## DIAGNOSTIC NUCLEAR MEDICINE

# Quantitative Hepatic Arterial Perfusion Scintigraphy and Starch Microspheres in Cancer Chemotherapy

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**Hepatic arterial infusion chemotherapy results in a higher concentration of drug delivered to the tumor with less systemic exposure than is possible with intravenous therapy. However, extrahepatic blood flow and/or shunting to the lung can impose a limitation. This study describes a quantitative method for calculating the extrahepatic component and monitoring its changes due to a new adjunctive therapy, degradable starch microspheres (DSM). DSM temporarily occlude the hepatic arterial circulation, thereby increasing the uptake of therapeutic drugs. Twenty patients with metastatic liver cancer underwent hepatic arterial perfusion scintigraphy (HAPS) using Tc-99m MAA to determine blood-flow distribution and to quantitate extrahepatic uptake. The percent shunt index (PSI) was determined at baseline and after each incremental dose of DSM. The baseline PSI ranged from 6–26% (mean 12.3 ± 5.8 s.d.) and changed progressively after each injection of DSM/Tc-MAA suspension. The patterns of change in shunting are described. Quantitative HAPS provides a means of measuring the extrahepatic component, warns of potential side effects, and helps guide chemotherapeutic decisions.**

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Regional arterial chemotherapy of hepatic tumors has significant advantages over systemic intravenous therapy in many patients. Tumors can be perfused with higher concentrations of appropriately selected therapeutic agents, with less likelihood of systemic toxicity (*1*). Radionuclide techniques have been described for evaluating catheter position and guiding catheter placement by assessing the perfusion patterns (*2–4*). Ideally the perfusion bed of the catheter should include the entire liver with no regions of extrahepatic pefusion either in the abdomen or chest. Drug delivery to these areas can impair the benefits of the regional approach. The purpose of this report is to describe our initial experience with a quantitative method for calculating the extrahepatic component of perfusion using Tc-99m macroaggregated serum albumin (Tc-99m MAA) and to describe how the extrahepatic component changes with the use of a new adjunctive form of therapy, degradable starch microspheres.

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### METHODS AND MATERIALS

Twenty patients (12 M, 8 F) with cancer metastatic to the liver were studied. Seventeen had colon cancer and one each had melanoma, carcinoid, and islet-cell carcinoma of the pancreas. All patients had tumor in both lobes of the liver. The age range was 29 yr to 70 yr (mean 57).

Nineteen patients had operative placement of a silastic catheter in the hepatic artery, attached to a subcutaneously implanted pump* with a sideport allowing direct percutaneous injection as previously described (*2*). One patient had the catheter inserted percutaneously via the brachial artery.

**TABLE 1**

| | Tc-MAA only | Starch/Tc-MAA Injections | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 |
| Number of Patients | 18 | 18 | 18 | 18 | 15 | 9 |
| Range PSI | 5.8–26 | 3.7–26 | 5.7–28 | 5.4–29 | 7.9–27.5 | 12.5–37 |
| Mean PSI | 12.6 | 12.1 | 14.8 | 16.4 | 20.9 | 26.8 |
| s.d. | 6.0 | 6.4 | 7.8 | 8.7 | 8.8 | 10.4 |

Hepatic artery perfusion scintigraphy (HAPS) using Tc-99m MAA (1–4 mCi) was done to determine blood-flow distribution, to ensure that the entire liver was perfused, and to determine whether there was extrahepatic flow in the abdomen or shunting to the lungs. Technetium-99m MAA was injected slowly, percutaneously via the pump's side port. Imaging was accomplished with a wide-field-of-view, single-crystal gamma camera with a low-energy, all-purpose, parallel-hole collimator. Anterior, posterior, and both lateral views were obtained. The camera was placed to include the liver, lung, and abdomen. In most cases, all the lung area was included, but in three patients the lung apices were outside the field of view. In some patients, only the upper abdomen was included. The anterior views of the abdomen and lungs were acquired with a nuclear medicine computer system.

To quantify extrahepatic perfusion, the liver and the total field were flagged as regions of interest. In some patients, a small area of activity was noted at the injection site in the side port of the infusion pump, the catheter, or catheter tip. This activity was shielded during imaging or excluded from the regions of interest. The percent extrahepatic flow (PEHF) was calculated as:

$$\text{PEHF} = \frac{\text{total field counts—liver counts}}{\text{total field counts}}$$

Images were also visually inspected to identify any focal areas of extrahepatic abdominal uptake. In the absence of extrahepatic abdominal uptake, the calculated percentage (PEHF) represents the amount of Tc-99m MAA being shunted to the lungs, and in those cases will be designated as the lung "percent shunt index" (PSI).

In addition to the baseline Tc-99m MAA studies (HAPS), these patients received incremental doses of biodegradable starch microspheres (DSM) in suspension with Tc-99m MAA, and the PSI was calculated after each dose. The purpose of the starch microspheres is to occlude temporarily the hepatic arterial circulation, thereby increasing the uptake of poorly diffusible chemotherapeutic agents such as BCNU and mitomycin. DSM is a product with specially formulated cross-linked microspheres 40 ± 5 $\mu$m in diameter, with 6 million microspheres per ml of saline suspension.

Fifteen milliliters of DSM are combined with 6 mCi Tc-99m MAA and then divided into five syringes of equal volumes (3 ml). An initial 60-sec image is obtained after the 1-min infusion of 500 $\mu$Ci Tc-99m MAA (without DSM) through the side port of the implanted infusion pump, followed by a 3 cc saline flush. The first dose (3 ml DSM/Tc-99m MAA suspension) is then injected into the port and flushed, and another 60-sec image is obtained. This is immediately repeated until all five syringes are used or until the patient feels discomfort (abdominal pain, nausea, or vomiting) or has significant extrahepatic flow. The entire study is completed within

**FIG. 4.** Hepatic artery perfusion scan (Tc-99m MAA). Note extrahepatic flow to stomach.

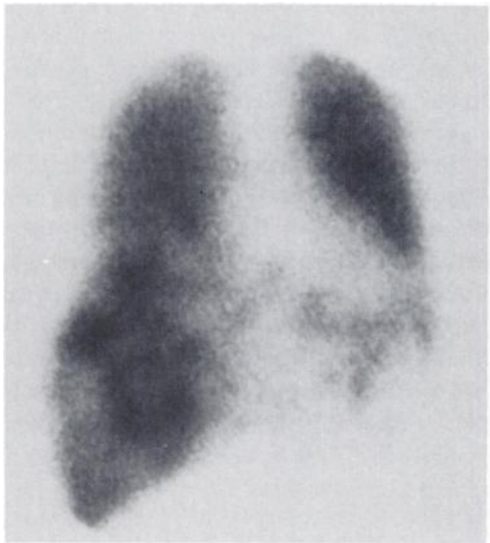

**FIG. 5.** Hepatic artery perfusion scan (Tc-99m MAA) showing prominent shunting to lungs.

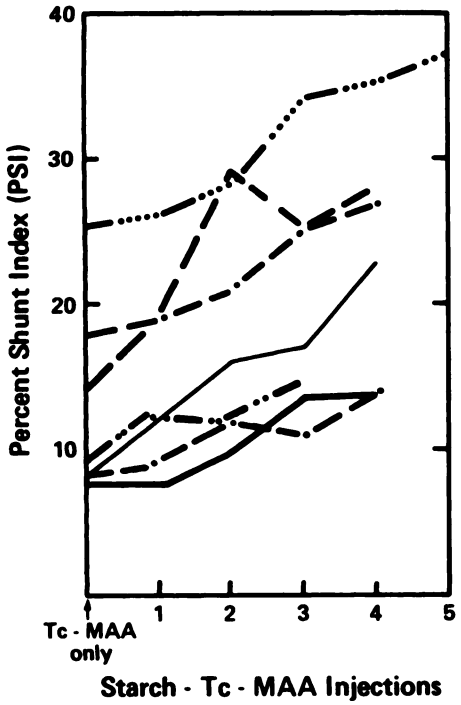


FIG. 1. Pattern 1: Progressive increase in percent shunt index from baseline.

approximately 12 min. The PSI was calculated after each injection.

## RESULTS

Twenty patients were studied. Two had demonstrable extrahepatic abdominal flow (i.e., through stomach, intestine, or spleen, Fig. 4). Both of these patients had subcutaneously implanted pumps†. The baseline (before starch microsphere infusion) PEHFs in these cases were 8.1% and 10.0%. In the remaining 18 cases, the extrahepatic component was restricted to the lung (Fig. 5). In this group, the baseline PSI ranged from 5.8–26%, with a mean of 12.6% ± 6.0 s.d. (Table 1).

Twenty-four studies with incremental starch hepatic artery perfusion scintigraphy (SHAPS) were done in twenty patients. Seventeen patients had one study, two patients had two studies, and one patient had three. In 14 studies, the patients received all five consecutive injections of starch microspheres. However, five studies used four injections and five others had three injections. due to adverse symptoms (abdominal pain, nausea/vomiting). All symptoms resolved rapidly after stopping the study. In the two patients noted above with extrahepatic abdominal flow, the studies were stopped after the third injection, due to a progressive increase in this flow. These patients are again not included in PSI statistics. The mean PSI changed with each injection of DSM/Tc-99m MAA suspension. Two distinct patterns of change in shunting were seen. The first was a progressive increase in the percent shunting from baseline. This was seen in studies of seven patients (Fig. 1). The second general pattern was a decrease in the PSI to a value usually lower than baseline at some point in the study, and usually followed by a rise to its highest level (Fig. 2). Seven patients had their lowest PSI after the first injection, two after the second, one after the third, and one after the fourth. The mean PSI of the entire group was actually less after the first starch injection than it was at baseline; it then rose progressively there-

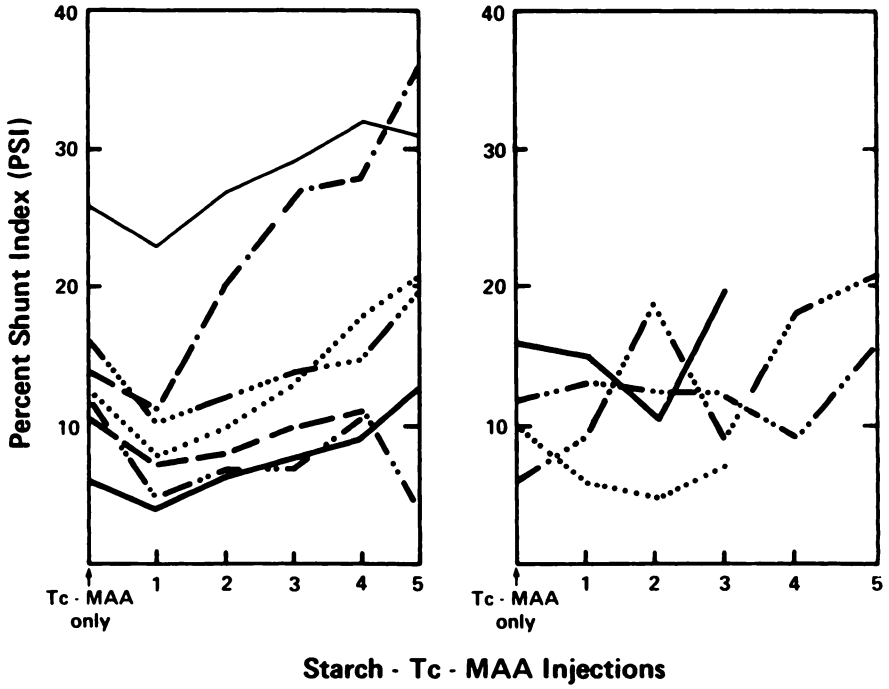


FIG. . 2. Left: Decrease in PSI after first injection. Right: Decrease in PSI after injections 2, 3 and 4.

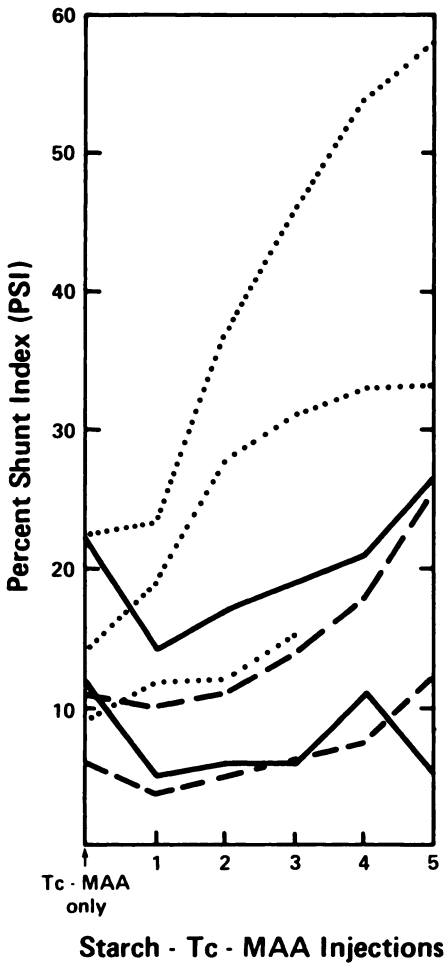


**FIG. 3.** Three patients who had repeat studies. One patient (. . .) had three studies and two patients (—), (- - -) had two studies each. Baseline and incremental PSI rose in patient's follow-up study.

after (Table 1). The patient who underwent three studies had a progressive increase in PSI from baseline in all studies (Fig. 3). The two patients with two studies had the lowest PSI each time after the first injection. However, the baseline and incremental PSI was higher in each of their respective follow-up studies. No change in the pattern of distribution of Tc-MAA within the liver and tumor was seen with increasing starch dose.

## DISCUSSION

Hepatic arterial infusion chemotherapy of liver tumors is pharmacokinetically sound for drugs with a short half-time or high hepatic extraction efficiency (*5,6*). The liver's ability to metabolize and excrete the drug will result in decreased systemic drug levels and less threat of toxicity to other tissues. Clinical studies have confirmed that greater tumor exposure to the drug does occur with hepatic arterial chemotherapy (*1*) and the therapeutic response rate is improved (*7–9*).

However, extrahepatic blood flow and shunting to the lung may cause a relative limitation of this regional technique. Both result in less drug delivery to the tumor with increased systemic exposure. A pattern of extrahepatic flow has been highly predictive of poor tumor response and is associated with gastrointestinal and systemic toxicity (*10,11*). Previous studies utilizing Tc-99m MAA via the hepatic arterial catheter have demonstrated this extrahepatic component (*4,10,12*) by imaging. This study extends these observations by quantifying the extrahepatic component.

Biodegradable starch microspheres (DSM) have recently been introduced as an adjunct to regional chemotherapy (*13–16*). When injected into the hepatic artery, the microspheres (40–50 $\mu$m in diameter) are entrapped in the arteriolar-capillary bed and block flow until they undergo enzymatic degradation (half-time = 15–30 min). Based upon differences in tumor and liver microcirculation (*17*), the administration of a suspension of DSM in an appropriate drug solution should lead to a more prolonged exposure of the tumor in the liver to the therapeutic agent and less systemic exposure and toxicity. This offers particular promise for drugs with a short half-time or low extraction efficiency. Pilot studies with BCNU [1,3-bis (2-chlorethyl)-1-nitrosurea] and mitomycin suggest that this will be a useful adjunct to regional arterial chemotherapy, with 30–90% (*13*) and 40–45% (*14*) reduction in systemic exposure, respectively.

The starch perfusion studies are an extension of this quantitative method of measuring the extrahepatic component. We have assessed changes in blood flow and shunting with increasing dosage of DSM and have evaluated the dose response on an individual basis. We have sought to determine the optimal quantity of starch microspheres that would lead to a hold-up of a drug solution in the microcirculation of tumor and liver. We have shown that the amount of shunting is related to the dose of starch microspheres, although significant baseline shunting may exist.

The decrease in PSI frequently observed in this study after injection of DSM is a transient phenomenon before the PSI rises. Presumably, this is the result of decreased blood flow caused by capillary blockade before backpressure opens up an increasing number of A-V shunts. The observation is empirical, incompletely understood, and requires further investigation.

The use of DSM with chemotherapy enhances the regional effect only if the shunt percentage stays reasonably low. SHAP studies can serve as a guide to the clinician to help determine the best dose of starch microspheres, to warn against potential complications, or suggest that changes are required in the dose of chemotherapeutic agent.

Studies correlating serum drug levels, starch dosage, SHAPS studies, and clinical response are in progress. The objective is to allow the chemotherapist to choose the most appropriate starch and drug dosage in an in-

dividual patient in order to maximize delivery of the drug to the tumor's microvasculature with minimal shunting.

Another reason for the development of quantitative techniques is in preparation for the use of yttrium-90, a pure beta emitter, in regional hepatic arterial radiotherapy of liver cancer. Some preliminary work, using yttrium-90 nondegradable microspheres (55 μm in diameter) has been reported (*18*,*19*). The results of this study suggest a quite variable range of shunting to the lung among patients and a continued low incidence of extrahepatic abdominal perfusion even with surgically implanted catheters. Quantitative hepatic artery perfusion studies will be necessary for safely applying this form of treatment for hepatic cancer.

## FOOTNOTES

* Model 400 Infusaid.
† Infusaid.

## REFERENCES

1. ENSMINGER WD, ROSOWSKY A, RASO V, et al: A clinical pharmacological evaluation of hepatic arterial infusions of 5 fluoro-2-deoxyuridine and 5-fluorouracil. *Cancer Res* 38: 3784-3792, 1978
2. ENSMINGER WD, NIEDERHUBER J, DAKHIL S, et al: Totally implanted drug delivery system for hepatic arterial chemotherapy. *Cancer Treat Rep* 65:393-400, 1981
3. KAPLAN WD, D'ORSI CJ, ENSMINGER WD, et al: Intra-arterial radionuclide infusion: A new technique to assess chemotherapy perfusion patterns. *Cancer Treat Rep* 62: 699-703, 1978
4. YANG PJ, THRALL JH, ENSMINGER WD, et al: Perfusion scintigraphy (Tc-99m MAA) during surgery for placement of chemotherapy catheter in hepatic artery: Concise communication. *J Nucl Med* 23:1066-1069, 1982
5. CHEN H-SG, GROSS JF: Intra-arterial infusion of anticancer drugs: Theoretic aspects of drug delivery and review of responses. *Cancer Treat Rep* 64:31-40, 1980
6. ECKMAN WW, PATLAK CS, FENSTERMACHER JD: A critical evaluation of principles governing the advantages of intra-arterial infusions. *J Pharmacokinet Biopharm* 2: 257-285, 1974
7. OBERFIELD RA, MCCAFFREY JA, POLIO J, et al: Prolonged and continuous percutaneous intra-arterial hepatic infusion chemotherapy in advanced metastatic adenocarcinoma from colorectal primary. *Cancer* 44:414-423, 1979
8. FREI E, III: Clinical and experimental cancer chemotherapy. In *Accomplishments in Cancer Research*. JG Fortner, JE Roades, Eds. JB Lippincott Co, 1980, pp 169-179
9. PATT YZ, MAVLIGIT GM, CHUANG VP, et al: Percutaneous hepatic arterial infusion (HAI) of mitomycin C and floxuridine (FUDR): an effective treatment for metastatic colorectal carcinoma in the liver. *Cancer* 46:261-265, 1980
10. KAPLAN WD, ENSMINGER WD, COME SE, et al: Radionuclide angiography to predict patient response to hepatic artery chemotherapy. *Cancer Treat Rep* 64:1217-1222, 1980
11. ANSFIELD FJ, RAMIREZ G, DAVIS HL, et al: Further clinical studies with intrahepatic arterial infusion with 5-fluorouracil. *Cancer* 36:2413-2417, 1975
12. BLEDIN AG, KANTARJIAN HM, KIM EE, et al: $^{99m}$Tc-labeled macroaggregated albumin in intrahepatic arterial chemotherapy. *AJR* 139:711-715, 1982
13. DAKHIL S, ENSMINGER W, CHO K, et al: Improved regional selectivity of hepatic arterial BCNU with degradable microspheres. *Cancer* 50:631-635, 1982
14. GYVES J, ENSMINGER WD, et al: Improved regional selectivity of hepatic arterial mitomycin by starch microspheres. Annual Meeting of AACR, April 28-May 1, 1982 (abst)
15. LINDELL B, ARONSEN K-F, NOSSLIN B, et al: Studies in pharmacokinetics and tolerance of substances temporarily retained in the liver by microsphere embolization. *Ann Surg* 187:95-99, 1978
16. ARONSON KF, HELLEKANT C, HOLMBERG J, et al: Controlled blocking of hepatic artery flow with enzymatically degradable microspheres combined with oncolytic drugs. *Eur Surg Res* 11:99-106, 1979
17. GYVES JW, ENSMINGER WD, THRALL JH, et al: Dependence of hepatic tumor vascularity on tumor size. *Clin Res* 30:747A, 1982
18. ARIEL IM: Treatment of inoperable primary pancreatic and liver cancer by the intra-arterial administration of radioactive isotopes ($Y^{99}$ radiating microspheres). *Ann Surg* 162:267-278, 1965
19. GRADY ED: Internal radiation therapy of hepatic cancer. *Dis Col Rect* 22:371-375, 1979