 1.](https://example.com/figure1.png)
every 15 days. Three months before admission, she had an episode of congestive heart failure and received treatment consisting of rest, diuretics, and digitalis. She denied previous use of drugs. Physical examination showed her to be healthy, eugonic, and normocytic, 168 cm tall and weighing 71 kg. Blood pressure was 150/90 mm Hg, heart rate 80 beats/min, rectal temperature 36.8°C, and respiratory rate 16 breaths/min. Heart auscultation showed a markedly accentuated second heart sound and a grade 2 pansystolic murmur along the left sternal border. The remainder of the examination was unremarkable.

An ECG revealed a right axis deviation and a right ventricular hypertrophy. Chest roentgenogram showed enlarged pulmonary arteries, with attenuation of peripheral vascular markings and enlargement of the right ventricle. Results of plasma electrolyte and renal and liver function tests, complete blood count, and coagulation profile were normal. There was no laboratory evidence of connective tissue disorder. Ventilation/perfusion lung scan and pulmonary arteriogram showed no evidence of pulmonary thromboembolic disease. Lung function tests were normal, except for a reduction in the diffusion capacity for carbon monoxide at 17.9 ml/min/mm Hg. M-mode and two-dimensional echocardiography showed a normal-sized left ventricle, normal aortic and mitral valves, and a markedly dilated right ventricle. The pulmonic valve E-F slope was reduced, and the A wave was almost absent; a mid-systolic notch was apparent. Contrast echocardiography disclosed no atrial or ventricular right-to-left shunt.

Right heart catheterization (Table 1) showed marked pulmonary hypertension, normal filling pressures of the heart, and a lowered cardiac output. Arterial PO₂ was normal in the presence of marked alveolar hyperventilation and respiratory alkalosis. The O₂ transport and mixed venous PO₂ were low. Administration of nifedipine, 20 mg sublingually, did not change pulmonary artery pressures, but increased cardiac output and O₂ transport, while pulmonary vascular resistances were reduced by 35 percent. Arterial oxygenation increased, while mixed venous blood oxygenation returned to within normal limits.

The V/Q distributions in patient 2 before and after nifedipine were determined according to the same study protocol as in patient 1 (Fig 2). Before nifedipine administration, the majority of blood flow was distributed to a mode around the units with V/Q ratio of 1.7, and there was an additional mode of blood flow to units with low V/Q ratios (3.9 percent of total blood flow to units with V/Q<0.2). Dead space was normal, at 37 percent of tidal volume. The shunt was negligible (0.7 percent of total blood flow). After nifedipine administration, the perfusion of units with low V/Q ratios was decreased (to 9.4 percent of total blood flow to units with V/Q<0.2). Dead space slightly decreased to 32 percent of tidal volume, a probably insignificant change, in relation to the absence of modification in pulmonary artery pressures. There was no shunt. A good agreement was found between measured and predicted arterial PO₂ before as well as after nifedipine, indicating the absence of impaired diffusion.

After seven months of treatment with nifedipine, 20 mg orally four times per day the patient had no syncope, and exertional dyspnea decreased to the point that she was able to enjoy swimming again.

**DISCUSSION**

Dantzker and Bower⁶ have recently shown by the multiple inert gas elimination technique that V/Q relationships in patients with chronic obliterative pulmonary vascular disease (idiopathic or secondary to recurrent pulmonary emboli) are only minimally abnormal, with a mean of 10 percent of cardiac output perfusing units with low V/Q. The same authors demonstrated that in such patients reduction of pulmonary vascular tone by an infusion of nitroprusside or

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**Figure 2.** V/Q distributions before and after nifedipine, 20 mg sublingually, in patient 2.

Isoproterenol deteriorates gas exchange without negative effect on arterial oxygenation, because mixed venous PO₂ is increased as a consequence of increased cardiac output. Our observations are in agreement with these studies. We manipulated the lung model used to predict arterial PO₂ and quantified the nifedipine-induced changes (Table 2). It is apparent that negative effects on gas exchange by pulmonary vasodilation were slightly overcompensated by positive effects of increased cardiac output (and reduction of atrial right-to-left shunt in patient 1). Crevey et al.⁸ observed no modification in V/Q relationships in five patients with pulmonary hypertension (which was primary in four of them) after diltiazem administration, but this was probably due to the absence of physiologically relevant hemodynamic changes.

<table>
<thead>
<tr>
<th>Table 2—Theoretical Effects of Nifedipine-induced Changes on Arterial PO₂ in Two Patients With Primary Pulmonary Hypertension</th>
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<tr>
<td><strong>Baseline Arterial PO₂</strong></td>
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<tr>
<td>Nifedipine-induced changes</td>
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<tr>
<td>V/Q deterioration</td>
</tr>
<tr>
<td>Shunt decrease</td>
</tr>
<tr>
<td>Mixed venous PO₂ increase</td>
</tr>
<tr>
<td>Due to cardiac output increase</td>
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<tr>
<td>Resulting arterial PO₂</td>
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Calcium channel-blocking agents can influence cardiovascular hemodynamics by a complex interplay of systemic arterial vasodilation, a negative inotropic effect, and reflex phenomena. Among these drugs available for clinical use, nifedipine has been shown to be the most potent when administered in equal doses by weight to isolated tissue preparations. In vivo, marked systemic vasodilation by nifedipine elicits a β-adrenergic response that accounts for an increase in cardiac output and an acceleration in heart rate, as observed in our patients. Pulmonary vasoconstriction is dependent on the availability of calcium to the effector cells, and calcium channel-blockers have thus also been tried to induce pulmonary vasodilation in patients with primary or secondary pulmonary hypertension. A well-tolerated reduction in pulmonary vascular tone by nifedipine has been reported by Simonneau et al in patients with decompensated chronic obstructive pulmonary disease, and by Camerini et al in one patient with primary pulmonary hypertension. Verapamil was less effective in the study by Landmark et al in 12 patients with pulmonary hypertension (which was primary in nine of them). Pulmonary artery pressures decreased as a consequence of decreased cardiac output, and pulmonary vascular resistances remained unchanged. In the patients of Crevey et al, diltiazem induced at rest only a slight decrease in pulmonary artery pressures, without change in cardiac output or in pulmonary vascular resistances. Kambara et al reported a marked pulmonary vasodilation by diltiazem in a younger patient. Thus, the available data on a limited number of patients suggest that nifedipine, and diltiazem to a lesser degree, may present an interesting effectiveness/toxicity ratio in the treatment of primary pulmonary hypertension.

PGE1 has been effective in reducing pulmonary hypertension, without side effects or excessive systemic vasodilation, in patients with decompensated chronic obstructive pulmonary disease and in one patient with primary pulmonary hypertension. In our patient 1, PGE1 appeared to be a more active pulmonary vasodilator than hydralazine. PGE1 is regretfully not available for oral use, but may be helpful at right heart catheterization to determine the functional part of pulmonary hypertension.

How did nifedipine treatment improve the clinical state in our patients? Their absolute level of pulmonary artery pressures decreased moderately (17 percent in patient 1) or did not change at all (patient 2), but cardiac output increased in both. Limitation of cardiac output because of obstruction to flow through the lungs is likely to account at least in part for exertional dyspnea, syncope, and sudden death in advanced primary pulmonary hypertension. In this respect, a pharmacologic increase in cardiac output, even without fall in pulmonary artery pressures, may be the main hemodynamic event leading to symptomatic improvement. Another tentative explanation for the reduction in dyspnea in our patients might be a vagolytic effect of nifedipine that would reduce the afferent discharges from intrapulmonary mechanoreceptors.

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The First World Congress on Cardiovascular Pharmacotherapy will be held in Geneva, Switzerland, April 11-15. For information, contact Adam Schneeweiss, M.D., Scientific Secretary, c/o Interconference, 12 Ave des Amazones, 1224, Chene-Bourgeries, Geneva, Switzerland.