Calculation of Portal Contribution to Hepatic Blood Flow with ^{99m}Tc-Microcolloids. A Noninvasive Method to Diagnose Liver Graft Rejection

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The portal contribution (PC) to hepatic blood flow was calculated in 13 liver graft patients and 13 normal volunteers. The method is based on the quantification and normalization of the liver and spleen activity after the administration of 7 mCi (259 MBq) of ^{99m}Tc microcolloid. Forty examinations were performed in liver grafts and 13 in normal subjects. The PC was significantly higher in normal native liver (64.0 ± 3.0%) than in functioning grafts (58.8 ± 3.1%). In acutely rejecting patients, PC was significantly lower (52.4 ± 2.0%) than in functioning grafts and similar to that observed in cholangitis (53.5 ± 0.7%). The PC increases again once rejection has resolved (57.3 ± 2.6%). During hepatitis post-transplant PC values (59.7 ± 3.4%) were similar to those observed in functioning grafts. Overall, PC values over 55% are very unlikely to be due to rejection.

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Orthotopic liver transplantation is a therapeutic option in end-stage liver disease. One of the major complications in the post-operative period is the well-known acute rejection (AR). Initially, the frequency of AR was thought to be lower than in other organ transplants (*1*), but in recent series (*2,3*) it ranged from 35% to 71%. Early and accurate diagnosis of rejection is important because it may alert physicians and allow vigorous antirejection therapy before serious hepatic function impairment. Unfortunately, this diagnosis is difficult owing to the concurrence of other complications such as infection, hepatic arterial obstructions, biliary tract complications, etc., with which differential diagnosis must be established. There is no noninvasive procedure to diagnose AR. Enzyme determinations are nonspecific and unable to differentiate among these processes (*4*), and graft biopsy frequently performed for histologic diagnosis leads to complications. In looking for an early and noninvasive method, which should allow the diagnosis of liver graft rejection before significant dysfunction occurs, we have attempted to determine the portal contribution to the total hepatic blood flow as an indicator of the function of the liver.

In this study we present our early experience.

MATERIALS AND METHODS

Thirteen liver graft patients were studied. Their mean age was 41 ± 16 yr, (range 27–60 yr). Six were female and seven were male. The indications for transplantation were hepatocarcinoma (seven cases), alcoholic cirrhosis (two cases), and acute hepatotoxicity, acute hepatic failure, Budd-Chiari disease, and sclerosing cholangitis (one case each).

The grafts were considered to be functioning grafts when clinical and biochemical data were normal. Acute rejection was diagnosed on the basis of enzyme elevation persistent for longer than 48 hr and was, in all cases, confirmed by liver biopsy according to Snover et al. (*5*).

Postrejection resolution was considered when there was a biochemical improvement after increased steroid dosage following a histologically proved rejection. Hepatitis was diagnosed on the basis of histologic data when portal cellular infiltrates were predominantly lymphocytic and of variable intensity. Two patients suffered from acute viral hepatitis (one

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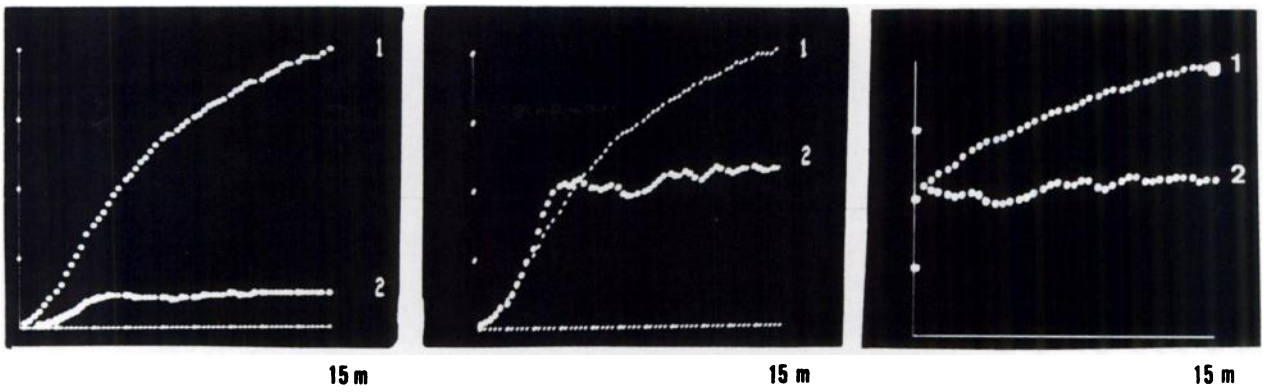

FIGURE 1
Raw liver and spleen time/activity curves (left). Scaled curves (center). Integrated segments (right). 1: liver curve; 2: spleen curve.

AgHBs negative and one AgHBs positive) and four patients suffered from nonspecific hepatitis (all cases AgHBs negative). Finally, cholangitis was diagnosed when there was fever, biliary leakage, cholestatic syndrome, and when graft biopsy excluded rejection. The interval between scintigraphy and graft biopsy was no longer than 48 hr.

Thirteen normal volunteers were also studied. Their mean age was 20 ± 2 yr (range 18–23 hr). Seven were female and six were male.

The examination was performed with the patient lying in supine position and the gamma camera detector centered over heart, liver, and spleen. A bolus of 7 mCi (259 MBq) of (^{99m}Tc) tagged microcolloid (Amerscan Hepatate II, the Radiochemical Center Amersham, particle size 0.05–0.6 μm) was injected intravenously and the activity changes in the liver and spleen were registered for 15 min (1 frame/sec the first min and 1 frame/min the remaining 14 min) and stored in a computer.

To obtain an estimation of the portal contribution to the total hepatic blood flow, we calculated the activity index PC which is based on the following assumptions.

1. The time behavior of the hepatic and spleen arterial blood flow are quite similar, thus the end of the arterial phase in both cases occurs at the same time.

2. The end of the hepatic arterial phase can be determined as the time to the first maximum (t_o) of the spleen curve, thus the activity of the liver curve after t_o "L(t)" represents predominantly the portal contribution to hepatic blood supply.

3. In order to obtain an estimation of the arterial liver curve, the spleen curve was scaled to the value the liver curve at t_o (because both arterial phases, hepatic, and splenic, are similar, assumption No. 1). To scale the curves, the liver/spleen activity ratio at t_o was calculated and all the points of the spleen curve were multiplied by this factor from t_o to the end of the study (Figs. 1 and 2).

4. An indirect estimation of the portal contribution to the total liver perfusion is obtained by the ratio (L / (L + S)) × 100, where L and S are, respectively, the areas under the liver and the scaled spleen curves from t_o to the end of the test (15 min).

5. The index calculated (PC) is an indirect estimation of portal blood flow because it depends not only on the portal blood flow but also on the microcolloid liver uptake.

Patients were examined under different clinical conditions, the first time with functioning graft and the second time with acute rejection. A total of 40 examinations were performed in the 13 patients distributed as follows: 16 examinations were performed in ten patients with functioning graft, nine in seven patients showing acute rejection, seven in four patients in the post-rejection resolution phase, two in two patients with cholangitis, and six in three patients with hepatitis.

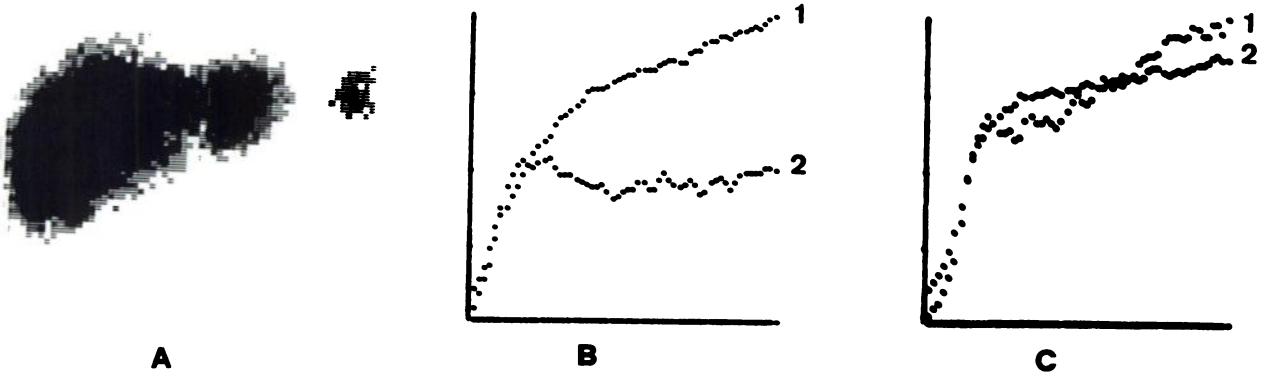

FIGURE 2
A: Anteroposterior scan of a functioning graft. Regions-of-interest were taken around the liver and the spleen. B: Liver (1) and scaled spleen (2) time/activity curves of a functioning graft. C: Liver (1) and scaled spleen (2) time/activity curves during acute rejection.

RESULTS

Mean values of PC obtained in the different groups are shown in Table 1.

Portal contribution in functioning graft livers was significantly lower than in native livers of volunteers ($p < 0.005$). There were no statistically significant differences between functioning grafts, hepatitis, and post-rejection resolution studies. In acute rejection portal contribution was significantly ($p < 0.001$) lower than in all the other groups but cholangitis.

Figure 3 shows the distribution of results in all groups. In only one out of the nine acute rejections studied was portal contribution over 53%. In functioning graft studies portal contribution ranged from 54 to 65 and was in all cases but one $\geq$ 55%. Similarly in only two out of the seven studies performed once rejection resolved was portal contribution lower than 55%. The values in all normal volunteers were >60%.

Four patients were examined once with functioning grafts and some days later during an acute rejection. The PC decreased in three while in the fourth did not change (Fig. 4).

Figure 5 shows the data of a patient examined seven times from the 11th to the 80th Day after transplantation. On Day 11 he suffered from cholangitis. On Days 13, 25, and 70 the graft was functioning. On Day 45 an acute viral hepatitis was diagnosed, and finally on Days 60 and 80 he suffered from an nonspecific hepatitis. Only during the cholangitis was PC lower than 55%.

In Figure 6 the results obtained in five cases that could be examined with functioning graft and during a hepatitis episode are shown. The PC was always over 55, though in two cases a decrease of PC was seen during hepatitis.

DISCUSSION

During acute rejection there is edema and mononuclear cell infiltration of portal tracts as well as infiltration of the portal vein and hepatic arteries (*1*). Subsequently, a decrease in liver blood supply occurs. As portal blood flow is the main component of liver blood supply, its measurement may reflect that decrease better than the measurement of arterial blood flow. The PC used in our experience is an indirect indicator of portal blood flow, but it also indicates the uptake of microcolloid by Kuppfer cells.

Our results in native livers are slightly lower than those reported by other authors (*6*). However, portal contribution in this group is significantly higher than in normally functioning grafted livers. This may be due to the fact that a number of Kuppfer cells in the donor's liver die during transplantation (*7*), and this may reduce total liver colloid uptake.

Portal contribution was significantly ($p < 0.001$) lower in acute rejection than in functioning graft, rejection resolution, and even in hepatic dysfunction due to hepatitis. The PC was in all cases but one lower than 54%. In three out of four patients examined before and during acute rejection, a decrease of PC was seen during AR. According to our results portal contribution values over 55% are very unlikely to be due to rejection. Using this criterion only one out of the nine rejections studied would be misdiagnosed (and this one case was studied in the early rejection, <36 hr of evolution). On the other hand values under 53% were seen only in acutely rejecting patients.

Brölsch et al. (*8*) in a previous report found similar alterations in the arterial fraction of hepatic flow during rejection, but their results show lower portal contribution during rejection than ours. Those authors also found a significant difference in the portal contribution between cirrhotic and tumor patients during AR as well as in functioning grafts that we did not find. The difference may be due to the relative extension of collateral circulation in the patients which, if significant, can reduce the portal blood flow. In this context special reference may be made to a cirrhotic patient who was examined six times; on three occasions with a functioning graft, twice suffering from hepatitis and once with cholangitis (graft biopsy was performed in all cases). Portal contribution ranged from 54–56% in all cases but one (59%) in which biopsy demonstrated hepatitis. This patient was transplanted for an alcoholic cirrhosis and had a very expanded collateral network. In fact PC values lower than 54% were only seen during AR, cholangitis, and in one functioning graft even when patients were examined repeatedly like this chirrihotic patient or the case showed in Figure 4.

Unfortunately, statistical analysis did not show differences between acute rejection and severe cholangitis, perhaps because of small sample size. However, cholangitis may be easily differentiated from cholestatic rejection by other diagnostic procedures such as cholangiography or IDA scan.

One important limitation of the method is that it cannot be performed in splenectomized patients because a splenic curve can not be obtained. In these

TABLE 1
Portal Contribution (%) to Hepatic Blood Flow in Normal Volunteers and Liver Graft Recipients

	N	X ± s.d. (%)	Range
Normal	13	64.0 ± 3.0	60–69
Functioning graft	16	58.8 ± 3.1	54–65
Postrejection recovery	7	57.3 ± 2.6	54–61
Hepatitis	6	59.7 ± 3.4	56–66
Acute rejection	9	52.4 ± 2.0	50–57
Cholangitis	2	53.5 ± 0.7	53–54

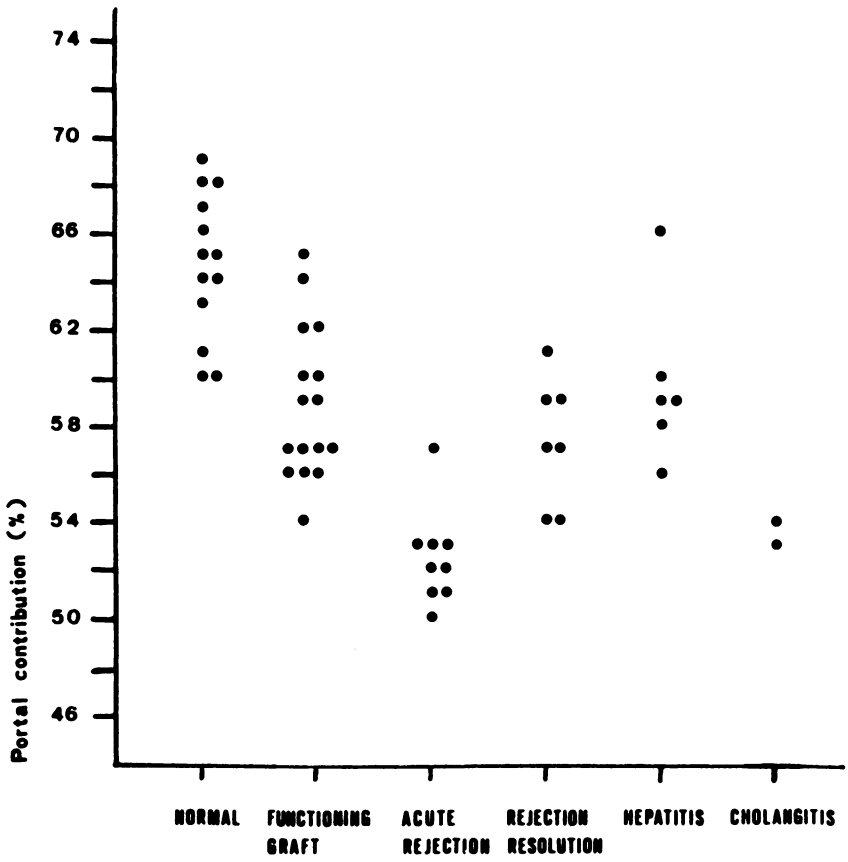

FIGURE 3
Portal contribution (PC %) to hepatic blood flow in normal volunteers and liver graft recipients.

patients we turn to IDA scanning which has been used by other authors (*9,10*). IDA scanning has the advantage of giving information on hepatocellular function and may be useful in diagnosing biliary leakage and obstruction, but in the opinion of some investigators (*11*) the information is unable to differentiate between rejection and viral hepatitis, two of the most frequent complications of the postoperative period. However, in our experience, though some patients showed a decrease of PC during hepatitis, it was always over 55% while all acutely rejecting patients but one showed a PC lower than 54%.

The method described is noninvasive, does not unduly disturb the severely ill patient, and has the advantage over biopsy that it can be repeated if necessary, without increasing the risk to the patient. In the authors' opinion therefore the ^{99m}Tc colloid method represents a valuable aid in management of patients with liver transplant. The procedure may be especially useful when patient condition precludes biopsy or when histologic data are difficult to interpret. In this situation a portal contribution >55% makes rejection very unlikely.

These results are preliminary but promising. In the future the repercussion of spleen size or of vascular complication needs to be studied. In fact larger experience is necessary to establish the actual usefulness of

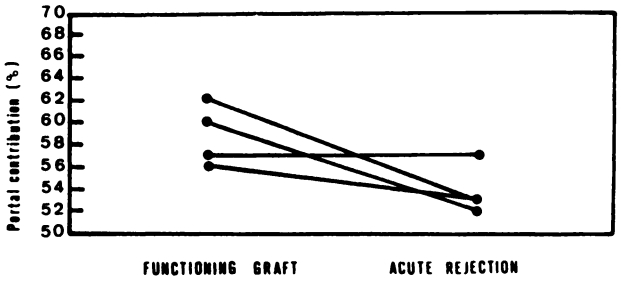

FIGURE 4
Portal contribution before (functioning graft) and during acute rejection.

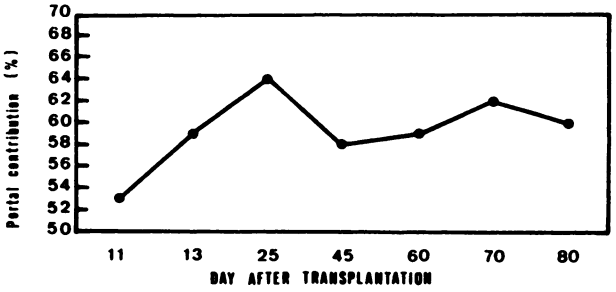

FIGURE 5
Portal contribution in a patient suffering from cholangitis (Day 11), hepatitis (Days 45, 60, and 80) and with a functioning graft (Days 13, 25, and 70).

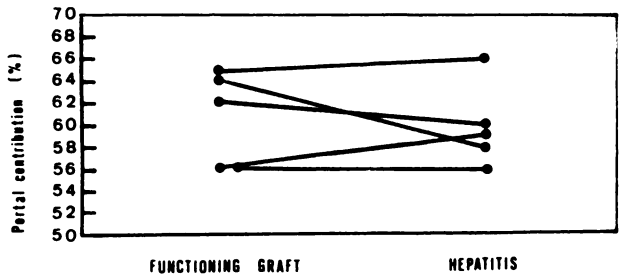

FIGURE 6
Portal contribution in five patients with functioning graft and during hepatitis.

portal contribution to hepatic blood flow calculation in the diagnosis of acute liver graft rejection.

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