Effects of Indomethacin on Hepatogenic Pulmonary Angiodyplasia

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A patient had liver cirrhosis associated with marked hypoxemia. With administration of indomethacin (75 mg/day for six days), PaO₂ was elevated up to 50 mm Hg from 44 mm Hg. At that time, dynamic pulmonary perfusion imaging revealed a plateau time course curve of MAA uptake in the lungs, as compared with findings obtained during the state of severe hypoxemia without indomethacin. These observations suggest that part of hepatogenic pulmonary angiodyplasia is a functional vasodilatation that is presumably modulated by vasoactive substances, such as prostaglandins and/or other eicosanoids.

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The pathogenetic mechanism of hepatogenic pulmonary angiodyplasia is still unknown. Dilated alveolar capillaries and small arteriovenous shunts seem to be the major cause of severe hypoxemia in these patients. Clinical evidence of resolution of the intrapulmonary arteriovenous shunt ratio has been noted following liver transplantation in a patient with primary biliary cirrhosis and during a period of improved hepatic function in cirrhotic patients. In view of these findings, venous admixtures in the pulmonary circulation may be caused by a functional vasodilatation rather than an anatomically fixed arteriovenous shunt in patients with hepatogenic pulmonary angiodyplasia.

Abnormal production of various circulating vasoactive substances such as prostaglandins, atrial natriuretic polypeptide, renin-angiotensin system, and some other substances have been linked to the pathophysiologic conditions in the patients with liver cirrhosis. As these vasoactive substances could affect the pulmonary circulation and gas exchange, development of hepatogenic pulmonary angiodyplasia may be influenced by these vasoactive substances. We report herein comparative findings concerning serial dynamic pulmonary perfusion imaging before and after the administration of prostaglandin synthesis inhibitor, indomethacin, in a patient with hepatogenic pulmonary angiodyplasia.

Case Report

A 62-year-old cyanotic man was admitted to the hospital with exacerbating dyspnea. Physical examinations disclosed cyanosis of mouth, lips, and nail beds, and marked clubbing of the fingers. Routine laboratory data were as follows: red blood cell count, 566 x 10⁶; hemoglobin, 12.7 g/dl; white blood cell count, 1,900/µm; platelet count, 6.6 x 10⁶; serum total bilirubin, 2.0 mg/dl; serum albumin, 3.2 g/dl; serum SGPT, 28 IU; serum SGOT, 13 IU; and LDH, 396 IU. Additional studies revealed a prothrombin time of 13.3 s with control of 11.0 s, and plasma retention rate of indocyanine green of 15 minutes, 46 percent. Serum hepatitis B surface antigen was negative. On a laparoscopic observation, the liver was nodular, and histologic findings revealed an established cirrhosis.

Arterial blood gas analysis revealed PaO₂ of 44 mm Hg, arterial oxygen saturation (SaO₂) of 82 percent, PaCO₂ of 25 mm Hg, alveolar-arterial oxygen pressure difference (P[(A-a)O₂] of 81 mm Hg, a pH of 7.45, and HCO₃⁻ of 20 mmol/L. The 7 mm Hg of decrease in PaO₂ was noted in the standing position. The "true" shunt ratio (QS/QT) was 18 percent, when the standard shunt equation was used under conditions of 100 percent oxygen inhalation (PaO₂ was elevated to 317 mm Hg). Chest roentgenograms, echocardiogram, and cardiopulmonary function were within normal limits except for low diffusion capacity (35 percent). Contrast-enhanced echocardiography disclosed delayed opacification of the left ventricle. The pulmonary perfusion imaging by technetium 99m MAA revealed a significant uptake in both lungs and in the liver, spleen, and both kidneys (Fig 1). The shunt ratio was 61 percent, as estimated by the quantitative radionuclide method. The dynamic pulmonary perfusion imaging by ¹¹¹I-MAA revealed that the MAA particles passed through the lungs in about 15 s (Fig 2A).

The PaO₂ was elevated to 49 mm Hg from 43 mm Hg by intravenous infusion of prostaglandin (PG) F₂α (0.4 µg/kg/min) for 30 minutes. The PaO₂ was returned to 43 mm Hg 30 minutes after termination of PG F₂α infusion. The urinary excretion of PGs and arterial blood gases were measured before and after indomethacin (75 mg/day for six days), which was reported to potentiate hypoxic pulmonary vasoconstriction and improve pulmonary gas exchange. Urinary 6-keto-PGF₁α (6-keto-Prostaglandin F₁α) (RIA Kit, New England Nuclear, Boston, Mass), thromboxane B₂ (thromboxane B₂ RIA Kit, New England Nuclear), and PGE (prostaglandin E RIA Kit, Baxter, Calif) were measured by radioimmunoassay under the

![Figure 1. Pulmonary perfusion imaging with ¹¹¹I-MAA reveals a significant radioisotope uptake in the lungs, liver, spleen, and both kidneys.](image_url)
Indomethacin obtained after decreased indomethacin before foretween thrombin respectively P(A-a)O, reduced Urinary time shunt the diet ofphysiologic renal function, which was elevated from 76 Hg, 44 mmHg, to 865 mmHg, 23 mmHg, and 81 mmHg, respectively. Note the more gentle slope (arrows) after the resolution of hypoxemia with indomethacin, as compared with the steep slope obtained in the period of severe hypoxemia without indomethacin.

daily diet containing 7 g of sodium chloride.

Urinary 6-keto-PG Fα and PGE were reduced from 865 ng/day and 405 ng/day to 650 ng/day and 334 ng/day, respectively, after indomethacin. Urinary excretion of thromboxane B2 was also decreased to 270 ng/day from 1,425 ng/day. On the other hand, PaO2 was elevated to 50 mm Hg from 44 mm Hg, and P(A-a)O2 was reduced to 76 mm Hg from 81 mm Hg after indomethacin. At that time, dynamic pulmonary perfusion imaging was performed, and the time course curve of uptake in lungs revealed a plateau curve after the peak activity as compared with time course curve obtained in the period of severe hypoxemia without indomethacin (Fig 2B). The shunt ratio was slightly decreased to 55 percent from 61 percent. Liver function (SGOT, SGPT, LDH, bilirubin, and prothrombin time) was basically unchanged. Because of mild deterioration of renal function, indomethacin therapy was discontinued.

**DISCUSSION**

In the present case, the pulmonary perfusion imaging by 99mTc MAA revealed a significant uptake in the lungs, liver, spleen, and both kidneys, and discrepancy was noted between physiologic shunt ratio and percentage of right-to-left shunt as estimated by the quantitative radionuclide method. Moreover, PaO2 worsened in the standing position, and contrast-enhanced echocardiography disclosed delayed opacification of the left ventricle. These results are consistent with hepatic pulmonary angiodyplasia. Recently, Stoller et al. reported that the reversibility of intrapulmonary right-to-left shunt ratio became evident following liver transplantation. Other investigators have shown similar results. These findings suggest that hepatic pulmonary angiodyplasia is a functional vasodilatation rather than pathoanatomic change.

Impaired hypoxic pulmonary vasoconstriction was noted in patients with liver cirrhosis. Indomethacin recovered the vascular sensitivity to vasoconstrictor such as angiotensin II in patients with liver cirrhosis. In addition, indomethacin potentiates hypoxic pulmonary vasoconstriction and improves the pulmonary gas exchange. From this evidence, we speculated that one of the pathogenetic factors of hepatic pulmonary angiodyplasia would be associated with the predominance of vasodilatative eicosanoids that could interfere with pulmonary gas exchange. Thus, we gave PGFα, vasoconstrictor on pulmonary vascular channel, intravenously and indomethacin orally to a patient with hepatic pulmonary angiodyplasia. As expected, PGFα and indomethacin elevated the arterial oxygen pressure and indomethacin suppressed urinary excretion of PGs.

Dynamic pulmonary perfusion imaging depicts the passage of MAA particles through the pulmonary teleangiec-tasia and the time course curve of lung uptake of MAA tends toward a plateau after resolution of hypoxemia in patients with hepatic pulmonary angiodyplasia. In the present case, the time course curve of the lung uptake of MAA was significantly changed, and the down slope was more gentle and tended toward the plateau after therapy with indomethacin and some resolution of the hypoxemia (Fig 2B, arrows). These observations suggest that, in the state of some resolution of hypoxemia with indomethacin, pulmonary capillaries would be more narrowed. The MAA particles would pass through the pulmonary vasculature more slowly and more MAA particles would be captured by pulmonary capillary beds.

The degree of resolution of hypoxemia in this case was mild and not always complete after administration of indomethacin. Various pulmonary vasooactive substances are speculated to be the causal factors of hepatic pulmonary angiodyplasia and other more effective factors may affect the pulmonary circulation. Although further studies are needed to arrive at a definite conclusion, we believe that our findings on dynamic pulmonary perfusion imaging before and after indomethacin therapy are interpreted as suggesting that predominance of vasodilatative PGs and/or other eicosanoids is one of the pathogenetic factors of hepatic pulmonary angiodyplasia.

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**REFERENCES**

Benign Thyroid Hyperplasia Presenting As Bilateral Vocal Cord Paralysis

Complete Remission Following Surgery

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A 52-year-old woman developed respiratory arrest on two separate occasions that required mechanical ventilation. Fiberoptic bronchoscopy demonstrated bilateral vocal cord paralysis, and a CT scan of the neck demonstrated a right neck mass. On surgical exploration, the mass was found extending from the thyroid gland and was identified as benign thyroid tissue. Thyroid hyperplasia should be considered in the differential diagnosis of bilateral vocal cord paralysis. (Chest 1991; 99:1029-30)

Trauma, most often iatrogenically-induced, and malignancy are the major causes of bilateral vocal cord paralysis. To our knowledge, a patient with bilateral vocal cord paralysis caused by benign thyroid gland hyperplasia has not as yet been reported.

CASE REPORT

A 52-year-old black woman with a history of hypertension, obesity, and previous alcohol abuse presented to a local hospital with increasing dyspnea and stridor requiring endotracheal intubation. She had no history of respiratory problems and had not previously been intubated. After successful weaning from the ventilator, she was discharged well, but two weeks later, experienced respiratory arrest. Once again, she was weaned from the ventilator and transferred to our unit for further evaluation.

On presentation, she admitted to inspiratory stridor, but experienced no difficulty in phonation. She was in no distress with a respiratory rate of 20 per minute. The temperature was 37.0°C; pulse, 72; and blood pressure was 130/82 mm Hg. The neck was supple without adenopathy or masses. Chest examination revealed minimal diffuse expiratory wheezing. Cardiac examination was normal. The abdomen was distended without palpable organomegaly. Neurologic examination results were normal.

Laboratory evaluation included the following: hemoglobin, 11.9 g/dl; hematocrit, 37.7 percent; white blood cell count, 18,400/ cumm; platelet count, 133,000/cumm; normal levels for blood urea nitrogen, creatinine, electrolytes, and liver functions. A thyroid profile revealed: T4, 6.07 μg/dl (4.5 to 11.5 μg/dl); T₃ resin uptake 51.4 percent (35 to 45 percent); T₃ index 3.12 (1.6 to 5.2); and TSH 1.9 mcu/ml (<10 mcu/ml). The Westergren erythrocyte sedimentation rate was 50 mm/hour. The serum antinuclear antibody and rheumatoid factor were negative. A morning cortisol level was 10.5 μg/dl. The rapid plasma reagin was nonreactive. Arterial blood gas values on room air showed a pH, 7.45; Pco₂, 36 mm Hg; and Paco₂, 60 mm Hg. Pulmonary function studies demonstrated FVC of 1.53 L (57 percent of predicted); FEV₁, 1.40 L (69 percent of predicted); FEV₁/FVC, .91; and a flattened inspiratory flow loop. Roentgenographic examination of the chest was normal.

With the patient's history of inspiratory stridor, bronchoscopy was performed that showed paramedian vocal cords. A tracheotomy was performed. A CT scan of the neck showed a retrotracheal and paraesophageal mass on the right side at the C₄-C₅ level. Needle aspiration of the mass showed atypical cells with scattered clusters of cytologically benign epithelial cells consistent with thyroid origin.

Right neck exploration was performed. The mass identified on CT scan was found to be extending from the thyroid gland. A right hemithyroidectomy was performed. The postoperative course was uneventful, and she was discharged with a tracheostomy tube in place.

Histologic examination of the neck mass revealed normal thyroid tissue. Eight weeks postoperation, a flexible fiberoptic laryngoscopic examination revealed normally functioning vocal cords permitting tracheostomy tube removal at that time. The patient was examined 11 months following the operation and was doing well without recurrence of stridor.

DISCUSSION

The differential diagnosis of vocal cord paralysis is broad, encompassing causes of peripheral neuritis such as alcoholism, influenza, syphilis, diphtheria, typhoid fever, and drug