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Hepatic Arterial and Portal Venous Components of Liver Blood Flow: A Dynamic Scintigraphic Study

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Assessment of liver hemodynamics can be obtained by analysis of first pass flow studies through the liver and spleen using ^{99m}Tc compounds which are not actually trapped by these organs. This study examines new and existing methods for determining the relevant contribution made by the hepatic artery and portal vein to total liver blood flow, from these first pass studies. Eighty-two studies were performed in 56 patients with both normal and abnormal liver function. Using region of interest analysis, time-activity curves were obtained for the lungs, liver, spleen, and left kidney. These curves were analyzed by four different methods. Two of these methods are based upon measurement of the slopes of the uptake and washout curves from the liver and spleen and the other two methods employ deconvolution analysis to permit area measurement under the deconvolved curves as an indicator of blood flow. All four methods showed a small intraobserver variation after reanalysis. In 11 patients who underwent repeat studies, the correlation between the deconvolution based methods (r = 0.79–0.89) was significantly better than that for the slope based methods (r = 0.55–0.58). The deconvolution based methods provided the most significant separation between normals and patients with various liver disorders and would appear to be the most suitable techniques for monitoring the effects of various drugs and surgical procedures on the relative arterial/portal contribution to hepatic blood flow.

The relative contribution made by the hepatic artery (HA) and portal vein (PV) to total liver blood flow (TLBF) may be altered by physiologic, pathologic, and pharmacologic factors. This dual blood supply to the liver assumes major clinical importance in patients with cirrhosis where hepatic architectural changes may radically alter portal vascular resistance and flow resulting in portal hypertension. Therefore, while total hepatic perfusion may not be significantly altered, the arterial venous ratio may be considerably disturbed. In addition, drugs employed in the management of portal hypertension may affect PV or HA flow with variable effects on total liver blood flow. Consequently there is a need to define simply, accurately, and noninvasively the hepatic arterial and portal venous contribution to total blood flow in patients with chronic liver disease.

Although clearance methods (e.g., indocyanine green)

yield estimates of total liver blood flow, determination of the hepatic arterial and portal venous contribution have relied largely upon invasive procedures. In recent years, two different radionuclide techniques for the assessment of liver hemodynamics have evolved.

The first technique is based on the use of technetium-99m-(^{99m}Tc) labeled sulfur colloid (*1*). This agent is routinely used for static liver imaging. Hence, in patients undergoing routine liver/spleen scintigraphy, information on liver hemodynamics can be obtained with no additional inconvenience or radiation exposure to the patient. However, this technique is based upon the assumption that both the liver and spleen have an equal extraction efficiency for colloidal particles (*2*) and that the extraction efficiency is close to 100%. Although these assumptions are probably valid in normal subjects; they may not be true in patients with liver disease (*3*).

The second technique, which is the subject of this study, is based on the use of ^{99m}Tc-labeled compounds which are not actively trapped by the liver and spleen.

This technique was first described by Biersack et al. (4) and is based upon the analysis of a first-pass flow study through the liver and spleen. However, while the basic technique is simple, its analysis is more complex. The purpose of this study is to examine existing and new methods for analysis of the first-pass studies. This requires an examination of the various factors affecting measurement of the arterial to portal blood flow ratio and the determination of the reproducibility of the liver blood flow parameters obtained.

We have applied this method to the study of hepatic hemodynamics in control subjects, in patients with chronic liver disease, and in a smaller group of patients with portal vein occlusion.

PATIENTS AND METHODS

A total of 82 studies were performed in 56 patients. Table 1 provides the breakdown of the clinical status of these patients vis-a-vis their liver function. All patients were studied after an overnight fast. They were checked for medication known to alter liver blood flow, and patients on such medication were not studied. Control patients were selected from patients undergoing routine brain, bone, or cardiac scintigraphy for conditions unrelated to liver function. None of the control patients had any known liver abnormalities and all had normal liver function by blood analysis. Confirmation of the presence of splenic or portal vein thrombosis was obtained from angiography in the five cases presented in Table 1.

For radionuclide angiography, patients were positioned supine beneath a large field-of-view gamma camera (General Electric, Maxi II). The camera was positioned to include the lungs, liver, and spleen within the field of view. Patients were allowed to relax for 5–10 min prior to scintigraphy in order to ensure that blood pressure was at a basal value. In patients with liver disease, 10 mCi of [^{99m}Tc]pertechnetate was injected into an anti-cubital vein followed rapidly by a 30-ml bolus of saline in order to ensure rapid transit of the radionuclide into the heart. In control subjects, ~15–20 mCi of ^{99m}Tc-labeled human serum albumin, methylene diphosphonate or glucoheptonate was injected in a similar manner, depending on whether the patient was referred for cardiac, bone, or brain scintigraphy, respectively.

Images from the gamma camera were stored on an A^2 computer system (Medical Data Systems, Ann Arbor, MI). Images were acquired into a 64 × 64 word mode matrix at a rate of 0.5 s/image for 100 s. Computer acquisition was commenced with the onset of the injection.

Preliminary Data Analysis

The first 30 images of each study were summed to form a composite image showing the arterial phase of bolus transit through the hepatobiliary system. Regions of interest (ROIs) were then drawn over the lungs, liver, spleen, and left kidney (Fig. 1). Great care was taken in drawing the liver ROI to ensure that this region did not include the right kidney or the descending aorta. This meant that the left lobe and the medial/inferior portion of the right lobe of the liver were always excluded from the analysis. These ROIs were then used to generate time-activity curves (TACs) (Fig. 2). It was found that interference from the lungs into the liver ROI degraded the early portion of the liver TAC (Fig. 2, left). To correct for this, a small narrow ROI was drawn between the lung and liver ROIs (Fig. 1) and a TAC generated (Fig. 2, center). This TAC, representing cross-talk from lung into liver, was then scaled to the same height as the liver curve over the early portion of the liver curve, i.e., before the arterial phase of liver blood flow, and subtracted from the liver curve. The resultant liver curve was then initialized by setting to zero any negative curve values (Fig. 2, right). We have found that the curve
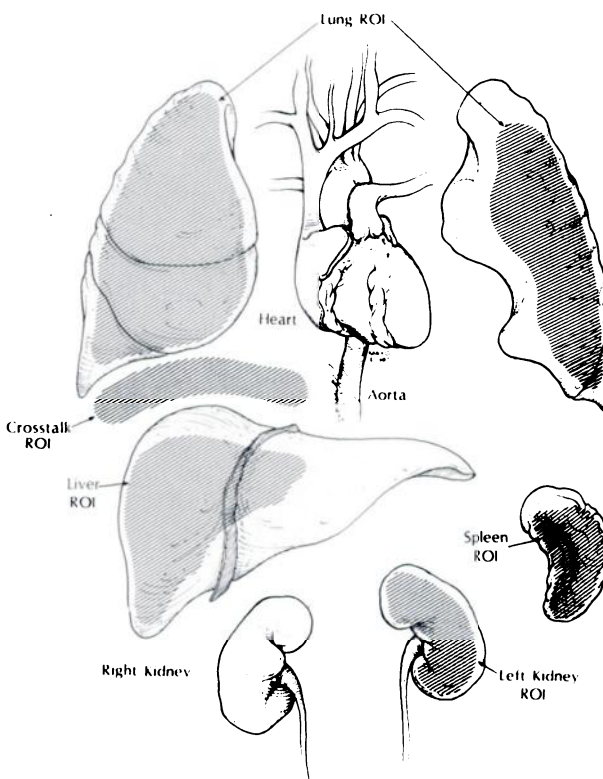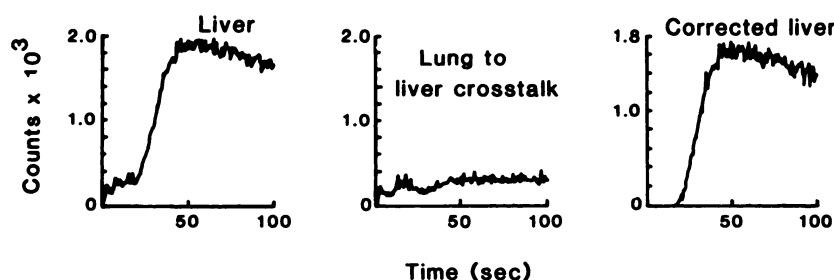

FIGURE 1
Schematic diagram showing an exploded view of the lungs, liver, spleen, and left kidney. Regions of interest are drawn over these organs and over a boundary region used to correct for cross talk from the lungs into the liver region of interest.

TABLE 1
Clinical Status of Patients with Regard to Liver Function

Clinical status	No. of patients
Normal liver function	21
Cirrhosis	19
Alcoholic	
Wilson's Disease	2
Haemachromatosis	1
Hepatitis	8
Splenic vein thrombosis	2
Portal vein thrombosis	3
Total	56

FIGURE 2
Left: Time-activity curve for the liver region of interest. Center: Lung to liver cross talk curve generated from region of interest in Fig. 1 and scaled to same height as liver curve over the time period 0–20 sec. Right: Liver minus cross talk curve. Negative curve values set to zero.

generated from the lung ROI cannot be used for this cross talk correction as it does not contain the variation in activity that is a result of respiratory motion, which is clearly seen in the cross talk curve. A similar cross talk correction was required for the splenic TAC in five of the 82 studies performed. The criterion to apply a left lung to spleen cross-talk correction was the presence of significant activity (>1% of peak splenic activity) in the early portion of the splenic TAC.

Curve Analysis

The time-activity curves for the liver, spleen, left kidney, and lungs were analyzed by two basic methods. The first method is based upon the measurement of the slope of the curves, while the second is based upon area measurements under the curves following deconvolution analysis. Two variations of each method were examined. All these methods are based on the fact that for a bolus injection, the arterial and portal phases of liver blood flow are separated in time.

Method 1. This method uses the technique of Sarper et al. (5). Briefly, the initial arrival of the bolus in the liver (T_a) was defined as the onset of the arterial flow (Fig. 3, left). The onset of the portal phase of liver blood flow (T_p) was determined from the time of maximum activity in either the spleen or left kidney (Fig. 3, right). The slopes of the arterial (L_A) and portal phases (L_p) were then measured from a linear fit to the curve over the regions T_a to $T_a + 7$ sec and T_p to $T_p + 7$ sec, respectively. The percentage arterial flow to the liver was then calculated as:

$$\% \text{ Arterial Flow} = L_A/(L_A + L_p) \times 100\%.$$

Method 2. This method is a refinement of Method 1 and was first described by Sarper and Tarcan (6). The spleen curve is analyzed in a similar manner, and over the same time period as the liver curve (Fig. 3, right). This analysis yields the slopes S_a and S_p. The ratio S_a/S_p is assumed to represent the fraction of the arterial flow that is present in the portal phase of the liver curve. The corrected portal slope is now given by $L_p (\text{corr}) = L_p - L_A(S_p/S_a)$ and the arterial flow by

$$\% \text{ Arterial Flow} = L_A/[L_p(\text{corr}) + L_A] \times 100\%.$$

Method 3. This method is based upon the use of deconvolution analysis in order to provide better temporal separation of the arterial and portal phases of liver blood flow. It also takes account of recirculation and, hence, permits analysis of the deconvoluted curves by area under the curve as a measure of blood flow. The liver, spleen, and left kidney curves were deconvoluted with the lung curve using a modified fast Fourier transform (FFT) technique first described by Juni et al. (7). This technique involves expansion of the curves from 200 out to 1,024 data points by addition of an exponentially decreasing "tail" in order to eliminate the artifacts generated by the sharp cutoff of the curves at 100 sec. Figures 4, left and 4, center show examples of the liver and spleen curves obtained from a patient with cirrhosis both pre- and postdeconvolution, respectively. If we assume that blood flow through the spleen is similar in pattern to blood flow through the hepatic artery, then the spleen curve can be used as a model for hepatic arterial blood flow. In order to compensate for differences in absolute blood flow and in attenuation by overlying tissues, the spleen curve is multiplied by a constant so that the upslope of the spleen curve matches the early portion of the liver curve (Fig. 4, right). Under this condition, the modified spleen curve can be considered equal to the hepatic arterial curve. The liver and modified spleen curve are integrated to give the areas under the curve, A_L and A_S, respectively (Fig. 4, right). The arterial flow is then given by

$$\% \text{ Arterial Flow} = A_S/A_L \times 100\%.$$

A similar analysis can be performed using the left kidney curve in place of the splenic curve.

Method 4. This employs the method of Juni et al. (8) and is similar to Method 3. In order to eliminate any artifacts due to the deconvolution process, particularly in the tails of the deconvolved curves, a gamma variant fit is performed on the modified spleen curve (Fig. 5, left). This gamma variant curve is then subtracted from the liver curve and a second gamma
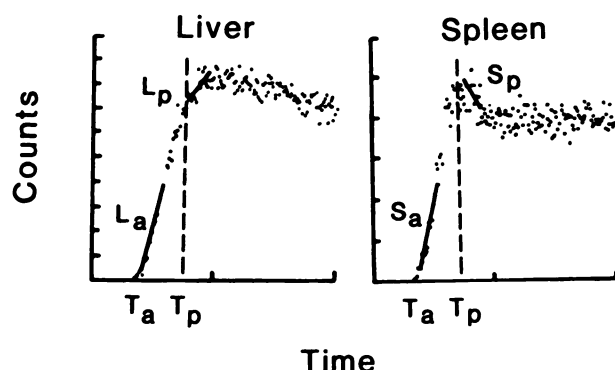
FIGURE 3
Left: Corrected liver curve showing the onset of the arterial (T_a) and portal (T_p) phases of blood flow. L_A and L_P represent the slopes of the arterial and portal phases measured over seven seconds from T_a and T_p, respectively. Right: Spleen curve showing the onset of arterial (T_a) and peak arterial flow (T_p) through the spleen. S_a and S_p represent the slopes of the curve in a similar manner to L_A and L_p.

FIGURE 4

Left: Corrected liver curve and spleen curve. Center: Liver and spleen curves following deconvolution analysis. Right: Magnitude of the spleen curve modified so that its upslope matches that of the liver curve. A_S and A_L represent the areas under the modified spleen and liver curves, respectively.

Time (sec)
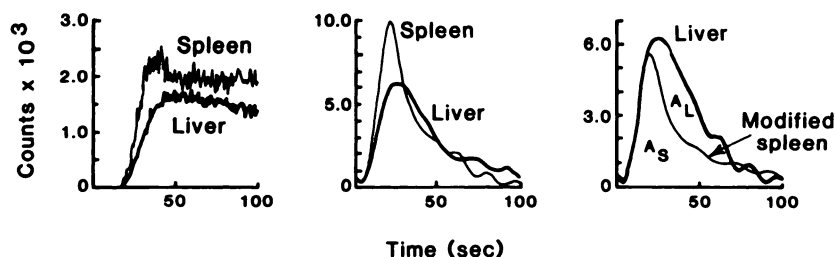
variant fit (Fig. 5, center) performed on the subtracted liver curve. The area under the first (A_a) and second (A_p) gamma variant curves are then used to calculate the arterial flow (Fig. 5, right).

$$\% \text{ Arterial Flow} = A_A/(A_A + A_p) \times 100\%.$$

As for Method 3, a similar analysis was performed using the left kidney curve in place of the splenic curve. In several studies on patients with cirrhosis (seven studies in five patients), the subtracted liver curve did not show a single dominant peak but instead showed either a broad flat topped peak (Fig. 5, center) or else a series of decreasing peaks and valleys. In such cases, the gamma variant fit was performed on the early portion of the first peak only.

Reproducibility

The reproducibility of the four methods was assessed in two ways. First, 20 studies were reanalyzed by the four methods described above without reference to the first analysis. This was done to assess the intraobserver variability in the different methods. Second, 11 patients with documented liver disease underwent repeat studies. The time interval between the first and second study ranged from 7–114 days with a mean value of 54 days. No significant alteration in the patient's clinical or biochemical status was known to have occurred in the time period between the two studies.

RESULTS

Of the 56 patients studied, the data from one patient could not be analyzed due to overlap of the right kidney and liver. A repeat study in this patient failed to yield a satisfactory result. Analysis of the liver curve with both the spleen and left kidney curves was possible in 30 of the 80 successful studies. In 42 cases only the spleen curve was available for analysis and in eight cases only the left kidney curve. Figure 6 shows the correlation between studies analyzed using the spleen and left kidney curves for Methods 2, 3, and 4. With Method 2 (Fig. 6, left), the use of the splenic or left kidney curves makes little difference to the estimation of the percent arterial flow. However, with both Methods 3 and 4 (Fig. 6, center, 6, right), the use of the kidney curve in place of the splenic curve tends to give a consistently lower estimation of arterial flow. Hence, in the eight studies in which no splenic curve was available for analysis, the estimations of arterial flow using Methods 3 and 4 were adjusted to those that would have been obtained with splenic curves, using the linear fits to Figures 6, center and 6, right as the conversion factors. Hence, all results presented below refer to analysis of the data using the liver and spleen curves only.

Methods 3 and 4, and to a lesser extent Method 2, are dependent upon the assumption that there is simultaneous arrival of the arterial bolus in the liver and spleen. To examine this assumption, a linear fit was performed to the initial upslope of the spleen and background corrected liver curves, over the period T_a to T_a plus 7 sec (Fig. 3). The intercepts of the liver and spleen curve fits on the x axis were obtained and the absolute difference between the arrival time of the bolus in the two organs was determined. In studies where a time difference of greater than 0.5 sec existed, the spleen curve was shifted laterally along the x axis to compensate for the time difference. The absolute difference in arterial flow caused by this shift is shown in Figure 7 for Method 3 (results are similar for Method 4). Out of 80 studies, 64 showed no change in arterial flow and 14

FIGURE 5

Left: Gamma variate fit to the modified spleen curve (= arterial liver blood flow). Center: Gamma variate curve from (left) is subtracted from liver curve and a second gamma variate fit performed on the subtracted liver curve (= portal liver blood flow). Right: The two gamma variate fits from (left) and (center) are assumed to represent liver arterial, and portal blood flow. The areas under these curves are given by A_A and A_P, respectively.

Time (Sec)
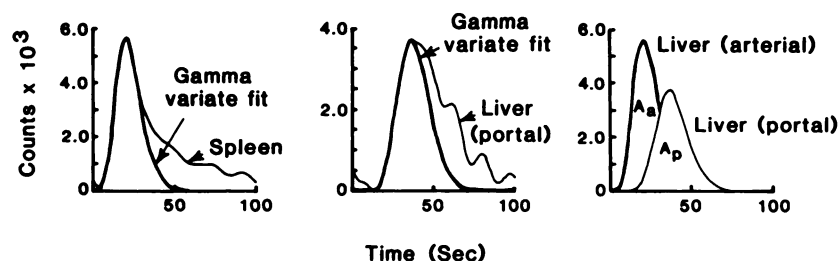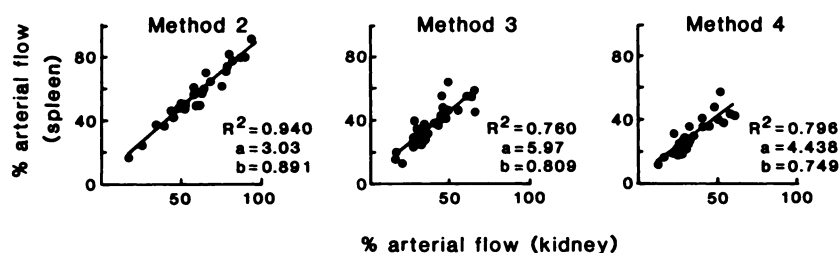
FIGURE 6
Left: Correlation between the values for % hepatic arterial flow obtained using the spleen and left kidney curves for (left) Method 2, (center) Method 3, and (right) Method 4.

showed a mean absolute change of 5% in arterial flow. In one patient who showed a 4-sec difference between spleen and liver arrival times, the data could not be analyzed until the shift correction was made. A repeat study in this patient displayed the same time difference in bolus arrival in the liver and spleen.

Although four methods of analysis are presented, these can be divided into two categories—those measuring slope and those measuring area under the curve. The correlation between the four methods was obtained by linear regression analysis and the results are presented in Table 2. While there was a good correlation between the two slope based methods and between the two area based methods, the correlation between area and slope based methods was poor (Table 2).

The intraobserver variation in the measurement of the % hepatic arterial flow was small with a mean *absolute* difference in % hepatic arterial flow of 3.2–5.1% after reanalysis for the four methods. Figure 8 shows the reproducibility of the four methods in 11 patients who underwent repeat studies. For Methods 1

and 2, the mean absolute difference in hepatic arterial flow was 9.5% and 11.0%, respectively, while for Methods 3 and 4 it was only 4.1% and 3.6%, respectively. It is possible that the poorer reproducibility of Methods 1 and 2 is a result of their greater dependence upon the quality of the injected bolus. To investigate this possibility, the full width half maximum (FWHM) of the bolus in the lungs was measured and the difference in FWHM between the first and repeat study was calculated and plotted against the mean absolute difference in % hepatic arterial flow. No correlation was found between the differences in bolus quality and the differences in hepatic arterial blood flow for any of the four methods.

Figure 9 shows the % arterial flow as a function of the patient's clinical status for Methods 2, 3, and 4. Results for Method 1 have not been presented as they are similar to those of Method 2. For simplicity, results are only presented for three patient categories—normal, cirrhosis and portal vein thrombosis. Patients with cirrhosis have been sub-divided into mild (grade A) and severe (grade B–C) disease using Child's classification (*9*). While the results for patients with severe cirrhosis were significantly different (p < 0.001) from those for normals for all methods, only Methods 3 and 4 showed a significant difference (p < 0.02 and p < 0.01, respectively) between normals and patients with mild cirrhosis. Method 4 provides the most significant separation between normals and patients with cirrhosis of varying severely; however, it underestimates the true arterial flow in patients with documented portal vein thrombosis.
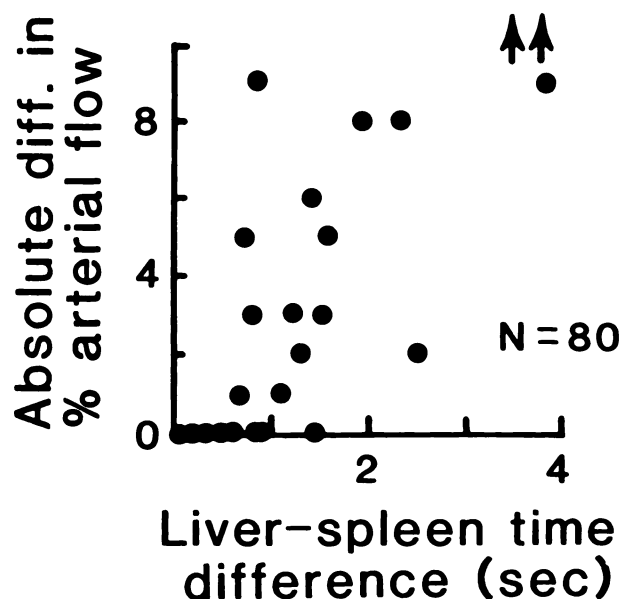
FIGURE 7
The difference in the arrival times of the bolus in the liver and spleen plotted against its effect on the calculation of % hepatic arterial flow using Method 3.

TABLE 2
Correlation Between Values Obtained for % Hepatic Arterial Blood Flow by Methods 1 to 4 Using Linear Regression Analysis

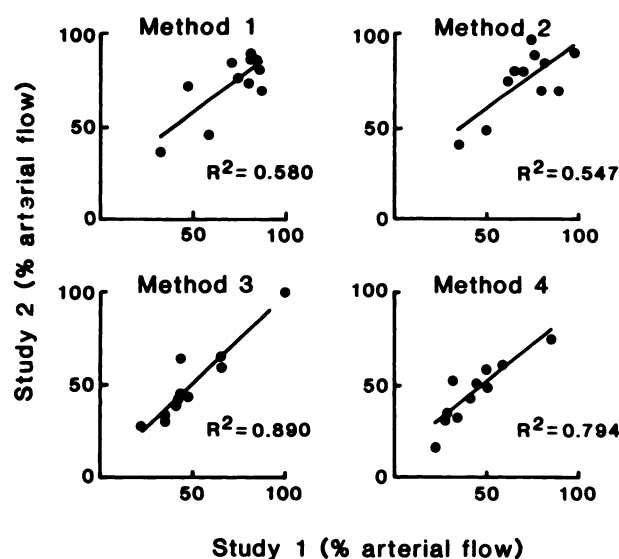| Comparison between methods	Correlation coefficient – R^2	Linear fit (y = a + b)	
		a	b
1 and 2	0.910	1.93	0.95
1 and 3	0.498	0.77	0.67
1 and 4	0.450	2.60	0.54
2 and 3	0.596	−3.35	0.74
2 and 4	0.543	−1.33	0.59
3 and 4	0.930	2.73	0.80

FIGURE 8
Reproducibility of the four methods in the eleven patients who underwent repeat studies. The straight lines represent linear fits to the data points. (upper left) Method 1, (upper right) Method 2, (lower left) Method 3, and (lower right) Method 4.

DISCUSSION

The purpose of this study was to examine the reproducibility and reliability of a number of different radionuclide techniques for the measurement of the arterial to portal ratio of hepatic blood flow.

A number of assumptions are inherent to all four methods described above. Because we can only select a small portion (upper right quadrant) of the liver for analysis, it is assumed that the remainder of the liver will behave in an analogous manner. This assumption is probably true in normals and patients with diffuse liver disease. It may not be true in patients with liver metastases, although the results of Leveson et al. (10) indicate that the technique has a high sensitivity in the detection of patients with liver metastases. A second assumption common to all methods is that the arrival time of the bolus at the spleen and liver via the hepatic artery is identical. Figure 7 shows that while this assumption is valid in 80% of cases, it can lead to a significant error in the measurement of arterial flow in certain studies. This error has a greater effect on area based methods than on slope based methods since

differences in arrival times of the arterial bolus in the liver and spleen would alter the compensation factor by which the spleen curve is modified.

Although slope based methods are simpler to apply and are less prone to the error described above, they are not as reproducible as area base methods. Figure 8 shows that Methods 1 and 2 are inferior to Methods 3 and 4 in terms of reproducibility following repeat studies. This poor reproducibility of the slope based methods has also been observed in a previous study (11). Slope based methods appear to be highly dependent upon accurate cross talk correction and require good counting statistics in the early portion of the liver and spleen curves. We used ~10 mCi of $[^{99m}Tc]$pertechnetate per study compared with 25 mCi used by previous investigators (5,10–12). This reduced dose would give rise to poorer counting statistics and may account in part for the poor reproducibility of Methods 1 and 2. Parker et al. (11) administered a 25 mCi bolus of ^{99m}Tc but failed to obtain good reproducibility in a study of eight patients with Method 2, indicating that other factors such as the selection of the time points T_a and T_p, may be responsible for the lack of reproducibility. We found that in normal subjects the selection of these time points was relatively simple. However, in patients with severe liver disease, selection of the time of peak splenic activity (T_p) was considerably more difficult thereby introducing an error in the estimation of the slope of the portal phase of the liver curve (L_p).

Methods 3 and 4 both gave excellent reproducibility in repeat studies with Method 3 slightly superior to Method 4 (Fig. 8). Although these two methods correlate well with each other (Table 2), Method 4 gives consistently lower estimates of arterial flow. When the calculated hepatic arterial flow is compared to the patient's clinical status, it can be seen (Fig. 9) that in patients with documented portal vein thrombosis, Method 4 underestimates the true % hepatic arterial flow by ~25%. Hence, the application of gamma variate fits to the deconvoluted curves may not be valid since it assumes that the response of the arterial and portal components of liver blood flow to a bolus of activity will equate to gamma variate fits, irrespective of the disease process within the liver.

In patients with portal hypertension, there is a known reduction in portal blood flow with severity of disease. This leads to an increase in arterial blood flow as a

FIGURE 9
% Hepatic arterial flow as a function of the patient's liver status. Results presented for normals, patients with mild (grade a), and severe (grade b/c) cirrhosis and patients with portal vein thrombosis using (left) Method 2, (center) Method 3, and (right) Method 4.
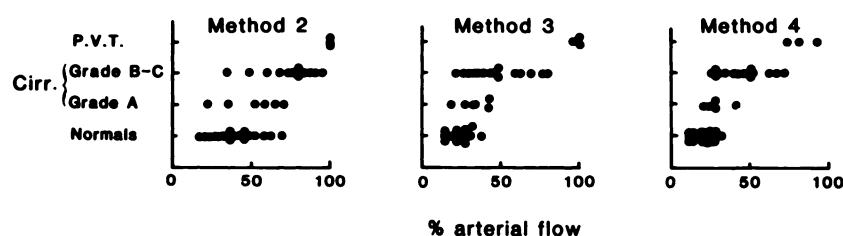
percent of total hepatic blood flow. While all four methods showed a significant difference (p < 0.001) in % hepatic arterial flow between controls and patients with severe cirrhosis, this was best seen with Methods 3 and 4. Furthermore, these two methods also showed a significant difference between controls and patients with mild cirrhosis (Fig. 9).

Thus both Methods 3 and 4 provide the best separation between normals and patients with various liver disorders and would appear to be the most suitable for monitoring the effects of various drugs and surgical procedures on the relative arterial/portal contribution to hepatic blood flow, while Method 3 is the most suitable method for the detection of portal vein thrombosis.

In summary, we have described an approach to dynamic hepatic scintigraphy involving deconvolution analysis and gamma variate fits of the liver and spleen time activity curves in order to define the arterial and portal components of hepatic blood flow. This noninvasive technique may provide valuable data on vessel pathway (e.g., hepatic arterial or portal vein thrombosis) and the effects of food or drugs on the hepatic circulation in health and disease.

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