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# Reversibility of hepatopulmonary syndrome evidenced by serial pulmonary perfusion scan

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**Summary:** A patient with liver cirrhosis who exhibited marked hypoxemia is presented. An abnormal dilatation of intrapulmonary capillaries was evidenced by perfusion lung scan, contrast-enhanced echocardiography, and histological examinations of lungs. Serial perfusion lung scan disclosed that the radioisotope uptake by extrapulmonary organs was significantly increased and uptake by both lungs was significantly decreased during the state of severer hypoxemia. Shunt quantification method revealed that intrapulmonary right-to-left shunt ratio also paralleled the extent of hypoxemia. The pathophysiology of hepatopulmonary syndrome appeared to involve a reversible intrapulmonary vascular dilatation. The perfusion lung scan could semiquantitate the severity of intrapulmonary vascular dilatation and could offer the efficient method to follow their progress. *Gastroenterol Jpn 1993;28:126-131*

**Key words:** *hepatopulmonary syndrome; liver cirrhosis; perfusion lung scan; pulmonary circulation; reversibility.*

## Introduction

Patients with liver cirrhosis sometimes exhibit associated hypoxemia which may be moderate to severe and the term "hepatopulmonary syndrome" has been advocated for these pathophysiologic conditions[1-4]. The major causes of hypoxemia include a ventilation perfusion mismatching and a diffusion limitation[5,6]. An abnormal dilatation of the intrapulmonary capillaries seemed to explain these pathophysiologic abnormalities[7,8].

The intrapulmonary vascular dilatation (IPVD) may represent reversible conditions in patients with hepatopulmonary syndrome[9,10]. Some cases of resolution of IPVD after liver transplantation have been documented[9,10]. The purpose of our report is to present another case of reversibility of IPVD with a discussion of the role of nuclear medicine therein.

## Case Report

### *Methods*

Arterial blood gases were measured using a Radiometer ABL-300 analyzer (Copenhagen, Denmark). The physiological shunt ratio (QS/QT) was estimated while the subjects breathed 100% oxygen and was based on an assumed arteriovenous oxygen content difference of 5 ml/dl[11].

Contrast-enhanced echocardiography was performed after the injection of indocyanine green into a peripheral vein. The late opacification of the left ventricle indicates a IPVD because the contrast dye is normally dissipated by a single pass through the pulmonary capillary bed[7].

Quantitative perfusion lung scans were performed as follows: Macroaggregated albumin particles (20 to 50 μm in diameter) labeled with 10 mCi of Tc-99 m were given intravenously to the patient in supine position. Whole body imaging

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**Table 1.** Clinical course and serial changes in arterial blood gases

| Date | 1988 Jan. 20 | Mar. 3 | 1990 Mar. 29 | Oct. 8 | 19 | Dec. 7 |
|---|---|---|---|---|---|---|
| Arterial blood gas | | | | | | |
| Room air | | | | | | |
| $PaO_2$ (mmHg) | 46 | 50 | 38(31) | 40 | 25 | 41 |
| $PaCO_2$ (mmHg) | 29 | 24 | 28(27) | 30 | 25 | 31 |
| $SO_2$ (%) | 82 | 88 | 77(67) | 82 | 54 | 80 |
| A-$aDO_2$ (mmHg) | 75 | 76 | 84(92) | 80 | 100 | 78 |
| 100% $O_2$ | | | | | | |
| $PaO_2$ (mmHg) | 167 | – | – | 219(118) | 109 | 170 |
| QS/QT (%) | 24 | – | – | 22(26) | 26 | 24 |
| DLCO (ml/min/mmHg) | 7.4 | – | – | 7.6 | – | 6.7 |
| %DLCO (%) | 35 | – | – | 38 | – | 35 |
| Shunt ratio* (%) | 61 | 55 | – | 68 | 77 | 68 |
| Dyspnea | ++ | ++ | ++ | ++ | +++ | ++ |

$PaO_2$=arterial oxygen tension, $PaCO_2$=arterial carbon dioxide tension, $SO_2$=oxygen saturation, A-$aDO_2$=alveolar arterial oxgen difference, QS/QT=physiological shunt ratio, DLCO=single-breath diffusion capacity. *: Shunt ratio calculated by quantitative radionuclide method. Data in parentheses were obtained in the standing position. All other data were obtained in the supine position.

was performed, and regions of interest (ROI) were drawn around each lung and around whole body using the digital image. The ratio of systemic to pulmonary radioactivities was used for a semiqaunitative estimation of the magnitude of the intrapulmonary right-to-left shunt. The details of this method is described elsewhere[12].

*Case*

A 60-year-old man was admitted to the hospital with cyanosis and dyspnea on January 4, 1988. He had smoked 5 cigarettes a day for 35 years and had had a daily alcohol intake of 66 g for 30 years. Examination revealed severe cyanosis on his lips and nail beds, and clubbed fingers. Many vascular spiders were noted on the chest wall. Liver and spleen were not palpable. No ascites was exhibited and remainder of the examinations was negative.

Routine laboratory chemistry revealed red cell count 566 × $10^4$; hemoglobin 12.7 g/dl; white cell count 3700; platelet count 6.6 × $10^4$; total bilirubin 2.0 mg/dl; albumin 3.2 g/dl; aspartate aminotransferase 28 IU, alanine aminotransferase 13 IU, lactate dehydrogenase 396 IU, *r*-glutamyl transpeptidase 19 IU. Additional studies revealed prothrombin time of 13.3 sec, as compared with the control value of 11.0 sec and a plasma indocyanine green retention rate of 46.1% at 15 minutes. The patient was positive for antibody to hepatitis C virus but negative for hepatitis B surface antigen. Abdominal ultrasound revealed a nodular liver, and a liver biopsy specimen disclosed established cirrhosis.

Arterial blood gas analysis revealed a $PaO_2$ 46 mmHg, $PaCO_2$ 29 mmHg, arterial oxygen saturation 82%, alveolar-arterial oxygen difference 75 mmHg (**Table 1**). Chest radiographs showed a bilateral increase in basilar interstitial markings. The results of pulmonary functions were within normal limits, except for a low diffusion capacity (**Table 2**).

Contrast-enhanced echocardiogaphy showed a delayed opacification of the left ventricle (**Figure 1**) and perfusion lung scan revealed a significant uptake in both lungs and in the liver, spleen, and both kidneys (**Figure 2**).

The patient's long-term clinical course is summarized in Tabel 1. Three years later, he developed severe dyspnea. The $PaO_2$ fell to 25 mmHg on October 19, 1990. The alveolar arterial oxygen difference was increased to 100 mmHg. At that time, perfusion lung scan disclosed an decrease in radioisotope uptake by both lungs, and increase in radioisotope uptake by extrapulmonary organs, such as brain, and kidneys (**Figure 2**). The intrapulmonary right-to-left shunt ratio, as evaluated by quantitative radionuclide method, was also significantly increased to 77%.

**Table 2.** Results of respiratory function tests

| | |
|---|---|
| VC | 4250 ml |
| %VC | 124 % |
| $FEV_{1.0}$ | 3120 ml |
| $\%FEV_{1.0}$ | 75 % |
| CV | 0.50 L |
| DLCO | 7.4 ml/min/mmHg |
| %DLCO | 35 % |
| Qs/Qt | 24 % |

VC: Vital capacity. $FEV_{1.0}$: Forced expiratory volume. CV: Closing volume. DLCO: Diffusion capacity. Qs/Qt: Physiological shunt ratio.

A several days later, spontaneous and gradual resolution of hypoxemia was noted. The $PaO_2$ rose from 25 mmHg to 41 mmHg, and the alveolar arterial oxygen difference was reduced from 100 mmHg to 78 mmHg on December 7, 1990. Moreover, perfusion lung scan disclosed a signficant decrease in radioisotope uptake by extrapulmonary organs, as compared with the findings obtained during the period of severer hypoxemia (**Figure 2**). The intrapulmonary right-to-left shunt ratio also decreased from 77% to 68%.

He died of hepatic failure on 25 December, 1990. The autopsy finding confirmed the macronodular cirrhosis. For further evaluation of the lungs in hepatopulmonary syndrome, a barium solution with 5% gelatin was injected into the pulmonary artery using previously described method[1]. Numerous spider nevi filled with barium-gelatin suspension was noted on the lung's pleural surface (**Figure 3**). Microscopically, there were numerous thin-walled vessels noted within the lungs (**Figure 4**). These were thought to be close to seemingly normal alveoli.

## Discussion

A worsening of $PaO_2$ in the standing position (orthodeoxia) and a diffusion limitation were found in the present case. Contrast-enhanced echocardiography disclosed a delayed opacification of the left ventricle. Perfusion lung scan with Tc-99m-macroaggregated albumin revealed a significant uptake in the lungs, liver, spleen, and both kidneys. These findings are compatible with the findings described in cases with hepatopulmonary syndrome[7].

Resolution of the hepatopulmonary syndrome has been observed following liver transplantation[9,10]. Other investigators also reported a reversibility of IPVD during the patients's clinical course[13,14]. Therefore, pathophysiology of IPVD seems involve functional vascular dilatation[7].

In the present case, significant correlation was noted between the extent of hypoxemia and the patterns of perfusion lung scan. The radioisotope uptake by both lungs was significantly decreased and the uptake by extrapulmonary organs, such as

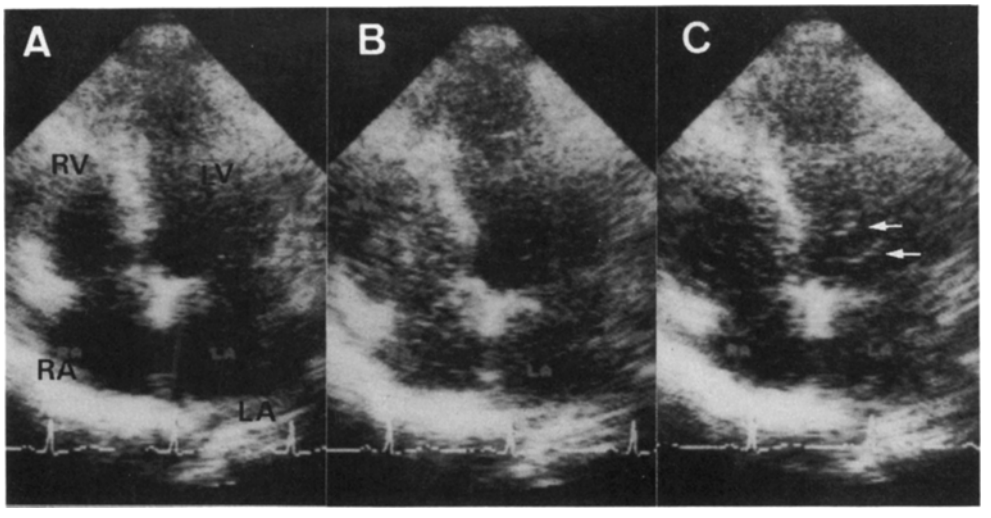


**Figure 1.** Four-chamber view of ultrsonic echocardiogram. Before (A), immediately after injection (B), three cycles after injection of indocyanine green (C). All four chambers have normal dimensions and late opacification of the left ventricle is evident. LA=left atrium; LV= left ventricle; RA=right atrium; RV=right ventricle.

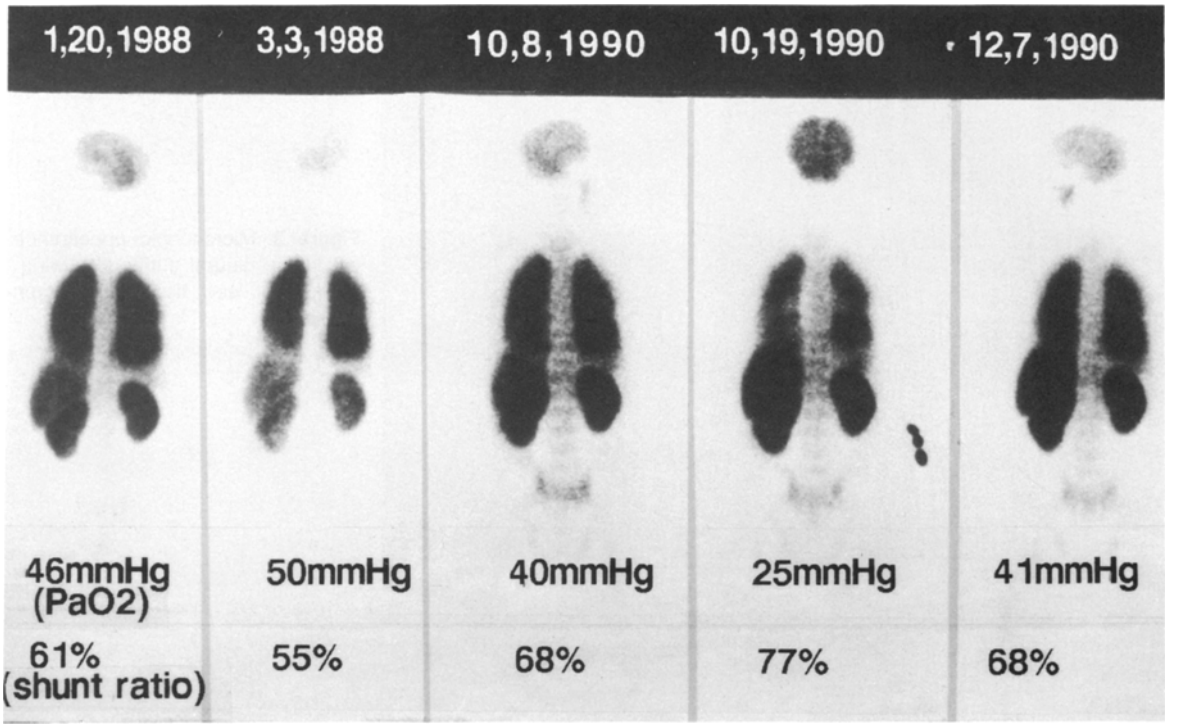


**Figure 2.** Whole body imaging of perfusion lung scan with Tc-99m-macroaggregated albumin. Note the significant uptake of radioisotope in the extrapulmonary organs. The pulmonary uptake is significantly decreased and the uptake by extrapulmonary organs, such as brain, kidneys, and spleen, is significantly increased in severely hypoxemic state. "Shunt ratio" indicates the semiquantitative estimation of the intrapulmonary right-to-left shunt ratio, as estimated by the ratio of systemic to pulmonary radioactivities. Estimated shunt ratio also parallels the extent of hypoxemia.

brain, kidneys, and spleen, was significantly increased in severely hypoxemic state. The intrapulmonary right-to-left shunt ratio, as evaluated by quantitative radionuclide method, also paralleled the extent of hypoxemia. These finding indicate that the perfusion lung scan should depict the progress of IPVD.

Contrast-enhanced echocardiography has been recommended as the preferred method to demonstrate IPVD, because of its sensitivity and ability to differentiate IPVD from intracardial shunting[7]. Contrast-enhanced echocardiography appears to be the most efficacious method as a screening test for IPVD. However, contrast-enhanced echocardiography is the method of qualitative analysis but can not quantitate the severity of IPVD. Perfusion lung scan is a simple, nonoperator-dependent, noninvasive method to investigate IPVD inpatients with chronic liver disease. Moreover, quantitative perfusion lung scan can semiquantitate the severity of IPVD and provides early evidence of progression of IPVD[10,13,14].

The etiology of hepatopulmonary syndrome is unclear at this time, even though a variety of mediators are possibly responsible for pulmonary vasodilatations[7,15]. Excess production of various vasoactive substances, such as prostaglandins, angiotensin II, and human atrial natriuretic polypeptide, has been noted in patients with cirrhosis of the liver[16,17]. These vasoactive substances can also influence the pulmonary vascular tone and gas exchange[18]. Therefore, some of these substances may contribute to IPVD in patients with this syndrome[19,20].

We conclude that the pathophysiology of hepatopulmonary syndrome involves a state of reversible IPVD. Perfuusion lung scan can semiquantitate the disease severity and offers an efficient method to follow the progress of IPVD in

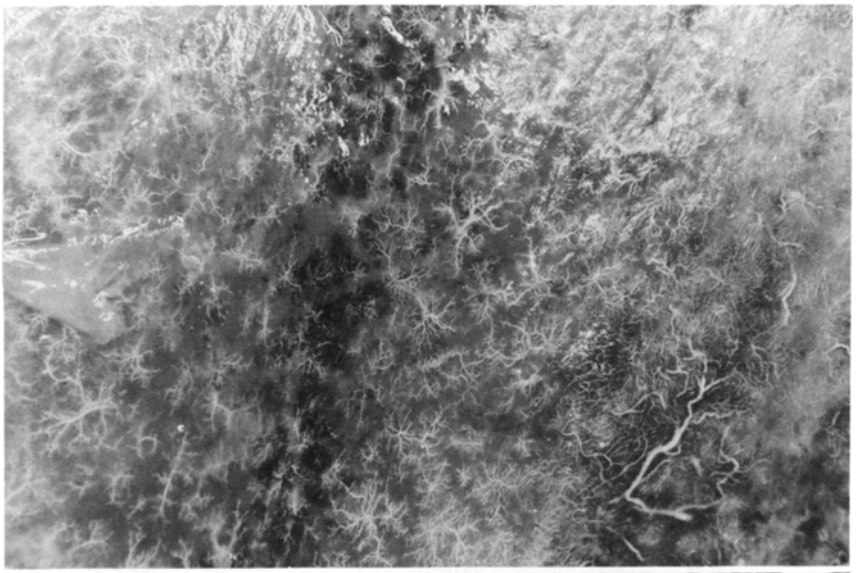

**Figure 3.** Microscopic appearance of the left lung's pleural surface showing numerous spider nevi filled with barium-gelatin suspension.

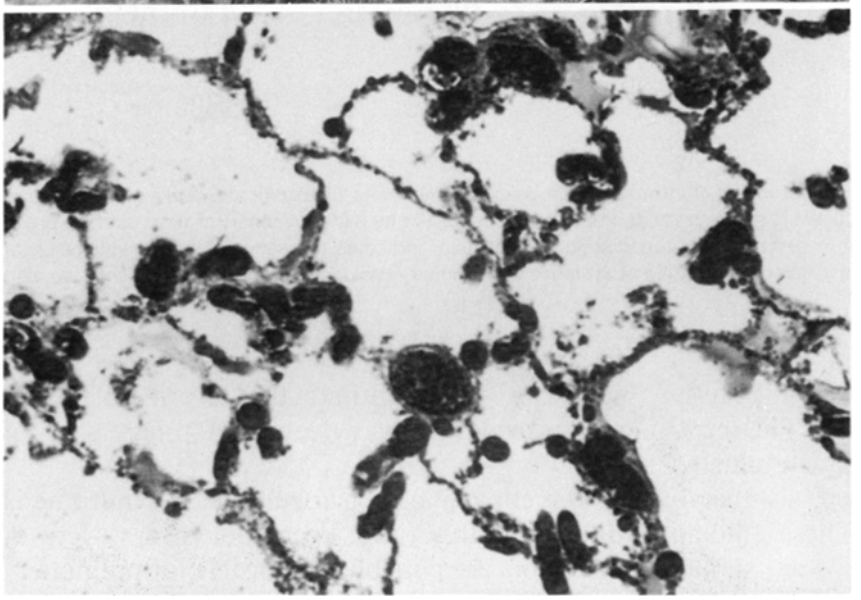

**Figure 4.** Section of patient's left lung perfused with barium-gelatin suspension (Elastica van Gieson, ×40). Note the markedly dilated septal vessels. Average minimal luminal diameter of largest vessels is 50 to 100 μm.

patients with this syndrome.

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