Prostaglandin $F_{2\alpha}$ and Indomethacin in Hepaticogenic Pulmonary Angiodysplasia

Effects on Pulmonary Hemodynamics and Gas Exchange

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We treated a 68-year-old man with cirrhosis of the liver associated with moderate hypoxemia. Contrast-enhanced echocardiography revealed late opacification of the left ventricle, and pulmonary perfusion imaging with $^{99m}$Tc macroaggregated albumin showed evidence of a significant uptake in both lungs and in the liver, spleen, and kidneys. Right cardiac catheterization revealed pulmonary hypertension, low pulmonary vascular resistance, and high cardiac output. We administered prostaglandin $F_{2\alpha}$ intravenously (0.2 µg/kg/min for 30 minutes) and indomethacin orally (75 mg/day for three days). There was some degree of resolution of the hypoxemia and increases in both pulmonary arterial pressure and pulmonary vascular resistance. These findings suggest that the pathophysiology of hepatic pulmonary angiodysplasia is a reversible intrapulmonary vascular dilatation. These conditions can to some extent be modulated by vasoactive substances such as prostaglandins or other eicosanoids.

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Large intrapulmonary right-to-left shunt, ventilation-perfusion mismatching, and diffusion limitation seem to be major causes of moderate to severe hypoxemia in patients with cirrhosis of the liver.1,2 Krowka2 stated that intrapulmonary vascular dilatation may account for these pathophysiologic abnormalities. Resolution of intrapulmonary right-to-left shunt ratio can occur following liver transplantation for a patient with primary biliary cirrhosis3 and also during the treatment of cirrhotic patients.4 Therefore, intrapulmonary vascular dilatations in the case of cirrhosis of the liver seem to be reversible changes modulated by vasoactive substances.

Various circulating vasoactive substances, including glucagon, endothelin, atrial natriuretic polypeptide, PGs, and other substances may be etiologic factors linked to the intrapulmonary vascular dilatation seen in patients with cirrhosis of the liver.5 We report herein comparative studies concerning pulmonary hemodynamics and gas exchange before and after the administration of PGF$_{2\alpha}$ and indomethacin to a patient with hepaticogenic pulmonary angiodysplasia.

CASE REPORT

A 68-year-old man was referred to our hospital because of dyspnea. He had no history of tobacco or alcohol abuse. On admission, physical examination disclosed mild cyanosis of the lips and nail beds, and clubbing of the fingers. Routine laboratory chemistry revealed the following values: red blood cell count, 360 × 10⁶/cu mm; hemoglobin, 9.7 g/dl; white blood cell count, 2,100/cu mm; platelet count, 7.0 × 10⁹/cu mm; serum total bilirubin, 1.5 mg/dl; serum albumin, 3.2 g/dl; serum AST, 73 IU; serum ALT, 33 IU; and LDH, 224 IU. Additional studies revealed a prothrombin time of 14.5 seconds (with control 11.8 seconds), partial thromboplastin time of 58.0 seconds (with control 37.1 seconds), and plasma retention rate of indocyanine green at 15 minutes, 48.6 percent. Serum hepatitis B surface antigen, antibody to hepatitis B surface antigen, and antibody to hepatitis C virus antigen were all negative. On laparoscopic observation, the liver was nodular, and histologic findings revealed an established macronodular cirrhosis.

Arterial blood gas analyses obtained in the supine position showed the following: $P_{O_2}$, 62 mm Hg; $P_{CO_2}$, 92 percent; $P_{CO_2}$, 32 mm Hg; and $P(A-a)O_2$, 55 mm Hg (Table 1). The $P_{O_2}$ was decreased 6 mm Hg when the man was standing. The physiologic shunt ratio ($Q_s/Q_t$) was 2.8 percent when the standard shunt equation was used under conditions of 100 percent oxygen inhalation ($P_{O_2}$ was elevated to 626 mm Hg). Chest roentgenograms, electrocardiogram, echocardiogram, and pulmonary functions were within normal limits, except for a low diffusing capacity (44 percent). Contrast-enhanced echocardiography showed a delayed opacification of the left ventricle, findings suggesting intrapulmonary vascular dilatation. The pulmonary perfusion imaging by $^{99m}$Tc macroaggregated albumin revealed a significant uptake in both lungs and in the liver, spleen, and both kidneys (Fig 1). The shunt ratio was 13 percent, as estimated by the quantitative radionuclide method. Right cardiac catheterization revealed pulmonary hypertension, low pulmonary vascular resistance, and high cardiac output (Table 2). With the intravenous infusion of PGF$_{2\alpha}$ (0.2 µg/min/kg for 30 minutes), known to be a vasodilator in the pulmonary circulation,6 $P_{O_2}$ was elevated to 73 mm Hg from 62 mm Hg, and $P(A-a)O_2$ decreased to 44 mm Hg from 55 mm Hg (Table 1). The results of a hemodynamic study after PGF$_{2\alpha}$ revealed an increase in pulmonary vascular resistance, pulmonary arterial pressure, and cardiac output (Table 2).

Arterial blood gas levels, pulmonary hemodynamics, and urinary excretion of PGs were estimated before and after indomethacin. In order to avoid the interference of right cardiac catheterization on pulmonary hemodynamics, indomethacin was given one week later. Indomethacin was administered at a dose and duration that sufficiently inhibits PG synthesis and affects the vascular reactivity (75 mg/day for three days).8 Urinary 6-keto-PGF$_{1\alpha}$, thromboxane $B_2$, and 6-epi-Prostaglandin $F_2$ were measured in a 24-hour urine sample before and after indomethacin administration. Urinary 6-keto-PGF$_{1\alpha}$"}

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**Table 1—Effects of PGF$_{2\alpha}$ and Indomethacin on Pulmonary Gas Exchange**

<table>
<thead>
<tr>
<th>Data</th>
<th>Before</th>
<th>After PGF$_{2\alpha}$</th>
<th>Before</th>
<th>After Indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{O_2}$ mm Hg</td>
<td>62</td>
<td>73</td>
<td>63</td>
<td>67</td>
</tr>
<tr>
<td>$P_{CO_2}$ mm Hg</td>
<td>32</td>
<td>33</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>$P_{CO_2}$ percent</td>
<td>92</td>
<td>95</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>$P(A-a)O_2$ mm Hg</td>
<td>55</td>
<td>44</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>pH</td>
<td>7.43</td>
<td>7.43</td>
<td>7.42</td>
<td>7.44</td>
</tr>
</tbody>
</table>

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and PGE₂ were measured using a commercially available radioimmunoassay kit (New England Nuclear). The patient was given a regular diet containing 7 g of sodium chloride. Urinary 6-keto-PGF₁α, PGE₂, and thromboxane B₂ were reduced from 406 ng/day, 294 ng/day, and 294 ng/day to 129 ng/day, 43 ng/day, and 56 ng/day after indomethacin, respectively. On the other hand, PaO₂ was gradually elevated to 69 mm Hg from 62 mm Hg, and Pa(A-a)O₂ was reduced to 48 mm Hg from 55 mm Hg (Table 1). The results of hemodynamic studies revealed an increase in pulmonary vascular resistance and a decrease in cardiac output, as shown in Table 2. Although significant changes in pulmonary hemodynamics and gas exchange were observed after the ingestion of indomethacin, hypoxemia remained. Moreover, results of contrast-enhanced echocardiography remained positive for intrapulmonary vascular dilatations. During these studies, hepatic functions (AST, ALT, LDH, bilirubin, and prothrombin time) did not basically change. Although clinically obvious hepatorenal syndrome did not occur, indomethacin was discontinued because of a reduction in creatinine clearance (from 62 ml/min to 54 ml/min).

Table 2—Effects of PGE₂ and Indomethacin on Pulmonary Hemodynamics

<table>
<thead>
<tr>
<th>Data*</th>
<th>Before</th>
<th>After PGE₂</th>
<th>72 hr after Indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qt, L/min</td>
<td>6.02</td>
<td>6.54</td>
<td>5.29</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>3.74</td>
<td>4.07</td>
<td>3.26</td>
</tr>
<tr>
<td>Fsa, mm Hg</td>
<td>89</td>
<td>107</td>
<td>95</td>
</tr>
<tr>
<td>Fra, mm Hg</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Ppa, mm Hg</td>
<td>9</td>
<td>13</td>
<td>10.5</td>
</tr>
<tr>
<td>Fcw, mm Hg</td>
<td>6</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Ppa-Fcw, mm Hg</td>
<td>3</td>
<td>4</td>
<td>3.5</td>
</tr>
<tr>
<td>TPRI, dynes/cm²·m²</td>
<td>193</td>
<td>256</td>
<td>258</td>
</tr>
<tr>
<td>PVRI, dynes/cm²·m²</td>
<td>64</td>
<td>79</td>
<td>86</td>
</tr>
<tr>
<td>SVRI, dynes/cm²·m²</td>
<td>1,904</td>
<td>2,103</td>
<td>2,339</td>
</tr>
</tbody>
</table>

*Qt, Cardiac output; CI, cardiac index; Fsa, mean systemic arterial pressure; Fra, mean right atrial pressure; Ppa, mean pulmonary arterial pressure; Fcw, mean capillary wedge pressure; Ppa-Fcw, driving pressure; TPRI, total pulmonary resistance index; PVRI, pulmonary vascular resistance index; and SVRI, systemic vascular resistance index.

DISCUSSION

In the present case, worsening of PaO₂ in the standing position (orthodeoxia) and diffusion limitation were noted. Contrast-enhanced echocardiography disclosed delayed opacification of the left ventricle, and pulmonary perfusion imaging by ¹²³I macroaggregated albumin revealed a significant uptake in the lungs, liver, spleen, and both kidneys. A discrepancy was noted between the physiologic shunt ratio and percentage of right-to-left shunt, as estimated by the quantitative radionuclide method. These observations are compatible with the findings in hepatic pulmonary angiodysplasia.³

Recent studies showed that cardiopulmonary hemodynamics in hepatic pulmonary angiodysplasia revealed evidence of pulmonary hypotension, low pulmonary vascular resistance, and high cardiac output.¹² Indeed, cardiopulmonary hemodynamics in our patient were also consistent with these findings. These pathophysiologic abnormalities seem to be caused by intrapulmonary vascular dilatations, and various circulating vasoactive substances may be the etiologic factors.³ Hypoxic pulmonary vasoconstriction can be blunted in patients with cirrhosis of the liver.⁹ The administration of indomethacin will lead to a recovery of vascular sensitivity to vasoconstrictors such as angiotensin II in patients with cirrhosis of the liver¹⁰ and potentiates hypoxic pulmonary vasoconstriction in animal experiments.¹¹ In addition, excess production of various PGs has been noted in patients with cirrhosis of the liver.¹⁰¹² All of this evidence taken together led to the notion that predominance of vasodilative PGs or other eicosanoids (or both) may be one etiologic factor related to intrapulmonary vascular dilatations in patients with cirrhosis of the liver.

We reported that some resolution of the hypoxemia occurred after the ingestion of indomethacin, together with a significant change in the pattern of dynamic pulmonary perfusion imaging in a patient with hepatic pulmonary angiodysplasia.¹⁰ The changing pattern was similar to findings seen with spontaneous resolution of hepatopulmonary angiodysplasia noted during treatment of a patient with decompensated cirrhosis of the liver.⁴ At that time, it was not possible to monitor the pulmonary hemodynamics. In the present case, some resolution of hypoxemia, an increase in pulmonary and systemic vascular resistance, and a decrease in cardiac output were evident after the administration of indomethacin. These hemodynamic changes are compatible with the data of Bruix et al.¹⁴ Indomethacin may improve oxygenation, not only by intrapulmonary vasoconstriction but also by decreasing cardiac output. On the other hand, increases in both cardiac output and pulmonary vascular resistance were noted after administration of PGE₂.¹⁵ These results are also similar to the data of Scherer et al.⁷ The PGE₂ may improve oxygenation mainly through intrapulmonary vasoconstriction.

Other investigators reported that the effects of indomethacin on the pulmonary circulation are relatively slight and with little clinical significance in patients with cirrhosis of the liver;¹³,¹⁴ however, these results were obtained after only one day of administration of indomethacin.¹⁴ In our study, three days were required for indomethacin to have sufficient effects on pulmonary hemodynamics and gas exchange. Thus, some time lag may be required for cyclooxygenase
inhibition. In addition, the effects of this drug may not be uniform in patients with cirrhosis of the liver, and cyclooxygenase inhibition may have greater effects on pulmonary hemodynamics and gas exchange in patients with hepaticogenic pulmonary angiodysplasia than in their counterparts. Although the effects of PGF<sub>2α</sub> and indomethacin on the pulmonary circulation were thought to be significant in this case, the hypoxemia remained. Thus, the predominance of vasodilatative PCs may not be the only etiologic factor linked to hepaticogenic pulmonary angiodysplasia.

In summary, hepaticogenic pulmonary angiodysplasia seems to be a state of reversible intrapulmonary vascular dilatation, and the predominance of vasodilatative PGs or other eicosanoids (or both) may contribute to the dilatation of intrapulmonary vascular systems.

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REFERENCES


Fatal Pulmonary Aspergillosis Presenting as Acute Eosinophilic Pneumonia in a Previously Healthy Child*

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A previously healthy boy presented with cough and diffuse pulmonary interstitial infiltrates. Acute eosinophilic pneumonia was diagnosed by bronchoalveolar lavage in the absence of a demonstrable infectious etiologic agent. Corticosteroid therapy resulted in immediate improvement but was followed by respiratory distress and death from invasive aspergillosis and Pseudomonas cepacia sepsis.

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Eosinophilic pneumonia and pulmonary aspergillosis each make up a clinical spectrum that may overlap and be difficult to differentiate. Corticosteroids are the mainstay of treatment in noninvasive disease. We describe a fatal case of invasive pulmonary aspergillosis presenting as an eosinophilic pneumonia treated with corticosteroids.

CASE REPORT

An 11-year-old boy was seen by his physician because of dyspnea, fever, and cough. A chest roentgenogram showed diffuse infiltrates. He was hospitalized and treated with intravenous erythromycin, but was transferred to Children's Hospital of Pittsburgh because of progressive dyspnea.

There was no history of wheezing or asthma in the patient or family members. The patient had played with his two siblings in a compost pile 8 h before his symptoms developed.

He was a white boy in respiratory distress with suprasternal and intercostal retractions. The temperature was 38.5°C; the respiratory rate, 60/min; the heart rate, 129/min; and the blood pressure, 110/56 mm Hg. On auscultation of the chest, there were no adventitious sounds.

The white blood cell count was 15,300/cu mm with 87 percent neutrophils, 3 percent band forms, 2 percent lymphocytes, 1 percent monocytes, and 8 percent eosinophils. Arterial blood gas values with the patient receiving 3 L O<sub>2</sub>/min by nasal cannula showed a pH of 7.46, P<sub>CO<sub>2</sub></sub> of 17 mm Hg, and a P<sub>O<sub>2</sub></sub> of 111 mm Hg. The admission chest roentgenogram showed diffuse pulmonary interstitial infiltrates (Fig 1). The IgG, IgM, IgA, and IgE levels were normal. The C3, C4, and CH100 (total complement) were normal.

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