Combined Hepatic Vein, Umbilicoportal Vein, and Superior Mesenteric Artery Catheterization in Portal Hypertension: Estimation of the Portal Fraction of Total Hepatic Blood Flow in Cirrhotic Patients

P. M. HUET, P. LAVOIE, A. LÉGARÉ, AND A. VIALLET

Clinical Research Center and Departments of Medicine, Surgery and Radiology, Hôpital Saint-Luc and Université de Montréal, Montréal, Québec, Canada

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Hemodynamic data were obtained in 13 cirrhotic patients with severe portal hypertension, undergoing combined hepatic vein, umbilicoportal vein, and superior mesenteric artery catheterization. The relative clearance of indocyanine green, the portohepatic gradient (difference between the free portal venous pressure and the free hepatic venous pressure), and the estimated hepatic blood flow were measured. The portal fraction (PF) of total hepatic blood flow was calculated in all patients using indicator dilution curves obtained from the portal bifurcation, a right hepatic vein, and when possible a left hepatic vein (six cases) after injection of $^{51}$Cr-labeled red blood cells ($^{51}$Cr RBC) into the superior mesenteric artery. Flows were overestimated because of loss of indicator through spontaneous portosystemic shunts; however, the ratio between hepatic and portal indicator dilution curves can be used to calculate the portal fraction of total hepatic blood flow since no extrahepatic shunts existed after the bifurcation of the portal vein (as shown on portography). In 10 patients, 15 series of curves were calculable and the PF varied between 30.1 and 100% (mean ± SE: 71.1 ± 6.2%). In the three other patients, only delayed activity from recirculation was detected from portal and hepatic vein samples and PF was 0%; in these three cases, portography and arteriography revealed spontaneous portacaval shunting with reverse and/or stagnant circulation in the portal vein. In the 13 patients, no correlation existed between PF and the relative clearance of indocyanine green or the portohepatic gradient, parameters generally used as indices of severity in cirrhosis. In 10 patients, no correlation was found between PF and the estimated hepatic blood flow.

These data indicate that $^{51}$Cr RBC dilution curves can be used for the estimation of the portal fraction of total hepatic blood flow in conscious cirrhotic patients before portacaval shunts. Using this methodology, it could be assessed whether any critical level of portal fraction exists above which poor clinical results occur after portacaval shunting. This measurement could eventually be helpful in determining the appropriate surgical procedure to be applied in individual cases.

The importance of portal inflow in hepatic perfusion and function has never been satisfactorily evaluated in awake man because of the double blood supply to the liver and the relative inaccessibility of the portal vein. A nonsurgical method, which would avoid anesthesia and dissection of vessels (as needed for the use of electromagnetic flowmeters), would be of great importance both physiologically and clinically in quantitating the components of the hepatic circulation. Recently, several indirect methods have been proposed for the separate measurement of hepatic arterial and portal blood flows (1–10); however, most of these studies are not based on an experimental model.

In a previous study, the use of portal and hepatic indicator dilution curves, after

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injection of $^{51}$Cr-labeled red blood cells (${}^{51}$Cr RBC) into the cranial mesenteric artery, has been validated for the estimation of portal blood flow, total hepatic blood flow, and the portal fraction of total hepatic blood flow in normal dogs (11). This technique was applied in 17 cirrhotic patients with severe portal hypertension undergoing combined umbilical-portal, hepatic vein and superior mesenteric artery catheterization.

In cirrhotic patients, flows are overestimated because of loss of an unknown part of the indicator through spontaneous portosystemic collaterals. However, if no extrahepatic shunts exist after the bifurcation of the portal vein, the same amount of indicator should be analyzed from the portal bifurcation and hepatic veins. Therefore, even though absolute flow values cannot be calculated, the ratio between the area of hepatic and portal indicator dilution curves can be used to calculate the portal fraction of total hepatic blood flow.

MATERIAL AND METHODS

Material

Seventeen cirrhotic patients with severe portal hypertension, 13 males and four females, aged 36–59 yr (mean: 49 yr), underwent a hemodynamic evaluation. At the time of the study, none of these patients had ascites, peripheral edema, jaundice, or alcoholic hepatitis. Diagnosis of cirrhosis was confirmed by needle biopsy of the liver in all patients: 16 of these patients had alcoholic cirrhosis. The relative clearance of indocyanine green (K-ICG) (12) was measured the week before the hemodynamic studies. Plasma disappearance curves for indocyanine green were obtained and the disappearance rate constant was derived from the function:

$$P_t = P_0e^{-Kt},$$

where $P_t =$ plasma concentration of dye at time $t$ in minutes and $P_0 =$ plasma concentration of dye at time 0; the disappearance rate constant $K$, or $K = 100$, is the fraction of retained dye which is removed per minute.

In all patients, a portal catheterization via the round ligament of the liver was performed (13) and retrograde splenography and portography were obtained using a rapid film changer.

Hepatic vein(s) and superior mesenteric artery catheterizations were performed 2 days after portal catheterization, under fluoroscopic visualization, using minimal amount of radiopaque material (less than 20 ml).

In all patients, a right hepatic vein was cannulated through an antecubital vein of one arm using a Cournand catheter (no. 8 or 9F). In six patients, a left hepatic vein was cannulated through a femoral vein by the Seldinger technique using a precurved polyethylene catheter (no. 8F). The superior mesenteric artery was then cannulated through a femoral artery on the opposite side by the Seldinger technique using a Cordis polyethylene catheter (Cordis Corporation, Miami). In two cases where a hepatic artery originated from the superior mesenteric artery the arterial catheter was advanced well into this artery beyond the take off of the hepatic artery.

Methods

(a) Pressures. Wedged hepatic vein pressure, free hepatic vein pressure, and free portal vein pressure were recorded using a Statham gauge transducer with the patient in a supine position (zero level assumed to be 5 cm below the sternal angle). Each pressure was recorded on at least two occasions.
(b) Estimated hepatic blood flow. Estimated hepatic blood flow was calculated using Bradley's method using a constant infusion of indocyanine green (14). Samples were obtained simultaneously from hepatic and portal veins at 4-min intervals for 20 min, after an equilibration period of 15 min.

(c) Portal fraction of total hepatic blood flow. Before performing indicator dilution curves (IDC), the portal catheter was withdrawn and positioned at the bifurcation of the portal vein under fluoroscopy without using radiopaque material. After a single injection of the indicator into the superior mesenteric artery, IDC were obtained simultaneously from the bifurcation of the portal vein and from hepatic vein(s) (Fig. 1). Indocyanine green was used to control the position of various catheters by direct recording of curves on photographic paper (15). However, a $^{51}$Cr RBC suspension (250 $\mu$Ci in 15 ml of autologous blood) prepared according to Wagner (16) (with three washings) was chosen as the ideal indicator as it gives, after sudden injection, a sharp peak, making it easily dissociable from recirculation (11, 17).

After instantaneous injections of 5 ml of $^{51}$Cr RBC into the superior mesenteric artery, the catheter was flushed with blood or saline. Known volumes (0.4 ml) of the same suspension counted on the automated gamma counter (Nuclear Chicago) were used as standards. Samples were collected using a peristaltic pump (30 ml/min) into

![FIG. 1. Schematic diagram illustrating the position of the injection and sampling catheters in man.](image)

![FIG. 2. Simultaneous indicator dilution curves (IDC) obtained from the portal vein (PV) and a right hepatic vein (RHV) after injection of $^{51}$Cr RBC into the superior mesenteric artery.](image)

PF: portal fraction of total hepatic blood flow.
two or three serial collection racks with heparinized tubes, running at a speed of one tube per second. A standard volume (0.4 ml) was withdrawn from each tube, counted separately, and results were plotted on semilogarithmic paper (Figs. 2 and 3). Extrapolation of the downslope to baseline, correction for background, expression of cpm per ml, and calculation of surface area were computed by a Wang calculator (11).

The portal fraction of total hepatic blood flow was calculated by the ratio between curve area simultaneously recorded from hepatic vein and portal vein. Twenty-two (22) studies were performed in the 17 patients. In six studies (six patients), samples were obtained simultaneously from one left and one right hepatic vein, and the mean curve area measured from these two different hepatic veins was used.

RESULTS

In four patients, complete hemodynamic data could not be obtained because of technical difficulties: in two patients, hepatic vein samples could not be obtained because of clotting obstruction of the catheter; in one patient, portal samples could not be obtained because the portal catheter was positioned in a narrow portal branch; and finally, in one patient, the arterial catheter was inadvertently withdrawn from the superior mesenteric artery into the aorta just before the injection, as verified by fluoroscopy. These four patients are not included in these data.

In the 13 remaining patients, complete hemodynamic evaluation was obtained.

(a) Relative clearance of indocyanine green (K-ICG). The K-ICG varied between 1.42 and 13.07% (mean ± SE: 6.28 ± 1.13%) (Table 1) (normal ≥ 16%).

(b) Portohepatography. In all cases, portohepatography was obtained. In 10 cases, the coronary vein was dilated and tortuous with esophageal varices graded as
Two IDC studies were performed in five cases (IV, VII, IX, XI, XIII).

K-ICG: relative clearance of indocyanine green.

E.H.B.F.: estimated hepatic blood flow (Bradley's method using indocyanine green).

Mean curve area obtained simultaneously from one right and one left hepatic vein. The difference between paired curve area was: 11% for patient VII, 7% for patient X, 12% for patient XI, and 30% for patient XIII.

1+ to 4+ (13) but no extrahepatic shunts were demonstrated after the portal bifurcation. In three cases (V, VI, and VIII), large spontaneous portacaval shunting was shown with reverse and/or stagnant flow in the portal vein (Figs. 4, 5), a finding subsequently confirmed by arteriographies in all 3 cases.

(c) Pressures. The mean (±SE) free hepatic venous pressure was 11.8 ± 1.3 mmHg and varied between 6.5 and 24.5 mmHg. The mean wedged hepatic venous pressure was 26.8 ± 1.6 mmHg and varied between 17 and 38 mmHg. The mean free portal venous pressure was 26.5 ± 1.6 mmHg and varied between 19 and 38 mmHg. The mean portohepatic gradient, or the difference between free portal venous pressure and free hepatic venous pressure, was 14.8 ± 1.0 mmHg (8–21 mmHg) and was used as an index of the portal hypertension (Table 1).

(d) Estimated hepatic blood flow (EHBF). In 12 cases, EHBF could be estimated and varied between 0.80 and 6.37 liters/min (mean: 2.16 ± 1.54 liters/min). However, in the two cases (XII and XIII) with high absolute values, the indocyanine green extraction was less than 5% and the reliability of the constant-infusion method is questionable (18). In one case (VIII), EHBF could not be estimated because there were no differences in the ICG concentrations in hepatic and portal veins.

(e) Portal fraction of total hepatic blood flow (PF). In 10 patients (I–IV, VII, and IX–XIII), 15 series of IDC were calculable. PF varied from 30.1 to 100% (mean: 71.1 ± 62%) (Table 1). In four of these patients (VII, X, XI, XIII), the mean difference between paired curve areas calculated simultaneously from two hepatic veins was 15.1% (7–30%) (Table 1); (Figs. 2, 3).
In the other three patients (V, VI, VIII), in whom reverse and/or stagnant flow in the portal vein was found on portography, only delayed activity from recirculation was detected from portal and hepatic veins samples (Fig. 6). In these cases, PF was 0% (Table 1). In two of these patients (V, VI), samples were obtained simultaneously from two different hepatic veins.

In the 13 patients, no correlation existed between the portal fraction of total hepatic blood flow and the K-ICG ($r: -0.234, P > 0.1$) or the portohepatic gradient ($r: 0.356, P > 0.1$). In the 10 patients in whom EHBF could be calculated and/or the indocyanine green extraction was more than 5%, no significant correlation existed between EHBF and PF ($r: 0.535, P > 0.5$).

In patient VIII, after injection of $^{51}$Cr RBC into the superior mesenteric artery, the arterial catheter was positioned into the hepatic artery under fluoroscopic visualization. Five milliliters of $^{51}$Cr RBC were injected into the hepatic artery and samples were simultaneously obtained from hepatic and portal veins. Similar IDC were obtained (Fig. 7) from these two sampling sites, demonstrating a complete inversion of portal flow. Total hepatic blood flow could be estimated from these IDC and was 2.0 liters/min using the portal IDC and 2.4 liters/min using the hepatic
FIG. 5. Umbilicosplenographies from two different series showing: gastric and esophageal varices originating from short gastric veins (a), reverse circulation into the inferior mesenteric vein with no opacification of portal vein (a and b), and large hemorrhoidal shunt (b and c) with opacification of the inferior vena cava (c) (Patient VIII).

IDC (difference: 17%) suggesting adequate mixing of the indicator within the hepatic circulation.

DISCUSSION

The use of portal and hepatic indicator dilution curves after injection of $^{51}$Cr RBC into the cranial mesenteric artery has been validated for the estimation of portal and total hepatic blood flows in normal dogs (11). With the introduction of portal catheterization via the round ligament of the liver (19), a sampling site from the portal vein is now available in man. Therefore, this technique can be applied to conscious cirrhotic patients with no surgical manipulation of hepatic vessels and no circulatory impairment to the liver.

In man, as in dogs, certain experimental conditions have to be fulfilled (11, 20, 21) for the use of the indicator dilution method: (1) the indicator must be conserved, i.e., it must not be metabolized or excreted by the liver; (2) the same amount of injected indicator must flow through the portal vein and the liver, i.e., there must be no loss of the injected indicator through extrahepatic shunts after the bifurcation of the
portal vein; (3) the indicator must be completely mixed with the blood studied at the sampling sites in the portal vein and the hepatic vein(s); (4) sampling must be representative of mixed portal and hepatic venous blood at the sampling sites; and (5) the intrahepatic circulation must be in a steady state. In cirrhotic patients, loss of an unknown part of indicator through spontaneous portosystemic collaterals resulted in overestimation of valves and absolute flows could not be calculated. However, no extrahepatic shunts occurred after the portal bifurcation, as shown on portography, and, therefore, the same amount of indicator was analyzed at the bifurcation of the portal vein and in hepatic vein(s). Thus, the ratio between the curve area obtained simultaneously from hepatic and portal veins can be used accurately for the measurement of the portal fraction of total hepatic blood flow.

In normal dogs, adequate mixing of the indicator injected into the cranial mesenteric artery was demonstrated in the portal vein (at least at its bifurcation) as well as within the hepatic circulation (11). In man, although the phenomenon of preferential lobar distribution of portal blood has never been clearly established, it has, nevertheless, been popular clinical teaching to attribute localization of liver metastases and abscesses to the selective distribution within the liver of blood flow from the area of the primary tumor or infection (22, 23). So far, in four patients, the differences found between the IDC obtained simultaneously from two different hepatic veins varied between 7 and 30% (mean: 15.1%). These preliminary findings sug-
gest that when using this indicator dilution method, adequate mixing of the indicator is achieved in the portal vein and the hepatic circulation in cirrhotic patients. Similar findings have been reported in normal and cirrhotic patients after injection of $^{131}$I albumin into the superior mesenteric or the splenic artery (24).

If confirmed, these data indicate that the indicator dilution method reported here can be used for the estimation of the portal fraction of total hepatic blood flow in cirrhotic patients. This portal fraction of total hepatic blood flow did not correlate in the 13 patients with the K-ICG and the portohepatic gradient, parameters generally used as indices of severity in cirrhosis.

This model can be applied also to study the behavior of substances removed from blood by the reticuloendothelial cells (Kupffer cells) (25) or, possibly, by the hepatocytes when compared to $^{51}$Cr RBC injected in a same mixture and used as vascular reference substance.

In conclusion, after a single injection of $^{51}$Cr RBC into the superior mesenteric artery, the portal fraction of hepatic blood flow can be estimated in conscious cirrhotic patients with portal hypertension. The measurement can be done without anesthesia which reduces total hepatic blood flow and, presumably, portal flow (26) and dissection of hepatic vessels which modifies the portal fraction of total hepatic blood flow in dogs (Huet et al, unpublished data). In patients with advanced cirrhosis and portal hypertension, therapeutic portacaval shunts have been shown to be effica-
FIG. 6. Activity recorded in samples obtained from the portal vein (PV-IDC), a right hepatic vein (RHV-IDC), and a left hepatic vein (LHV-IDC) after injection of $^{51}$Cr RBC into the superior mesenteric artery in a patient with reverse circulation in the portal vein.

FIG. 7. Simultaneous indicator dilution curves obtained from the portal vein (PV) and one right hepatic vein (HV) after injection of $Cr^{51}$ red blood cells into the hepatic artery.
cious in preventing recurrent variceal bleeding and to improve the 5-yr survival (27). However, the long-term benefits of surgery are accompanied by higher mortality due to early or progressive hepatic failure or other undesirable metabolic sequela such as encephalopathy (28). One of the consequences of standard portacaval shunts is the loss of all portal blood flowing into the liver which can aggravate the hepatic failure (29). So far, most of the splanchnic hemodynamic measurement generally used in selection of patients for portal systemic shunts cannot be correlated with the postoperative course. These include the wedged hepatic venous pressure or the free portal vein pressure (30), the hepatic blood flow (30), the maximum perfusion pressure (or the difference between pressure on the hepatic and splanchnic sides of a clamp occluding the portal vein at surgery) (31) and even the absolute portal blood flow (using electromagnetic flowmeters at surgery) (31). However, no study has been performed adding to other hemodynamic parameters the measurement of the portal fraction of hepatic blood flow. The methodology reported here can be applied in awake patients before portacaval shunts. Thus, it can be assessed whether any critical level of portal fraction exists above which poor clinical results occur after portacaval shunting. Eventually, portacaval shunts could be reserved for patients who have reduced portal fraction of total hepatic blood flow. In patients with high portal fraction, arterialization of the portal vein in association with portacaval shunt may preserve hepatic blood flow while relieving portal hypertension (32).

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REFERENCES

1. Chiandussi, L., Greco, F., Sardi, G., Vaccarino, A., Ferraris, C. M., and Curti, B. Estimation of hepatic arterial and portal venous blood flow by direct catheterization of the vena portae through the umbilical cord in man. Preliminary results. Acta Hepato-Splenol. 15, 166–171 (1968).
2. Curti, B., and Chiandussi, L. Estimation of segmental portal and splenic venous flow in man by retrograde catheterization of the vena portae via the umbilical cord. Preliminary report. Digestion 4, 141 (1971).
3. Marleau, D., Hoanca, O., Pointard, L., and Benhamou, J. P. A new method to assess separately portal and hepatic arterial blood flow in dog and man. (abstract) Digestion 4, 163–164 (1971).
4. Katz, M. L., and Bergman, E. N. Simultaneous measurements of hepatic and portal venous blood flow in the sheep and dog. Amer. J. Physiol. 216, 946–952 (1969).
5. Stone, R. M., Tenhove, W., Effros, R., and Leevy, C. M. Portal venous blood flow: its estimation and significance (abstract). Gastroenterology 62, 186 (1972).
6. Shizgal, H. M., and Goldstein, M. Measurement of portal and total hepatic blood flow by the intestinal xenon technique. Surgery 72, 83–90 (1972).
7. Strandell, T., Erwald, R., Kulling, K. G., Lundbergh, P., Marions, O., and Wiechel, K. L. Simultaneous determination of portal vein and hepatic artery blood flow by indicator dilution technique in awake man. Acta Med. Scand. 191, 139–140 (1972).
8. Reichle, F. A., Sovak, M., Soulen, R. L., and Rosemond, G. P. Portal vein blood flow determination in the unanesthetized human by umbilicoportal cannulation. J. Surg. Res. 12, 146–150 (1972).
9. Ueda, H., Unuma, T., Iio, M., and Kameda, H. Measurement of hepatic arterial and portal blood flow and circulation time via hepatic artery and portal vein with radio-isotope. Jap. Heart J. 3, 154–166 (1962).
10. Nakamura, T., Nakamura, S., Aikawa, T., Kera, K., and Sasaki, K. Measurement of hepatic arterial and portal venous blood flow in hepatic diseases. Angiology 22, 46–54 (1971).
11. Huet, P. M., Lavoie, P., and Viallet, A. Simultaneous estimation of hepatic and portal blood flows by an indicator dilution technique. J. Lab. Clin. Med. 82, 836–846 (1973).
12. Caesar, J., Shaldon, S., Chiandussi, L., Guevera, L., and Sherlock, S. The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin. Sci.* 21, 43–57 (1961).
13. Lavoie, P., Jacob, M., Leduc, J., Légaré, A., and Viallet, A. The umbilicoportal approach for the study of splanchnic circulation: technical, radiological and hemodynamic considerations. *Can. J. Surg.* 9, 338–343 (1966).
14. Levey, C. M., Mendenhall, C. L., Lesko, W., and Howard, M. M. Estimation of hepatic blood flow with indocyanine green. *J. Clin. Invest.* 41, 1169–1179 (1962).
15. Huet, P. M., Lavoie, P., et Viallet, A. Application du principe des courbes de dilution d’un indicateur à l’étude de la fraction portale du débit hépatique total. *Union Méd. Canada* 101, 656–665 (1972).
16. Wagner, H. N., Jr. Technical details of common procedures. In “Principles of Nuclear Medicine,” (H. N. Wagner, Jr., Ed.), Chap. 1, pp. 832–858. Saunders, Philadelphia, 1968.
17. Goeresky, C. A. A linear method for determining liver sinusoidal and extravascular volumes. *Amer. J. Physiol.* 204, 626–640 (1963).
18. Cohn, J. N., Khatri, J. M., Groszmann, R. S., and Kotelski, B. Hepatic blood flow in alcoholic liver disease measured by an indicator dilution technic. *Amer. J. Med.* 53, 704–714 (1972).
19. Gonzalez Carbalhaes, O. Portography: a preliminary report of a new technique via the umbilical vein. *Clin. Proc. Child. Hosp.* 15, 120–122 (1959).
20. Reichman, S., Davis, W. D., Storaasli, J. P., and Gorlin, R. Measurement of hepatic blood flow by indicator dilution techniques. *J. Clin. Invest.* 37, 1848–1856 (1958).
21. Shoemaker, W. C., Steenburg, R. W., Smith, L. L., and Moore, F. D. Experimental evaluation of an indicator dilution technique for estimation of hepatic blood flow. *J. Lab. Clin. Med.* 57, 661–670 (1961).
22. Berk, J. E., and Priest, R. J. Tumors of the liver. In "Gastroenterology," (H. L. Bockus, Ed.), Volume III, pp. 502–529. Saunders, Philadelphia, 1965.
23. DeBakey, E. M., and Jordan, L. G., Jr. Surgery of the liver. In "Diseases of the Liver," (L. Schiff, Ed.), Chap. 25, pp. 864–923. J. P. Lippincott Co., Philadelphia, 1969.
24. Groszmann, R. J., Kotelski, B., and Cohn, J. N. Hepatic lobar distribution of splenic and mesenteric blood flow in man. *Gastroenterology* 60, 1047–1052 (1971).
25. Huet, P. M., Lavoie, P., and Viallet, A. Sinusoidal fraction of portal blood flow: estimation by a multiple indicator dilution method in dogs (abstract). *Gastroenterology* 65, 547 (1973).
26. Shackman, R., Graber, I. G., Melrose, D. G. Liver blood flow and general anaesthesia. *Clin. Sci.* 12, 307–315 (1953).
27. Mikkelsen, W. P. Therapeutic portacaval shunt. Preliminary data on controlled trial and morbid effects of acute hyaline necrosis. *Arch. Surg.* 108, 302–305 (1974).
28. Read, A. E., Laidlaw, J., and Sherlock, S. Neuropsychiatric complications of portacaval anastomosis. *Lancet* I, 961–963 (1961).
29. Warren, W. D., Restrepo, J. E., Respess, J. C., Muller, W. H. The importance of hemodynamic studies in the management of portal hypertension. *Ann. Surg.* 158, 387–404 (1963).
30. Reynolds, T. B. Hepatic circulatory changes after shunt surgery. *Ann. N.Y. Acad. Sci.* 170, 379–391 (1970).
31. Burchell, A. R., Moreno, A. H., Panke, W. F., and Nealon, T. F. Hemodynamic variables and prognosis following portacaval shunts. *Surg. Gynecol. Obstet.* 138, 359–369 (1974).
32. Maillard, J. N., Rueff, B., Prandi, D., and Sicot, C. Hepatic arterialization and portacaval shunt in hepatic cirrhosis. *Arch. Surg.* 108, 315–320 (1974).