The Role of Isoproterenol in Pulmonary Artery Hypertension of Unknown Etiology (Primary)*
Short- and Long-term Evaluation
Eulo Lupi-Herrera, M.D.; David Bialostozky, M.D.; and Angel Sobrino, M.D.

The experience derived from the administration of isoproterenol in six patients with pulmonary hypertension of unknown etiology (PAH-UE) is presented. The diagnosis was made after exclusion of other known diseases capable of producing hypertension in the pulmonary circuit. Catheterization was performed, and basal cardio-pulmonary parameters, mean pulmonary artery pressure (PAP), pulmonary arteriolar resistance (PAR), cardiac index (CI), alveolar-arterial oxygen tension difference F(A-a)O2, and PaO2 were investigated. The effect of infusing 3 μg/min of isoproterenol into the pulmonary artery was studied in five cases. Isoproterenol was given sublingually to one patient who had previously received it intravenously; in another case it was given only sublingually. Significant P values (P < .05) as a group were obtained, in relation to heart rate, CI, PAR, and mean PAP after isoproterenol. A favorable effect on the heart and lungs was seen in two cases, maintained for three years with sublingual isoproterenol with a favorable cardiorespiratory effect. Use of isoproterenol in PAH-UE is justified at present in those cases with a favorable cardiopulmonary response while no specific therapy is available.

Pulmonary artery hypertension of unknown etiology (PAH-UE) is a rare entity.1-4 Unfortunately the disease is usually well advanced before the diagnosis is made, and no therapeutic measures have been successful in relieving all of the symptoms or in modifying the course of the disease. Pulmonary vasoconstriction has been proposed as one of the most probable mechanisms for pulmonary hypertension.4-8 Several vasoconstrictor agents, such as acetylcholine, tolazoline, and isoproterenol, have been shown to decrease pulmonary artery pressure (PAP) in short-term studies.7-10 Sublingual isoproterenol has also been shown to be beneficial for the long-term treatment of PAH-UE, giving symptomatic benefit despite progress of the underlying disease.11

The purpose of this investigation is to present the experience derived from the short-term administration of isoproterenol in six patients with PAH-UE with different degrees of PAP and the follow-up of two cases receiving long-term sublingual therapy, for three years.

*From the Cardiopulmonary Service, Instituto Nacional de Cardiología de México Ignacio Chávez, Mexico City, Mexico.
Manuscript received January 11; revision accepted April 15. Reprint requests: Dr. Lupi-Herrera, Instituto Nacional de Cardiología, Juan Badano No. 1 Tláhuac, Mexico D.F., Mexico 23

METHODS
Six patients with the diagnosis of PAH-UE were studied. All lived in Mexico City (altitude: 2,240 m). The diagnosis was made after the exclusion of other known diseases capable of producing pulmonary artery hypertension on the bases of clinical studies, laboratory tests, respiratory function tests, cardiopulmonary nuclear studies, phon-echo cardiographic, hemodynamic, and angiographic studies. In none was a lung biopsy specimen obtained. The patients were studied in the unanesthetized basal state, and no premedication was given. The procedure was explained and informed consent obtained.

Under local anesthesia, a Swan-Ganz catheter (KMA-9601, 7-F) was introduced into a peripheral vein, advanced to the heart, and positioned in the pulmonary artery. Cannulation of the brachial artery was also performed. Cardiac output (CO) was measured in duplicate, using the thermodilution technique12 and a thermodilution computer (KMA-2000). The data were reported as the averages of the determinations. All pressure measurements were referred to the mid-chest and were measured with strain gauge transducers (Statham P23Db) and on an oscillographic photographic recorder (Electronics for Medicine IR-4).

Mean pressures were obtained by integration of the phasic pressures. Control measurements included systemic arterial pressure (SAP), right atrial pressure (RAP), PAP, and pulmonary wedge pressure (WP). Right ventricular work (RVW), total pulmonary vascular resistance (TPR), pulmonary arteriolar resistance (PAR), and systemic arterial resistance (SAR) were derived from the foregoing measurements using the following calculations: RVW = (mean PAP-RAP)/CO × 0.0136 kg.m/min, TPR = mean PAP × 80/CO dynes sec cm-5, PAR = (mean PAP-WP) 80/CO dynes sec cm-5, SAR = mean SAP × 80/CO dynes sec cm-5, cardiac index (CI) = CO/BSA L/min/m2, where BSA = body surface.
area, according to the formula of DuBois and DuBois. Minute volume (MV) was measured using a dry gas meter (American SM 210). Expired air was collected for three minutes in a low resistance bag. Midway through the collection of expired air, samples of blood were obtained for gas analysis from the pulmonary artery and the brachial artery over a one-minute period (normal values for Mexico City: PaO₂, 70 ± 5 mm Hg and PaCO₂, 32.5 ± 2.5 mm Hg). The mixed expired air was immediately analyzed using an Instrumentation Laboratory gas analyzer (127 bath, 213 electrometers). From these data and from the blood gas analysis, the physiologic dead space (Vd ml), the alveolar arterial PO₂ difference (P(A-a)O₂) mm Hg, the rate of oxygen consumption (Vo₂ ml), CO₂ production (Vco₂ ml), respiratory quotient (RQ), and hemoglobin content arteriovenous oxygen difference (A-V Do₂ vol percent) were derived. Vo₂ was calculated using Bohr’s equation, alveolar PO₂ applying the alveolar air equation and RQ from the relation Vco₂/Vo₂.

After the control measurements, the effect of infusing 3 μg/min of isoproterenol into the pulmonary artery was investigated in five patients. After five minutes, the blood flow, expired air, and blood gases again were measured. Pressures were recorded continuously except during the blood sample collections. Two patients were given 15 mg of isoproterenol sublingually. One had received isoproterenol intravenously (IV) one hour earlier. After 15 minutes the cardiopulmonary parameters were again measured.

Statistical analyses were performed using Student’s t test for independent variables. All results were expressed as the mean plus or minus one SD. P values of less than .05 were considered significant.

Long-term sublingual administration of isoproterenol was started in cases with a favorable cardiorespiratory response to the drug during catheterization. Follow-up data for three years is presented.

**RESULTS**

Findings of the clinical history and the ECGs are shown in Figure 1. Table 1 shows the observed values expressed as percent of predicted normal values for the vital capacity, total lung capacity, mid-expiratory flow rate, residual volume, and maximal breathing capacity. Table 2 shows the physiologic dead space (Vd ml), the PaCO₂ mm Hg, the P(A-a)O₂ mm Hg, the PaO₂ mm Hg, A-V Do₂ vol percent, mean arterial pressure, SAR, and the right ventricular work before and after isoproterenol. Figure 2 shows the changes in the systolic pulmonary artery pressure, observed after the infusion or sublingual administration of isoproterenol. The relationship between the CI and the mean pulmonary pressure, and between CI and the calculated PAR is shown in Figures 3 and 4. The WP was found to be within normal limits at rest and remained unchanged after administration of isoproterenol.

Significant P values as a group were obtained in relation to the heart rate (at two min and five min), CI, PAR, and mean PAP, after isoproterenol.

After the favorable cardiorespiratory response, cases 4 and 6 began receiving sublingual isoproterenol. The asymptomatic patient (case 4) was given the sublingual 15 mg tablet every four hours, while the symptomatic patient (case 6) was given the glosset every three hours. After three years, isoproterenol has been well tolerated by case 4 with no side effects. During the first three weeks, case 6

<table>
<thead>
<tr>
<th>No</th>
<th>Case</th>
<th>Sex</th>
<th>Duration of illness (years)</th>
<th>Dyspnea</th>
<th>Chest pain</th>
<th>Syncope</th>
<th>Cyanosis (night)</th>
<th>Hemoptysis</th>
<th>Clubbing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>21</td>
<td>4</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>14</td>
<td>11</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>9</td>
<td>6</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>6</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>15</td>
<td>11</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>20</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
</tbody>
</table>

**Table 1—*Lung Volume Data***

<table>
<thead>
<tr>
<th></th>
<th>% Pred</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC</td>
<td></td>
<td>75</td>
<td>73</td>
<td>80</td>
<td>95</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>RV&gt;100</td>
<td></td>
<td>10</td>
<td>60</td>
<td>10</td>
<td>50</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>TLC</td>
<td></td>
<td>90</td>
<td>90</td>
<td>98</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>MEFR</td>
<td></td>
<td>50</td>
<td>60</td>
<td>80</td>
<td>70</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>MBC</td>
<td></td>
<td>90</td>
<td>70</td>
<td>80</td>
<td>75</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

*VC = vital capacity, RV = residual volume, TLC = total lung capacity, MEFR = mid-expiratory flow rate, and MBC = maximal breathing capacity.*

**ISOPROTERENOL IN PULMONARY ARTERY HYPERTENSION**

293

CHEST, 79: 3, MARCH, 1981
Table 2—Cardiopulmonary Function Data

<table>
<thead>
<tr>
<th>Case</th>
<th>Vd ml</th>
<th>P(A-a)O₂ mm Hg</th>
<th>PsO₂ mm Hg</th>
<th>PaCO₂ mm Hg</th>
<th>A-V Dif O₂ Vol %</th>
<th>Mean SAP mm Hg</th>
<th>SAR, dyn sec cm⁻²</th>
<th>RVW, kg m min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>1</td>
<td>270</td>
<td>350</td>
<td>5</td>
<td>12</td>
<td>85</td>
<td>75</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>198</td>
<td>10</td>
<td>5</td>
<td>70</td>
<td>80</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>220</td>
<td>250</td>
<td>30</td>
<td>30</td>
<td>50</td>
<td>45</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>180</td>
<td>140</td>
<td>24</td>
<td>16</td>
<td>55</td>
<td>60</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>110</td>
<td>110</td>
<td>16</td>
<td>15</td>
<td>72</td>
<td>75</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>250</td>
<td>15</td>
<td>12</td>
<td>80</td>
<td>85</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>X</td>
<td>176</td>
<td>215</td>
<td>16</td>
<td>15</td>
<td>68</td>
<td>70</td>
<td>32</td>
<td>31.6</td>
</tr>
</tbody>
</table>

±1 SD 65 86 9 8 13 14 2 2 1.35 1.39 10 6 221 270 1.1 1.4

*VD = physiologic dead space, P(A-a)O₂ = alveolar-arterial O₂ difference, A-V Dif O₂ = arteriovenous oxygen difference, SAP = mean systemic arterial pressure, SAR = systemic arterial resistance, RVW = right ventricular work, B = before isoproterenol, and A = after isoproterenol.

exhibited a beneficial symptomatic effect (relief of dyspnea). The favorable effect was lost, and side effects of the drug were noticed (mild tremors, headache, and transient palpitations). The dose was reduced to 15 mg every four hours, and the adverse reactions disappeared.

One year after treatment with the tablets of isoproterenol hydrochloride, a second study of the respiratory-cardiohemodynamic functions was performed. The medication was stopped 72 hours before the study. A similar basal mean PAP was found, and the same favorable cardiopulmonary response to 15 mg of sublingual isoproterenol obtained. This dose, given every three hours, was reinitiated, and no side effects were noted. Once every year hemo-

Figure 2. Changes in systolic pulmonary artery pressure (SPAP) observed after (A) infusion or sublingual administration of isoproterenol.

Figure 3. Relationship between mean pulmonary artery pressure (PAP) and cardiac index (CI) before (B) and after (A) isoproterenol. Significant p values obtained.
dynamic studies have been done while the patient receives the medication, and a favorable effect of chronic sublingual isoproterenol has been proved, since the mean PAP has been found in the levels of 25 to 26 mm Hg. Case 4 has been studied on a yearly basis, and a mean PAP of 16 to 18 mm Hg has been shown. Table 3 shows hemodynamic follow-up data on cases 4 and 6.

**Discussion**

The clinical and basal cardiopulmonary findings of the patient studied are similar to those previously described in PAH-UE. Hemodynamic effects of isoproterenol on the pulmonary vascular bed in man are well known. It is an effective pulmonary vasodilator given by IV infusion or sublingually. This last characteristic allows it to be used for longer-term treatment to lower the PAR in such cases as in PAH-UE. Vasocconstrictive factors, if not the direct cause of the disease, seem to play an important role in the pathogenesis of PAH-UE.

A reversible component of pulmonary vasoconstriction may be responsive to pulmonary vasodilators, as may occur with isoproterenol. Two types of responses of the pulmonary arteriolar vascular bed were observed when isoproterenol was administered. One group presented an unfavorable response, characterized by the usual positive chronotropic action of isoproterenol on the heart, followed by slight increase of pulmonary arterial blood flow. The PAR reduction remained four- to five-fold above the normal values (Fig 4). Some showed a worsening in lung gas exchange (Table 2). The decrease of PAR was mainly due to the chronotropic-inotropic action on the heart and not primarily to active pulmonary vasodilation. The effect was considered favorable when, after the main chronotropic-inotropic action of isoproterenol with the observed increase in CI, there was a significant fall of PAR to normal or close to normal values (Fig 3 and 4). This decrease of PAR was due to active pulmonary vasodilation and/or the observed increase in cardiac index, which also caused dilation of the pulmonary vascular bed. Therefore, the hemodynamic features suggest that isoproterenol counteracts the vasoconstriction of the pulmonary vessels present in some patients with PAH-UE. Isoproterenol could produce a favorable effect on lung gas exchange despite the cost of a nondesirable hemodynamic response. This situation is encountered in one case with a systolic PAP greater than 90 mm Hg (Table 2, case 2). However, in other cases both favorable responses could be elicited with this bronchovasoactive drug. The respiratory-hemodynamic data show that isoproterenol could not be prescribed in PAH-UE without prior monitoring of cardiopulmonary function.

Patients with systolic PAP < systolic SAP could show favorable cardiopulmonary response to isoproterenol. Unfortunately, the majority are not clinically detected until the disease is well advanced (systolic PAP or > systolic SAP). It would be rare to

<table>
<thead>
<tr>
<th>Case</th>
<th>B</th>
<th>A</th>
<th>After 1 Year</th>
<th>After 2 Years</th>
<th>After 3 Years</th>
<th>UT</th>
<th>UT</th>
<th>UT</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>PAP mm Hg</td>
<td>56</td>
<td>17</td>
<td>18</td>
<td>16</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CI L/m²</td>
<td>4.3</td>
<td>5.7</td>
<td>5.6</td>
<td>5.6</td>
<td>5.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PAR desc×²</td>
<td>1125</td>
<td>205</td>
<td>230</td>
<td>180</td>
<td>213</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>PAP mm Hg</td>
<td>35</td>
<td>26</td>
<td>36*</td>
<td>25</td>
<td>26</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CI L/m²</td>
<td>2.1</td>
<td>3.5</td>
<td>2.3</td>
<td>3.8</td>
<td>3.7</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PAR desc×²</td>
<td>800</td>
<td>210</td>
<td>750</td>
<td>247</td>
<td>273</td>
<td>258</td>
<td></td>
</tr>
</tbody>
</table>

Note: B = Before and A = after isoproterenol, UT = under treatment with sublingual isoproterenol, PAP = mean pulmonary artery pressure, CI = cardiac index, PAR = pulmonary arteriolar resistance desc ×² = dynes sec cm⁻⁵. *Medication was stopped 72 hours before the study.
obtain a favorable response with isoproterenol at
this stage. Despite an important reversible com-
ponent of pulmonary arterial constriction, which
may be responsive to isoproterenol, progression of
the underlying disease has been observed. With
isoproterenol this progression could be delayed. This
could be an explanation for the beneficial effect of
isoproterenol therapy on the evolution of Shetigar's patient and of cases 4 and 6 of our study. The asymptomatic cases may receive more benefit from treatment because of the relatively greater reversible component of pulmonary vaso-
constriction.

More cases of PAH-UE with a favorable cardiopulmonary response to isoproterenol should be studied. The prolonged follow-up will further understand the role of isoproterenol in PAH-UE. Meanwhile its use is justified in those cases with a favorable cardiopulmonary response until there is proof of deleterious effect and while no other specific therapy is available.

REFERENCES
1. Shepherd JT, Edwards JE, Burchell HB, Swan HJC, Wood EH. Clinical, physiological and pathological considerations in patients with idiopathic pulmonary hyper-
tension. Br Heart J 1957; 19:70
2. Wagenvoort CA, Wagenvoort N. Primary pulmonary hypertension; a pathological study of the lung vessels in 156 clinically diagnosed cases. Circulation 1970; 42:1163
3. Lupi HE, Bialostocky D. Respuesta cardiopulmonar al ejercicio en pacientes con hipertensión arterial pulmonar de etiología desconocida. Arch Inst Cardiol Méx 1979; 49:969
13. Dubois D, Dubois EF. A formula to estimate the approximate surface area if height and weight are known. Arch Intern Med 1916; 17:863