Primary Pulmonary Hypertension in a Child

Response to Pharmacologic Agents

By B. N. SATYANARAYANA Rao, M.B., B.S., James H. Moller, M.D., and Jesse E. Edwards, M.D.

SUMMARY
Clinical, pharmacologic, and pathologic findings presented are those in a 12-year-old boy with primary pulmonary hypertension associated with medial hypertrophy of the pulmonary muscular arteries and arterioles.

Intrapulmonary arterial administration of acetylcholine, tolazoline (Priscoline), or isoproterenol resulted in a fall in pulmonary vascular resistance and pressure.

Perforation of the right ventricle by an indwelling catheter terminated studies on the results of long-term intrapulmonary arterial administration of drugs shown to be effective.

Additional Indexing Words:
Acetylcholine  Tolazoline  Isoproterenol  Intrapulmonary arterial drug therapy

Since Romberg's description in 1891 of a case of primary pulmonary hypertension, numerous examples of this condition have been reported. From this background, the concept has evolved that primary pulmonary hypertension is a progressive, fatal condition, unresponsive to therapeutic attempts, and related to fixed pulmonary vascular changes.

In a few patients, however, administration of certain drugs has been followed by a decrease in pulmonary vascular resistance and pressure (table 1).

The primary purpose of this report is to describe the case of a 12-year-old boy with primary pulmonary hypertension in whom isoproterenol, tolazoline (Priscoline), and acetylcholine each resulted in a three to fourfold decrease in total pulmonary vascular resistance. After the patient died from an unfortunate complication, necropsy showed the principal structural abnormality of the pulmonary arterial vessels to be medial hypertrophy, a process which suggests the potential of vasodilatation.

Report of Case

Clinical Features

A 12-year-old boy, on admission to the University of Minnesota Hospitals, presented a history of well-being until 2 years earlier when dizzy spells, syncope, headaches, and chest pain began. Initially, these symptoms were considered to have resulted from an automobile accident in which the boy had been rendered temporarily unconscious. Neurologic examination following the accident failed to reveal any abnormality. Because of the symptoms named and the development of dyspnea on exertion, the patient was referred for evaluation. The family history was negative for collagen disease and pulmonary hypertension.

Physical examination revealed a slender, acyanotic, white boy in no apparent distress. The body weight was 74 pounds and the height was 58 inches. The brachial blood pressure was 92 mm Hg, systolic, and 55, diastolic, and the pulse rate was 70 beats/min. Slight cardiomegaly was associated with a diffuse left parasternal heave. While the first cardiac sound was normal, the pulmonic component of the second sound was markedly accentuated and no murmur was present. The liver was enlarged, its lower edge lying 2 cm below the right costal margin. There was no

From the Department of Pathology, the Charles T. Miller Hospital, St. Paul, Minnesota, and the Departments of Pediatrics and Pathology, University of Minnesota, Minneapolis, Minnesota.

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Table 1

Summary of Reported Response to Short-Term Intravenous or Intrapulmonary Arterial Administration of Various Drugs in Primary Pulmonary Hypertension*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Positive</th>
<th>Equivocal</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolazoline†</td>
<td>5(3-6)</td>
<td>1(2)</td>
<td>1(7)</td>
<td>7</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>3(8-10)</td>
<td>2(8,11)</td>
<td>2(8,11)</td>
<td>7</td>
</tr>
<tr>
<td>Hexamethonium</td>
<td>1(5)</td>
<td>0</td>
<td>1(2)</td>
<td>2</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>3(12)</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

* Except one patient of Wade and Ball who was 11 years old, each subject was an adult, the oldest being 48 years of age.
† Hemodynamic response unknown in two cases.1

clinical evidence of systemic disease, chronic pulmonary disease, or chronic obstruction of the airways.

An electrocardiogram revealed right axis deviation (+ 130°), evidence of right atrial enlargement, right ventricular hypertrophy, and inverted T waves in leads V1 to V4. The vectorcardiogram showed signs of severe right ventricular hypertrophy. Thoracic roentgenograms revealed normal cardiac size and dilatation of the pulmonary trunk and of both the pulmonary arteries. There was attenuation of the peripheral pulmonary vascular markings.

Laboratory studies gave the following results: hemoglobin, 14.9 g/100 ml of blood; hematocrit, 43%; sedimentation rate performed twice, 31 and 17 mm per hr.; LE clot test, negative; serum electrolytes, normal; urinalysis, normal; coagulation profile, normal.

Scintiscan of the brain gave negative results, and the electroencephalogram was mildly abnormal but without focal abnormalities.

On the basis of the clinical analysis, a presumptive diagnosis of primary pulmonary hypertension was made, and cardiac catheterization was performed. This study showed severe pulmonary hypertension with a pulmonary arterial pressure at rest of 82/45 and an electronically measured pressure of 60 mm Hg. Simultaneously determined systemic arterial pressure was 120/80, with a mean of 94 mm Hg. The pulmonary "arterial wedge" pressure was normal, the mean being 7 mm Hg. There was no evidence of any shunt. The right atrial pressure was normal (mean 6 mm Hg). The levels of systemic arterial blood gases were: Po2, 81.6 mm Hg; Pco2, 31 mm Hg; and pH, 7.42. These findings were considered to exclude veno-arterial shunting, obstructive pulmonary disease, and hypoxic pulmonary hypertension related to hypoventilation. Failure of the pulmonary arterial pressure to change during inhalation of 100% oxygen further excluded hypoxia as a basis for the pulmonary hypertension. Simultaneous analysis of alveolar gas (end expiration) and of arterial blood gases revealed no alveolar-arterial gradient of Pco2, thereby excluding any major ventilation-perfusion defects. Right ventriculography showed a large right ventricular cavity, massively dilated pulmonary arteries, and marked attenuation of the peripheral pulmonary vasculature. There was no evidence for the presence of gross pulmonary emboli.

The findings of the cardiac catheterization, therefore, strongly favored primary pulmonary hypertension, although multiple microscopically sized pulmonary emboli could not be excluded. To study the reactivity of the pulmonary vascular bed, hemodynamic measurements were made during exercise and during infusion of pharmacologic agents. The results are summarized in figure 1. At rest, the cardiac output was at the lower limits of normal and the pulmonary arterial pressure elevated, indicating a high degree of pulmonary vascular resistance. Inhalation of 100% oxygen at rest showed no significant change in any of the measured parameters.

Development of fatigue limited the amount of exercise possible. With exercise, the systemic blood pressure and cardiac output increased only slightly, while the pulmonary arterial pressure rose to nearly equal the systemic pressure. Infu-

Figure 1

Physiologic parameters in the resting state and under varying conditions, as obtained during the first study.
sion of acetylcholine (1 mg/min for 10 min) and isoproterenol (Isuprel) (2 μg/min for 13 min) separately were each accompanied by a significant increase in the cardiac output with marked reduction of the pulmonary arterial pressure. The mean systemic arterial pressure remained unchanged. The results, therefore, indicated a marked elevation of pulmonary vascular resistance at rest which was remarkably responsive either to acetylcholine or to isoproterenol. Following this study, the patient was discharged without any medication prescribed. Within a few weeks, he experienced further dizziness, syncope, and decrease in exercise tolerance. When the patient was readmitted for further evaluation, the effects of tolazoline and isoproterenol upon the pulmonary arterial resistance were tested with a view to subsequent therapy. The second cardiac catheterization (fig. 2) showed essentially the same fundamental abnormalities as the first. Infusion of 2 μg/min of isoproterenol for 10 min resulted in significant decrease in pulmonary arterial pressure and vascular resistance. This change persisted during the period of infusion and for a few minutes thereafter. Beyond that, there was a gradual elevation of pulmonary arterial pressure. Twenty minutes after discontinuation of the infusion, the pulmonary arterial pressure had risen to the pre-infusion level. Injection of 30 mg of Priscoline into the pulmonary artery over a period of about 45 sec was followed within a few minutes by a significant decrease in the pulmonary arterial pressure to about 40 mm Hg. The pressure remained at this level for more than 60 min. While in the hospital, the patient was then given Priscoline orally and his progress was followed including measurement of systemic blood pressure. The initial oral dose of Priscoline was 25 mg/day. The dose was gradually increased to 25 mg four times a day. There were no evident clinical changes, although he exhibited cutaneous flushing. The oral dose of Priscoline was further increased to 25 mg six times a day.

During this course, the systemic blood pressure remained unchanged, although the patient continued to have episodes of syncope, some of which were associated with convulsions. After 2 weeks of this therapy, cardiac catheterization was performed. The pulmonary arterial pressure (90/50) and calculated resistance (1400 dynes sec cm⁻⁵) were at the previous hypertensive levels. The administration of Priscoline by mouth was discontinued. The oral administration of guanethidine (10 mg/day) and digitalization did not alter the clinical picture.

It was then decided to place an indwelling catheter in the pulmonary artery for administration of drugs and measurement of pressure.

For this purpose a no. 5 Teflon catheter was advanced from an antecubital vein into the main pulmonary artery and secured. Initially, Priscoline was used in a constant infusion into the pulmonary artery but in pulmonary arterial pressure was only slightly reduced (fig. 3). Use of this drug was discontinued. Isoproterenol infusion was then started (0.1 to 0.4 μg/min). With this drug, the mean pulmonary arterial pressure fell to an even level between 20 and 35 mm Hg. During this period, the patient's blood pressure ranged from 90/60 to 120/80 mm Hg. Six days after the catheter had been secured in the pulmonary artery, the patient developed severe thoracic pain, respiratory distress, and cyanosis. Roentgenograms of the thorax revealed enlargement of the cardiac shadow. Withdrawal of a serosanguineous fluid (100 cc) from the pulmonary arterial catheter was considered evidence of perforation of the pulmonary artery or right ventricle, with the open end of the catheter in the pericardial cavity. The cardiac catheter was withdrawn. Temporary improvement was followed by recurrent signs and symptoms of cardiac tamponade. Thoracotomy revealed 500 cc of blood in the pericardial sac and a perforation in the outflow tract of the right ventricle. The blood was removed, and the perforation was sutured. During the operation, the patient had repeated episodes of bradycardia and cardiac arrest from which he was resuscitated. In the immediate postoperative period, the patient developed hypotension and bradycardia from which he could not be resuscitated and death occurred.

![Figure 2](http://circ.ahajournals.org/Download/281661)

**Figure 2**

Hemodynamic parameters in the various conditions, as obtained during the second study.

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Mean pulmonary arterial pressure under conditions of variations in administration of tolazoline (Priscoline) and isoproterenol (Isuprel).

Pathologic Features

Pertinent findings at necropsy were limited to the heart and lungs. The heart was enlarged (330 g) on the basis of a markedly dilated and hypertrophied right ventricle. The latter measured 0.8 cm in thickness. The left ventricular thickness was 1.4 cm. There was a small sutured perforation of the anterior wall of the right ventricular outflow tract just below the pulmonary valve. The pericardial sac contained a small amount of residual blood. Except for the right ventricular hypertrophy, there were no intracardiac lesions, either congenital or acquired. The foramen ovale showed a valvular competent patency. The ventricular septum was intact and no sign of a spontaneously closed defect was present. The ductus arteriosus was represented by a ligament with no unusual features.

The pulmonary trunk, which was markedly dilated, measured 7.0 cm in diameter and was wider than the aorta, which was 5.5 cm in diameter. The wall of the pulmonary trunk and of its two branches was thickened. Intimal atherosclerotic plaques were present in small numbers. There was no evidence of gross pulmonary emboli or infarcts.

Histologically, the pulmonary trunk showed thickening of the intima with accumulation of foam cells. Marked thickening of the media by elastic tissue and cystic medial necrosis were also present. The histologic pattern of the media was similar to that of the aorta. The muscular pulmonary arteries and arterioles in both lungs showed medial hypertrophy (fig. 4) as a general characteristic, and intimal fibrous thickening of minimal extent was present in isolated small arteries. The pulmonary capillaries, venules, and parenchyma were normal.

Comment

Primary pulmonary hypertension is commonly regarded as a progressive, eventually fatal, condition related to fixed pulmonary vascular changes.

In those cases following such a course, the process is understandable when the basis for pulmonary hypertension is organic fibrous obstruction of the small pulmonary arterial vessels. It is recognized, however, that, in addition to cases of primary pulmonary hypertension in which intimal lesions seem primary, there is a second type of primary pulmonary hypertension. The latter type is characterized structurally by medial hypertrophy of the small arterial vessels of the lung. On hypothetical grounds, such cases would be expected to respond with a fall in pulmonary arterial pressure under appropriate vasodilatory stimulus.

The case reported conforms anatomically to the latter type.
The structure of the media of the pulmonary trunk resembled that of the aorta. This suggests strongly that the pulmonary hypertension had been present from birth.\(^{14}\)

The significance of the clinical studies are that administration of certain drugs (acetylcholine, Priscoline, and isoproterenol) resulted in a fall in pulmonary arterial pressure. It was of practical importance, however, that high dosage and intrapulmonary arterial administration were required to achieve the desired effect. It is, as yet, unknown whether long-term intrapulmonary arterial administration would have (1) continued to be effective or (2) been followed by a break in the factor which led to the pulmonary arterial vasoconstriction responsible for the pulmonary hypertension. In our study, the complication of perforation of the right ventricle by the indwelling catheter terminated the life of the patient and therefore precluded the long-term study desired.

Review of the literature indicates that several drugs have been tested for hemodynamic response in primary pulmonary hypertension. The results of these studies are summarized in table 1. It is evident that, of the four drugs used, each by short-term intravenous or intrapulmonary arterial administration, tolazoline or acetylcholine were tried more than the other two drugs, namely, hexamethonium and isoproterenol. According to these reports, varying results were obtained with each of the two major drugs, although more commonly a favorable hemodynamic response was obtained than an equivocal or negative one.

References