Measuring Lung Shunting in Hepatocellular Carcinoma with Intrahepatic-Arterial Technetium-99m Macroaggregated Albumin

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With increased use of intraarterial administration of chemotherapeutic and radioactive particulate agents, it is necessary to assess agent delivery in the lung. **Methods:** Technetium-99m-labeled macroaggregated albumin (^{99m}Tc-MAA) delivered through the hepatic artery was used to determine the degree of lung shunting in 125 patients with hepatocellular carcinoma (HCC). **Results:** The percentage of lung shunting varied among patients and it ranged from less than 1% to 67.2%, with a median of 8.1%. The degree of shunting depended on the vascularity of the tumors but not on the tumor size. The effect of angiotensin II on lung shunting was tested on six patients and there was no significant difference found between those patients who were pre-treated with angiotensin II and those who were not. One patient who underwent a liver resection, had a significant decrease in lung shunting from 28.5% to less than 1% after surgery. **Conclusion:** The lack of effect of angiotensin II together with the almost complete ablation of lung shunting by tumor resection suggested neoplastic blood vessels were responsible for the shunting.

Key Words: hepatocellular carcinoma; lung shunting

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Regional targeted treatment using chemoembolization, radioactive Lipiodol-^{131}I and ^{90}Y microspheres are increasingly used in treatment of inoperable hepatocellular carcinoma (HCC) (*1*). However, arteriovenous shunting is known to occur in metastatic liver tumors (*2*). Large arteriovenous shunting makes regional chemotherapy less effective and increases systemic toxicity. In addition, the relatively low radiation tolerance of lungs has aroused much caution in treating HCC with ^{90}Y microspheres or Lipiodol-^{131}I. High lung shunting of radioactive isotopes may induce radiation pneumonitis. Technetium-99m-MAA has been employed to assess the degree of shunting into pulmonary circulation (*1,3–5*). These reports concentrated mainly on metastatic liver tumor. In the present study, 125 patients with HCC with cirrhosis were assessed by intrahepatic-arterial ^{99m}Tc-MAA in relation to lung shunting.

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MATERIALS AND METHODS

Patients with HCC (histology-proven or with raised alpha-fetoprotein of over 500 μg/liter and ultrasound evidence of a liver tumor) who underwent hepatic angiography as an assessment for resectability or selective internal radiation therapy were eligible for the study. Hepatic angiography was performed through the Seldinger technique. When the angiographic catheter was selectively placed in the hepatic artery, 111 MBq (3 mCi) of ^{99m}Tc-MAA (Amersham Pulmonate II, with 80% of the particles 10–60 μm in size and none greater than 150 μm) were injected into the hepatic artery following 20 μg of angiotensin II (Ciba-Geigy, Basel, Switzerland). The catheter was then removed.

The patient was then transported to the gamma camera suite and scintigraphic images of the lungs, liver and gastroduodenal regions were taken with an analog/digital gamma camera (Philips, Hamburg, Germany). The total count rate was computed from the digitized image. Regions of interest (ROIs) were carefully drawn around the organs (liver and lungs) and the percentage of activity shunted into the pulmonary circulation was calculated as the ratio of lung counts-to-total counts.

Tumor sizes were measured either by computerized tomography or ultrasound. The vascularity of the tumors on hepatic angiography was independently assessed by an interventional radiologist who did not know the results of the vascularity of the tumors by scintigraphic imaging. Vascularity on hepatic angiog-

TABLE 1
Lung-Shunting as Determined by ^{99m}Tc-MAA

% Shunting	No. of patients (%)
≤5.0	42 (33.6%)
5.1–10.0	33 (26.4%)
10.1–15.0	14 (11.2%)
15.1–20.0	7 (5.6%)
20.1–25.0	6 (4.8%)
25.1–30.0	11 (8.8%)
30.1–40.0	5 (4.0%)
40.1–50.0	4 (3.2%)
>50.0	3 (2.4%)
Total	125 (100%)

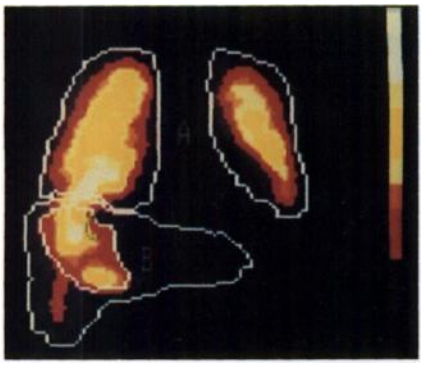

FIGURE 1. Technetium-MAA scintigram of a patient with 67.2% lung shunting.

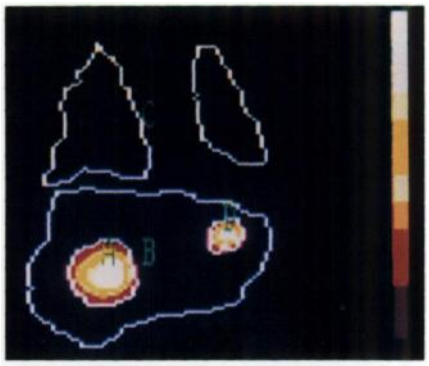

FIGURE 2. Technetium-MAA scintigram of a patient with 1% lung shunting.

raphy was graded by a scale from 0 (normal) to 4 (extremely hypervascular): Presence of mild tumor staining without an increase in the number of vessels was grade 1. Moderate tumor staining and increased number of vessels were grade 2. Intense tumor staining and markedly increased number of vessels which were also dilated and tortuous were grade 3. Tumors having all the grade 3 characteristics together with venous pooling were classified as grade 4. The degree of lung shunting was correlated with the size and vascularity of the biggest tumor in the patient.

In six patients who had implanted arterial port-a-catheters (Pharmacia, St. Paul, MN) in the gastroduodenal artery which led to the common hepatic artery, ^{99m}Tc-MAA scans were repeated with and without angiotensin II by injection of the radioisotope through the subcutaneous ports to assess the degree of change of lung shunting. For one patient who had liver resection for HCC and placement of an arterial port-a-catheter, the ^{99m}Tc-MAA scan was repeated after surgery and the degree of lung shunting was compared with that before the resection. Statistical analysis was performed using the Wilcoxon 2-sample test and paired Student's t-test.

RESULTS

From November 1990 to March 1993, 125 patients with HCC and cirrhosis were entered into the study. The degree of lung shunting was found to vary between patients and ranged from less than 1% to 67.2%, with a median of 8.1%. Table 1 illustrates the subdivision of 125 patients according to the degree of lung shunting. Two representative scintigrams are shown in Figures 1 and 2 which have 67.2% and 1% lung shunting respectively.

The size of the major tumor in each patient was measured and ranged from 2 cm to 26.2 cm with a median of 12.5 cm. Plotting tumor sizes against lung shunting showed no correlation (Fig. 3, coefficient of linear regression r = 0.0863).

The relationship between the percentage of lung shunting and the tumor vascularity grading as assessed on hepatic angiography is illustrated in Figure 4. The lung shunting percentage of patients having vascular scores 1 and 2 are compared with those having scores of 3 and 4 using Wilcoxon 2-sample test ($p < 0.0001$). This suggests those with more vascular lesions have larger lung shunting.

In six patients, lung shunting percentages were estimated by injecting ^{99m}Tc-MAA through an implantable intra-arterial port-a-catheter with and without angiotensin II pretreatment. There was no difference in lung shunting for these patients (paired Student's t-test, $p = 0.16$).

One of the patients had a 15-cm right lobe tumor, a vascular score of 4 on hepatic angiography and had undergone a right hepatic resection. The lung shunting dropped from 28.5% (pre-operative) to less than 1% after surgery.

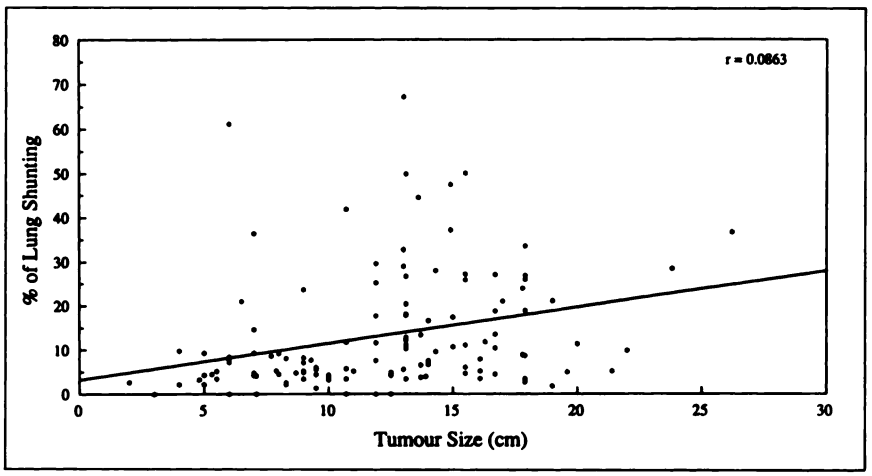

FIGURE 3. Correlation between lung shunting and tumor size.

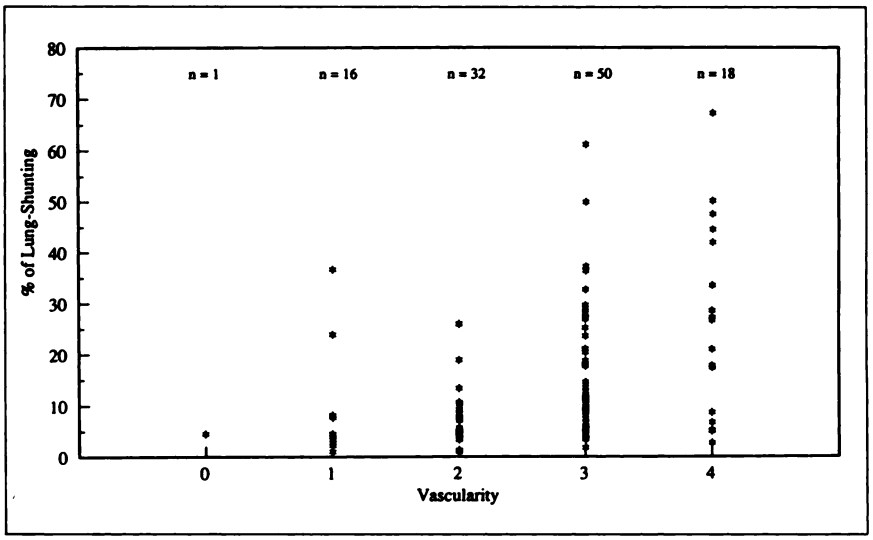

FIGURE 4. Scatter diagram plotting lung shunting against tumor vascularity.

DISCUSSION

HCC is usually very vascular due to neovascularization. Capillaries within the tumor are expected to be embolized by the ^{99m}Tc-MAA because of similarity in size and few can leak through if there is no arteriovenous shunting. However, arteriovenous shunting is well known in HCC. Therefore the leaked ^{99m}Tc-MAA will go through these abnormal vascular channels and be detected in extrahepatic organs. The lungs, being a first-pass organ and having similar capillary structure, will hold up the leaked ^{99m}Tc-MAA. Little MAA will leak to other organs because the capillary bed in the lungs is able to stop any further systemic leaking. Thus, measuring the degree of lung shunting can indirectly reflect the degree of arterovenous shunting in the liver tumor.

Other hepatic arterial perfusion scintigraphy using ^{99m}Tc-MAA was employed to assess the leakage of regional chemotherapy for liver metastases into the pulmonary circulation (*2,6*). The percentage of lung shunting was found to be between 6% and 26% (mean 12.3%) in a series of 20 patients (*2*) and between 0.4% and 32% (mean 6.2%) in another series of 67 patients (*6*). A much wider range (<1%–67.2%) of pulmonary shunting was observed in our 125 patients with primary liver cancer and cirrhosis. The degree of shunting appears to be higher in patients with HCC when compared to metastatic liver cancer from other reports. Zeissman et al. (*6*) found that 49% of their patients with metastatic tumors had a percentage equal to or larger than 5%, whereas 66% of our patients with HCC had a value equal to or larger than 5%. Though this may not be entirely comparable to each other, it may suggest a trend towards HCC having higher lung shunting.

Our results also showed that the degree of arteriovenous shunting to the lungs was influenced by the vascularity of the tumors but not by the tumor size. Thus, the pattern of blood flow through the tumor seems to be the determining factor of pulmonary shunting. This may be due to the tumor itself which is vascular and rich in blood supply and has more arteriovenous shunts with resultant increases in lung shunting. The poor correlation between tumor size and lung shunting may be due to the fact that tumor size correlates poorly with vascularity.

Angiotensin II was suggested to induce vasoconstriction of normal blood vessels but not neoplastic blood vessels (*7*). It was used extensively in selective internal radiation therapy using ^{90}Y microspheres (*8*) and for targeting cytotoxic-loaded microspheres into liver tumors (*9*). Comparison of the percentage of lung shunting with and without angiotensin II in our six patients showed no significant difference. This finding is in agreement with that of Goldberg et al. (*10*) and suggests that the vessels responsible for the shunting are neoplastic in nature. The dramatic decrease in lung shunting after resection for HCC in one patient concurred with Goldberg's findings, but more patients should be studied to prove the point.

In summary, arteriovenous shunting of ^{99m}Tc-MAA to the lungs after injection into the hepatic artery was found to vary somewhat and it was high in a large proportion of patients with HCC. The degree of shunting was related to tumor vascularity rather than tumor size. Assessment of lung shunting by a ^{99m}Tc-MAA scan before any regional targeted treatment is useful in excluding patients who may be at high risk for excessive pulmonary irradiation after internal radiation therapy or marked systemic toxicity after regional chemotherapy.

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ERRATUM

MIRD Pamphlet No. 14 "A Dynamic Urinary Bladder Model for Radiation Dose Calculations," appearing on pages 783–802 of the May 1992 issue of *JNM* contains results that are incorrect owing to an error in the computer code used in the calculations.

This error was discovered after publication of the pamphlet; the magnitude of the error introduced in the published results depends upon the radionuclide as well as the specific model parameters; however, the published values are, on average, approximately 40% lower (ranging from less than 10% to greater than 60% lower). In addition, typographical errors were identified in the expressions involving the model description.

The pamphlet describes a dynamic urinary bladder model developed to provide physiologically realistic features for bladder wall dose calculation, incorporates expanding bladder contents, and allows for variable urine entry rate, initial bladder contents volume, residual volume and first void time. Radiation dose estimates are calculated for the bladder wall surface for 11 radiopharmaceuticals. Extensive tables and graphs are presented for the dose to the bladder wall surface as a function of the variable parameters.

The MIRD Committee recognizes the importance of rectifying this situation. A revised Pamphlet No. 14, under preparation, will provide corrections and also take the opportunity to expand the list of radiopharmaceuticals presented. The availability and mode of distribution of this revision will be announced through the *Journal*. To assist the nuclear medicine community in the use of the dynamic bladder model, a computer code has been installed at the Radiation Internal Dose Information Center, Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee 37831. At this time, interested individuals may obtain the corrected tables for any of the published radiopharmaceuticals by direct contact with Oak Ridge (Michael G. Stabin at 615-576-3449).

The MIRD Committe sincerely regrets any inconvenience caused through errors in the publication.