Early Radionuclide Detection of Intrapulmonary Shunts in Children with Liver Disease

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In order to detect and quantify intrapulmonary shunts in children with liver disease, a radionuclide method was developed and evaluated in such a population. **Methods:** We studied 135 children in whom the severity of liver disease, in most cases, justified consideration of liver transplantation. Patients were separated into two groups according to their resting PaO_2 values under room air: 109 children were normoxic and 26 were hypoxic. A radionuclide scan was performed immediately after intravenous injection of human albumin macroaggregates. Activity of the lungs (L) and brain (B) was counted. A shunt index (SI) was calculated as SI = 100 · B/L. We compared this index with blood gases and clinical follow-up. **Results:** In the normoxic group, SI was 0.43 ± 0.30 (mean ± s.d.); none of the 102 children with SI < 1 developed hypoxemia during their follow-up. Two of the six children with SI > 1 developed subsequent hypoxemia. In the hypoxic group, the nine children with SI < 1 did not aggravate their hypoxemia during follow-up. The 17 hypoxic children with SI > 1 later developed severe hypoxemia. **Conclusions:** Scintigraphy with intravenous human albumin macroaggregates is more accurate than measuring arterial blood gases to detect IPS in children with cirrhosis.

Key Words: pediatrics; technetium-99m-albumin macroaggregates; intrapulmonary shunt; hypoxemia; hepatic cirrhosis; portal hypertension; liver transplantation

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Arterial hypoxemia due to shunting through intrapulmonary arteriovenous fistulas has been reported in patients suffering from liver disease. This condition predominantly occurs in children or young adults. Early diagnosis of intrapulmonary shunt (IPS) may be useful for the management of children with severe liver failure.

Several methods have been proposed for diagnosis of IPS. Measurement of arterial blood oxygen tension (PaO_2) while breathing 100% O_2 is easily performed in adults but requires cooperation which is difficult to obtain in infants. A more complex technique using multiple inert gas requires specific equipment and insertion of venous and arterial catheters (*1*). Echography after injection in a peripheral vein of contrast material or microbubbles has also been used (*2*). The latter technique may be improved by transesophageal echocardiography, but it requires esophageal intubation and instrumentation, which may be risky in patients with esophageal varices (*3*).

A radionuclide scan after intravenous injection of labeled macroaggregated albumin has been proposed for the demonstration of right-to-left intracardiac or intrapulmonary shunting. Normal pulmonary capillaries (8–15 μm) entrap these 20–100-μm particles. When IPS occurs, a fraction of these particles is trapped in systemic capillary beds in proportion to shunt blood flow, causing abnormal extrapulmonary activity (*4–12*). We are proposing a radionuclide scintigraphic index in order to detect and quantify IPS in children with liver disease and we report our experience to validate this method.

PATIENTS AND METHODS

Patients

Between April 1985 and December 1990, 135 children with biopsy-proven liver disease (69 males, 66 females; age, 4.7 ± 4.5 yr, range, 2 mo to 17 yr) were studied. In most cases, severity of liver disease justified indication of liver transplantation. Age distribution and diagnosis of liver disease are given in Table 1. Right heart catheterization (when hypoxemia was present) excluded intracardiac right-to-left shunt in all instances. Chest radiography excluded any overt primary lung disease.

Blood Gases

Arterial blood was sampled in the supine position from the radial or femoral artery. In 99 patients, PaO_2 was also measured at the end of a 15-min period of breathing 100% O_2. Arterial blood gases were measured using Corning 175 automatic pH/blood gas system (Corning Medical, Medfild, MA). Predicted normal value for arterial PaO_2 as a function of age was calculated using the following equation (*13*):

$$PaO_2 \text{ predicted} = 68.16 * (\text{Age})^{0.063},$$

where age is expressed in months.

Patients were separated into two groups according to their resting PaO_2 values under room air.

Group One (Normoxic)

In 109 children, age-corrected PaO_2 under air was higher or equal to 80% of predicted normal value. These children were considered as normoxic. In 80 of these children, PaO_2 was measured under 100% O_2 breathing; it was higher than 500 torr in 57,

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TABLE 1
Clinical Diagnosis of Patients

No. of children	Age (mo) mean (range)	Cause of liver disease
76	57 (10–205)	Biliary atresia
16	60 (2–178)	Familial cholestasis (Byler)
11	79 (8–178)	Alpha-1 antitrypsin deficiency
6	50 (24–63)	Alagille's syndrome
6	132 (53–229)	Sclerosing cholangitis
5	113 (88–162)	Budd Chiari syndrome
5	87 (9–166)	Chronic hepatitis (viral and autoimmune)
10	83 (6–202)	others*

*Other causes of liver disease include cryptogenic cirrhosis, hereditary thyrosinemia (type I), chronic portal vein obstruction, glycogen storage disease (type I), nodular regenerative hyperplasia and nonsyndromic ductular paucity.

between 300 and 500 torr in 20 and between 150 and 300 torr in 3 patients.

Group Two (Hypoxic)

In 26 children, age-corrected PaO_2 while breathing room air was lower than 80% of predicted normal value. Ages of these children were similar to those of Group 1 (66 ± 46 mo versus 57 ± 58 mo). In 19 of these children, PaO_2 was measured under 100% O_2 breathing: it was higher than 500 torr in 4, between 150 and 500 torr in 14 and equal to 68 torr in 1.

Scintigraphy

Radionuclide scanning was performed immediately after injection of 1.8 MBq/kg (with a maximum of 40 MBq) of ^{99m}Tc-labeled macroaggregated albumin (MAA) (TCK8, CIS Bio International Gif-sur-Yvette, France). Aggregate size ranged from 20 to 100 μm. The radiochemical purity of the ^{99m}Tc-MAA was confirmed by chromatography: it was 99.45% ± 0.66% of the technetium activity bound to the MAA. The albumin per test dose did not exceed 0.2 mg and 600,000 macroaggregates. The injection was made into a peripheral vein, with the patient in the supine position. Two minutes after injection, subjects were placed under a large field-of-view gamma camera (Acticamera or Gammatome 2, Sopha Medical), with a standard general-purpose parallel-hole collimator. Spectrometry was set up at a 20% window energy. Posterior views of the brain and lungs (2 min per image) were taken. Data were recorded by computer (S4000, Sopha Medical).

Several regions of interest (ROIs) were drawn on the images; one over the brain, another over the lungs and one in a background region away from the patient. Brain ROIs only outlined the encephalon (Fig. 1). When visualization of extrapulmonary activity was minimal or absent, ROIs of the brain were drawn in a contrast-enhanced image (Fig. 2). Lung ROIs (L) and brain ROIs (B) were counted and corrected for background activity. A shunt index (SI) was calculated as:

$$SI = 100 \cdot B/L.$$

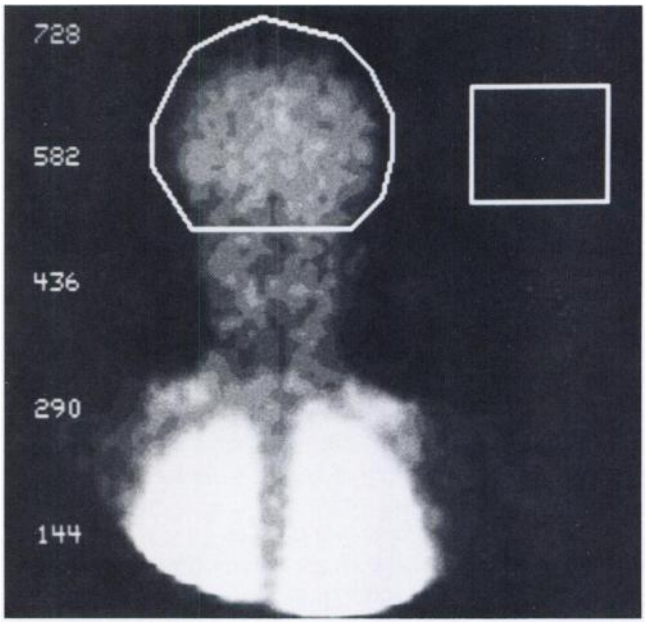

FIGURE 1. Brain and background ROIs in a patient with high intrapulmonary shunting (brain/lung SI = 4.5). For better visualization of encephalon edges, image scaling was decreased.

Statistics

Comparisons between groups were carried out with an unpaired t-test or a Mann-Whitney test. Data are expressed as mean ± s.d.

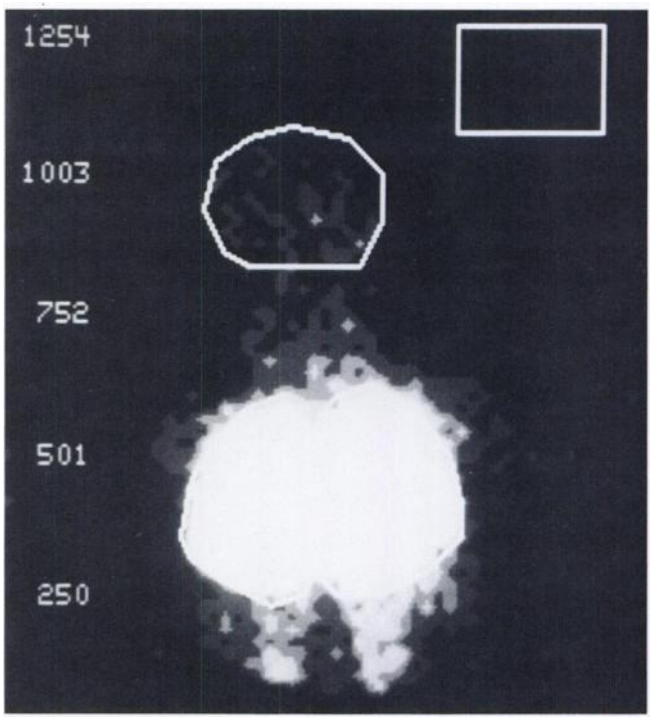

FIGURE 2. ROIs in the absence of evident shunting. Brain/lung SI = 0.21. The brain ROI was drawn at a distance from neck and pulmonary scattering.

RESULTS

Group One

The value of the radionuclide SI in the normoxic group was 0.43 ± 0.30, the median being 0.39 (Fig. 3). Only six normoxic children had SI above 1. In two of these patients, hypoxemia appeared during follow-up; in one child with SI of 1.4 and a PaO_2 increase under 100% O_2 breathing of 530 torr, severe hypoxemia (PaO_2 = 49% of predicted) was demonstrated 27 mo later with concomitant increase of SI to 10.4. In another child with SI of 1.05 (PaO_2 was not measured under 100% O_2 breathing), hypoxemia developed 6 mo later (PaO_2 = 50% of predicted) and SI increased to 5.8.

In the four remaining children, there was no sufficient follow-up. One child with SI of 1.04 and an increase of PaO_2 to 400 torr under 100% O_2 breathing died of liver failure 3 mo later while waiting for a liver transplant. One child with an increase of SI from 1.38 to 1.5 1 yr later is currently awaiting surgery with no aggravation of oxymetric data. Two children with SI of 1.86 and 1.50 respectively, were transplanted shortly after scintigraphic evaluation. In one of these, PaO_2 under 100% O_2 breathing was 590 torr.

The SI was below 0.90 in the remaining 102 normoxic children. None of them developed hypoxemia during a follow-up of 1.5 to 7 yr (mean 3 yr).

Group Two

Values of SI ranged from 0.18 to 29.3 in the 26 hypoxic patients. These children were separated into two subgroups according to SI (Fig. 4).

Subgroup 2A. In Subgroup 2A (n = 17 patients), the SI was higher than the mean value + 2 s.d. of the normoxic group (range 1.57–29.3). PaO_2 under 100% O_2 was measured in 13 of these patients. It was below 500 torr in 12, (mean 365 ± 114, range 157–477 torr). One patient with SI of 7.7, and PaO_2 of 529 torr developed severe hypoxemia (PaO_2 = 51% of predicted) 7 mo later with concomitant increase of SI to 17.

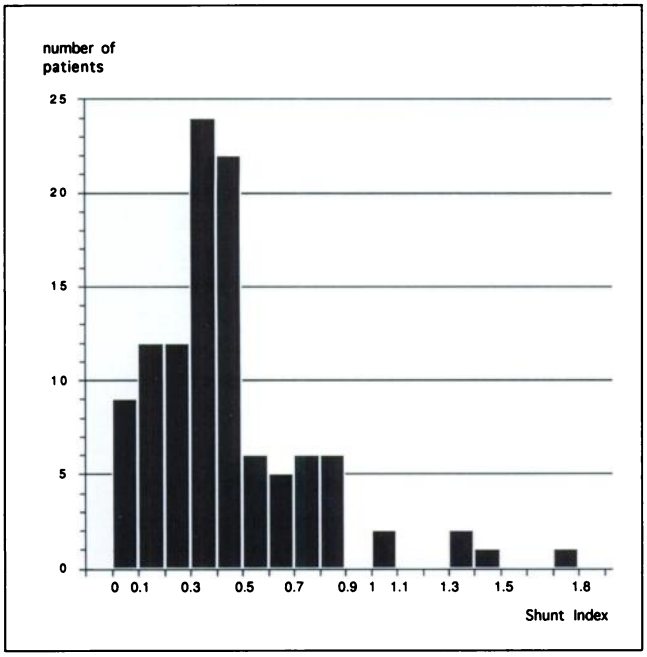

FIGURE 3. Shunt index distribution in 109 normoxic children.

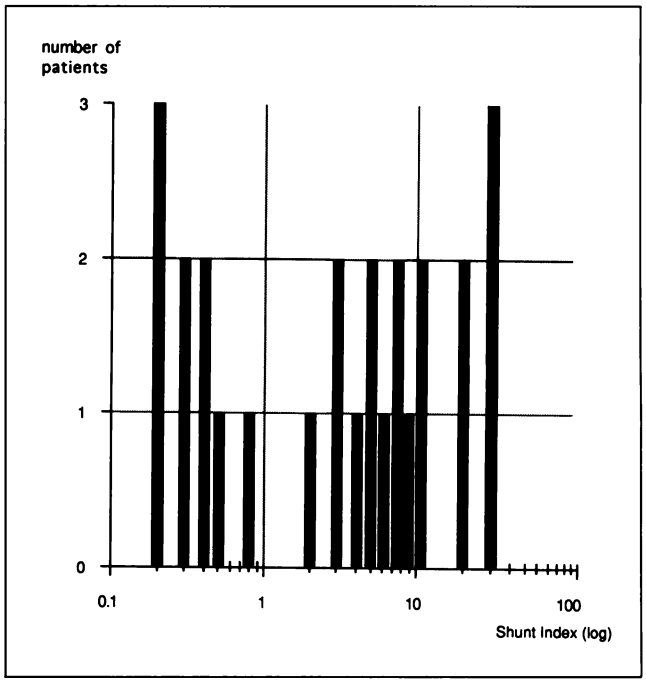

FIGURE 4. SI distribution in 26 hypoxic children. The mean + 2 s.d. of the normal value in normoxic children is used to separate these children into two subgroups: subgroup 2A (17 children with a SI value above 1) and subgroup 2B (9 children with a SI value below 1).

Subgroup 2B. In Subgroup 2B (n = 9 patients), the SI was under the mean value + 2 s.d. of the normoxic group (range 0.18–0.73). PaO_2 while breathing room air was not significantly different from the value in Subgroup 2A. These children were younger than those of Subgroup 2A (39 ± 30 mo versus 87 ± 45 mo, $p < 0.025$). Technical difficulties or cries during arterial blood sampling were noted in four patients. PaO_2 under 100% O_2 was above 500 in three children, 455 in two children, 68 in one child and was not measured in the remaining three patients. None of these hypoxic patients with normal SI developed worrisome deterioration of oxygenation during follow-up. Six patients had liver transplantation with a delay of 3–11 mo. Three patients with a follow-up of 3 yr have not yet undergone a transplant.

DISCUSSION

Impaired arterial oxygenation has been recognized for many years in approximately 11%–28% of cirrhotic adults (*14*). Various mechanisms have been suspected such as intrapulmonary shunts (IPS), ventilation/perfusion mismatch, increased closing volume, blunted hypoxic pulmonary vasoconstriction, reduced pulmonary diffusing capacity for oxygen, anastomoses between portal and pulmonary

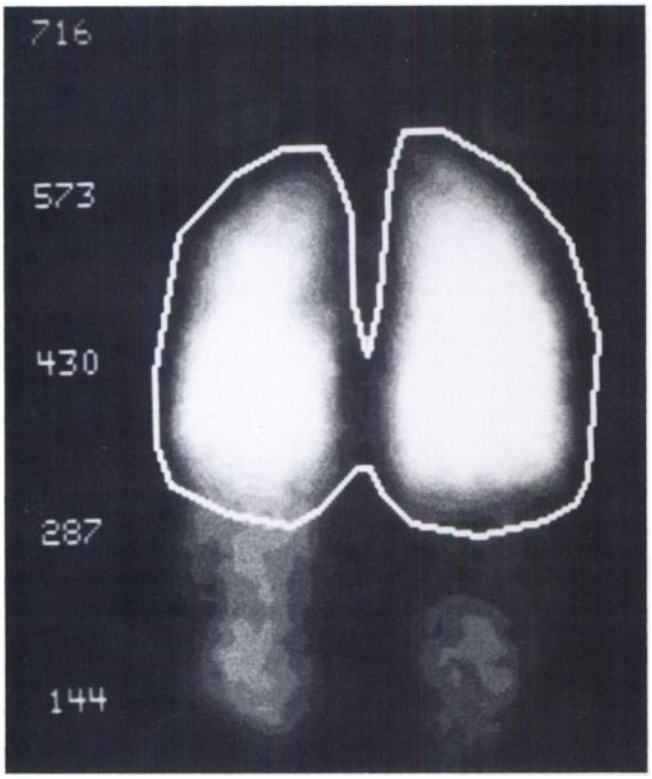

FIGURE 5. Pulmonary ROI. In children, lung bases are often superimposed over the kidneys. Intense pulmonary activity scatter may induce uncertainty about renal activity in the absence of major shunting.

veins via mediastinal veins and pleural spiders (*15–19*). Severe hypoxia is often due to IPS which is attributed to pulmonary arteriovenous fistulas. The pathogenesis of vascular abnormalities such as the opening of pre-existing channels which are becoming functional or formation of new channels is unknown. These abnormalities are tiny and may not always be demonstrated in vivo with angiography. At transplantation, the existence of large IPS with severe hypoxemia causes a significant intraoperative and postoperative risk and is a relative contraindication to liver transplantation (*3,20,21*). However, possible reversal of small IPS has been reported (*12,22,23*), even in children (*24*). Therefore, early diagnosis of IPS in a patient with liver disease may prompt an earlier transplantation.

Previous authors have used ^{99m}Tc-MAA to diagnose intrathoracic shunts and have established their absence of toxicity. Risk of scintigraphy is minimal (*25*). Irradiation is low; the gonadal dose is 1.5–2.3 μSv/MBq and the whole-body dose is 3.2 μSv/MBq (*26*). Systemic injection of MAA has been used for a variety of applications, including determination of cardiac output or its distribution among various organs, study of right-to-left intracardiac shunts and diagnosis of great vein abnormalities (*25–28*).

To diagnose of right to left shunt by using ^{99m}Tc-MAA, it is necessary to quantify extrapulmonary activity. Analogic images may be misleading. Indeed, an increase in brightness can cause a false-positive IPS. Conversely, a small IPS may be missed with too much of a decrease in brightness.

Whole-body scanning has been used to calculate the right-to-left shunt fraction (*5,28*). However, whole-body extrapulmonary activity may be falsely elevated for several reasons such as some conversion of bound to unbound pertechnetate during scanning, injection of particles smaller than 10 μm or extravasation at injection site (*5,10,26*). In addition, counting of whole-body extrapulmonary activity is not devoid of difficulties because of pulmonary scattering (Figs. 2 and 5).

Genovesi et al. measured activity over brain and kidneys and assumed renal and cerebral blood flow to represent a constant fraction of cardiac output, 19% and 13%, respectively (*6*). In our patients, renal activity was difficult to measure, because of lungs, spleen or liver superimposition and sometimes pulmonary scattering (Fig. 5). Moreover, renal blood flow is not necessarily a constant fraction of cardiac output; it may vary according to the clinical status and various treatments. The immunosuppressive drug, cyclosporine, has been shown to decrease renal blood flow.

To diagnose and quantify intrathoracic shunt in the present study, we chose an index based upon brain and pulmonary activity. These two brief images are easily and rapidly performed. Determination of brain activity by strictly outlining encephalon edges avoids pulmonary scattering and possible salivary or thyroid activity. Moreover, cerebral activity is not increased by pertechnetate unbinding (*26*).

Measurement of PaO_2 under 100% O_2 breathing is routinely used to assess and quantify right-to-left shunt. A normal response to 100% oxygen (PaO_2 > 500 torr) should preclude the existence of IPS (*18*). However, there may be some discrepancy between this method and ours. In infants, arterial sampling of blood by direct puncture often causes disturbance of ventilation through agitation and cries. This is the most likely explanation to the lack of normal increase of PaO_2 under 100% O_2 in 26% of our normoxic children. PaO_2 does not increase normally during O_2 breathing when perfusion of unventilated areas is maintained because of the bluntness of hypoxic pulmonary vasoconstriction (*31*). In this case, MAA should be entrapped in these morphologically normal capillaries. On the contrary, a porto-pulmonary shunt should be missed by the radionuclide method since the MAA is infused into a peripheral vein. However, it is unlikely that such shunt could contribute significantly to arterial desaturation since flow through this kind of shunt is small and portal venous blood has a relatively high O_2 saturation (*32*). PaO_2 under 100% O_2 breathing increased normally above 500 torr in one child and above 470 torr in two children with scintigraphic evidence of IPS. We may hypothesize that in these patients, slight dilation of capillary vessels allowed shunting of the MAA without impairing O_2 transfer (*19*). Further appearance of severe hypoxia concomitant with an increase of shunt index make this the most likely explanation.

In our study, the normal value of SI in normoxic children

was 0.42 ± 0.30. Normally 3%–6% of the ^{99m}Tc-MAA bypasses the pulmonary vasculature (7). It is noteworthy that none of the children with SI below 0.9 developed clinically evident hypoxemia during follow-up. All children with SI above 2 had rapid shunting and further appearance of severe hypoxemia. Because of the two patients who initially had an SI between 1 and 2, and who later developed severe hypoxemia, we now believe that there is a high probability of IPS with this value of SI. If early control (less than 3 mo later) confirms shunting, these children should be operated on as soon as possible.

In conclusion, this technique allows a sensible and specific detection of IPS before hypoxemia becomes significant and contraindicates surgery. The SI is more accurate than PaO_2 at rest or 100% breathing to detect small IPS in the beginning and scintigraphy is noninvasive. Only one venous puncture is needed during a short examination (<15 min) in these very sick children. We propose that scintigraphy should be performed once a year as the discovery of a small IPS may prompt more immediate liver transplantation.

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