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CURRENT RESEARCH REVIEW

Measurement of Hepatic Blood Flow

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Measurement of hepatic blood flow is fundamental to understanding hepatic physiology and biochemistry, quantitating drugs metabolized in the liver, and describing pathophysiologic states such as portal hypertension. However, the dual blood supply, altered handling of labels during disease states, and the relative inaccessibility of the portal system have made precise measurements of hepatic blood flow difficult. A variety of techniques can be utilized in both laboratory animals and patients; the more invasive techniques are generally available for animal studies, while semi-invasive and noninvasive methodologies yield information from patients. Each method has its inherent strengths and weaknesses, and may be utilized in a particular circumstance to accurately assess hepatic blood flow. It is therefore critical to select a measurement technique which yields the desired accuracy without interfering with the physiologic conditions under study. The methodology is presently available to achieve this end.

INTRODUCTION

Measuring blood flow to an organ or regional bed is fundamental to the understanding of the physiology and biochemistry of a particular tissue. Although precise blood flow measurements have been made on extremities, kidney, heart, brain, bowel, skeletal muscle, and lung, a variety of technical and anatomical difficulties complicates the measurement of hepatic blood flow. The dual blood supply—the hepatic artery and portal vein—imposes the need for two flow measurements to estimate total hepatic blood flow. While hepatic vein outflow equals the total of both inflow sources, the anatomical relationship of the liver to the inferior vena cava and the short length of the hepatic vein with its intrahepatic position and proximity to the diaphragm make measurements of blood flow through this vessel difficult. Other problems arise when extraction techniques are utilized to estimate blood flow, since markers that are cleared by the liver under normal conditions are usually not extracted as effectively during disease states. Finally, the inaccessibility of the portal system in most human studies forces reliance upon the measurement of splanchnic blood flow—the flow across two anatomic beds, the liver and gastrointestinal tract—instead of the measurement of hepatic blood flow.

Because of the central role of the liver in the regulation of metabolism of the body, numerous attempts have been made to accurately measure liver blood flow. Initially basic indices of liver metabolism and function such as oxygen uptake [1], bile production [2], and galactose elimination [3] appeared independent of liver blood flow. Assuming a constant ratio between hepatic and portal flow ignores the compensatory capacity for inflow between the hepatic artery and the portal vein. This dual system provides a unique regulation of the blood supply to the liver; for example, this physiologic regulation is extremely important following portacaval shunting [4] or arterial ligation for the treatment of hepatic metastases [5].

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As research efforts are directed toward understanding the liver in health and disease, the need for integrative blood flow measurements is essential. The literature over the past 10 years describes the following applications of hepatic blood flow measurements: (1) the study of liver metabolism, (2) evaluation of portal hypertension, and (3) investigation of drug metabolism. This paper will review methods available to measure hepatic blood flow in laboratory animals and humans, and will discuss the advantages and disadvantages of the individual techniques.

CLASSIFICATION

Hepatic blood flow measurements have been classified into direct and indirect methods [6]. Direct techniques are invasive, involving exposure and manipulation of the liver or hepatic vasculature. These methods are utilized in laboratory animals or during surgical procedures in patients. Indirect techniques are either invasive, semi-invasive, or noninvasive and thus have a wider range of clinical applicability. These methods involve clearance or dilution of a dye or marker, including the uptake and wash-out of radioactive labeled substances. A discussion of the various methods under each classification follows (see Table 1).

A. DIRECT METHODS

I. Direct Flow Measurements

(a) In-continuity systems. The original methods for measuring hepatic blood flow required the attachment of glass tubing to the vessel of interest (hepatic artery or portal vein). A marker substance [7] or air [8] was injected into the proximal tubing and the rate at which it was propelled was related to blood flow. An additional device, the "rotameter," involved a small weighted object propelled in a calibrated measuring tube to a height proportional to blood flow [9]. This approach served as the prototype for our present devices which measure gas flow in wall oxygen systems. All of these approaches are currently only of historic interest.

(b) Timed collection of hepatic vein output. This method is used in animal studies and involves a collection of blood leaving the hepatic vein and quantitation of the volume accumulation over time. This approach requires cannulation of the supra-hepatic inferior vena cava and ligation of the infra-hepatic vena cava. Inferior vena caval blood is diverted to the jugular vein using a long cannula [10, 11]. Double lumen balloon catheters introduced through the femoral vein [12] or jugular vein [13] have been manufactured to accomplish a similar diversion. Portal venous blood flow can be measured by cannulating the splenic vein after splenectomy and clamping the portal vein at the porta hepatis. These collecting methods are accurate, but their use and clinical application are limited. They serve, however, as reference methods for calibrating indirect blood flow measurements [10]. When compared with direct volume–time collections, Bromosulphthalein (BSP) extraction methods in the same animal yielded 7.3% higher flow values. This difference has been explained by extrahepatic uptake of BSP.

II. Plethysmography

This technique involves venous occlusion which results in organ swelling, reflecting an acute volume change. The early volume change is directly proportional to the rate of arterial inflow. This technique has been used to estimate renal blood flow, resting extremity blood flow, and liver blood flow in small animals (rabbits). This approach requires anesthesia and laparotomy for plethysmographic placement [14].

III. Transillumination of Microvasculature

A transillumination technique was developed to determine relative changes in blood flow in small hepatic vascular units [15]. Using anesthetized small animals, a laparotomy was performed and the liver exposed. A quartz rod light carrier was introduced under the margin of the liver. The transilluminated section was examined microscopically and photographed. The size of the sinusoid was measured at a

TABLE 1

Method	Advantages	Disadvantages
A. Direct methods		
I. Direct flow measure		
a. In-continuity systems "Stromuhr" Bubble Flowmeter Rotameter	Of historic interest only.	Of historic interest only.
b. Timed collection of hepatic vein output	1. Highly accurate. 2. Used to calibrate other methods.	1. Animal use only. 2. Highly invasive and animal must be sacrificed
II. Plethysmography	1. An accurate, acceptable method.	1. Highly invasive. 2. Can only be performed in anesthetized animals.
III. Transillumination of microvasculature	1. Assessment of microvasculature.	1. Invasive 2. Measures only sinusoidal flow.
IV. Metered flow probes		
a. Electromagnetic	1. Continuous recordings. 2. Small vessels down to 0.5 mm. 3. Acute and chronic animal preparations. 4. Can be used in humans intraoperatively. 5. Multiple flow meters in same preparation. 6. Cannulated and uncannulated vessels.	1. Invasive 2. Repeated zeroing and calibration necessary. 3. Probes and equipment costly.
b. Ultrasonic	1. Acute and chronic animal preparations. 2. Human use operatively. 3. Can be totally implanted for study during awake and unperturbed states. 4. Less expensive than electromagnetic. 5. Can provide absolute values. 6. No zero drift.	1. Invasive. 2. Probably less accurate than electromagnetic probes. 3. *In situ* calibration required.
V. Heat exchange	1. Single small probe used.	1. Only a relative measure of bloodflow. 2. Baseline differences depend on position.
B. Indirect methods (*injection methods*)		
I. Dye dilution technique (PAH)	1. Easiest method when catheters in place for other reasons (i.e., substrate sampling). 2. Can study unanesthetized animals under steady-state and non-steady-state conditions.	1. Invasive. 2. Limited to animal models. 3. Noncontinuous measurements.

TABLE 1—*Continued*

Method	Advantages	Disadvantages
II. Clearance methods		
a. Continuous infusion (ICG, BSP, galactose)	1. Accurate with normal livers. 2. ICG assay easy and reproducible. 3. New assay for galactose to measure low steady-state concentrations appears accurate.	1. Invasive: need to catheterize hepatic vein to measure extraction ratio. 2. Less accurate when extraction ratio estimated, especially in face of liver disease. 3. Noncontinuous measurements. 4. BSP has larger extra-hepatic uptake.
b. Single injection 1. Dyes 2. Radiolabeled colloid 3. 99-Tc pertechnetate uptake	1. Can provide moderately accurate values noninvasively. 2. Clinical applications with serial studies. 3. Accurate compared to continuous infusion methods with same marker.	1. Not accurate when Extraction Ratio assumed. 2. Extra-hepatic uptake and risk of excessive radiation exposure in radiolabeled colloid methods. 3. Only portal/hepatic ratio obtained in 99-Tc pertechnetate uptake method. 4. Counting devices and computer support necessary for isotopic techniques.
III. Inert gas washout (^{133}Xenon, ^{85}Krypton)	1. Noninvasive with inhalation techniques. 2. Accurate, absolute flow values can be obtained. 3. Reproducible.	1. Partition coefficients affected by drugs, fat content, and liver disease. 2. Counting device and computer required for isotopic techniques.
IV. Microsphere injection/ fractional distribution methods	1. Accurate hepatic artery flow.	1. Requires sacrifice of animal. 2. Does not measure portal flow. 3. Utilizes radioisotopes.

later time from enlarged photomicrographs. The intra-sinusoidal flow was determined by photometric counters [16] and the volume of flow calculated (expressed in mM^3/sec). This method provides information only on sinusoidal flow.

IV. Metered Flow Probes

Flowmeters are utilized in animal research for the measurement of hepatic blood flow by chronic implantation methods. Alternatively, probes may be applied acutely during laparotomy to measure flow in animals or patients. In the chronic animal studies, flowmeters can provide continuous recordings in awake, unanesthetized animals during acute perturbations, and these measurements are highly accurate [17].

There are two types of flow probes available—electromagnetic and ultrasonic.

a. Electromagnetic. Electromagnetic flowmeters function on Faraday's principle of electromagnetic induction, where the velocity of blood through a magnetic field generates an induction voltage which can be measured between two electrodes [18–20]. The voltage

generated is directly proportional to the blood flow. The method involves the placement of two electrodes on the outside of the vessel being studied at 90 degree angles to the vessel. Alteration of this axis decreases the signal as the sine function of the angle. A deviation of 10 degrees still yields, however, a 98.5% maximal signal [21]. It is important during studies that probe movement be eliminated. Investigators have implanted these probes in chronic preparations so that their position becomes fixed relative to the vessel when the studies are done.

Disadvantages of this method include improper placement of the probe on the vessel and turbulence caused by constriction of the vessel by a tight-fitting probe [22]. In general, the diameter of the probe should be approximately 5–10% less than the vessel diameter to ensure a snug fit without constriction. Also the ratio of the inner and outer diameters of the blood vessel influences the sensitivity of the method, since vascular walls have different conductivity than blood [23]. Thus in a small caliber vessel, like the hepatic artery, blood flow may be underestimated using this technique. When corrected for wall thickness, however, perivascular electromagnetic meters are accurate to ±5% [24]. Electromagnetic flowmeters require extensive calibration and repeated zeroing because of the drift from zero baseline that may occur [25]. The probes must first be calibrated with zero flow in the vessel. This is best achieved by clamping distal to the probe so that the vessel is filled with blood and the conductivity of the tissue within the probe is similar to that achieved during the physiologic state. It is suggested that each probe be calibrated under experimental conditions utilizing blood rather than saline, since changes in viscosity alter blood conductivity [26, 27]. There are, however, high input resistance instruments available that demonstrate almost no error with changes in hematocrit [26].

Advantages of this method include the use during both acute and chronic animal experiments, use on large and small vessels, and use in cannulated and uncannulated vessels [28]. Wiring from the probe can be buried in the subcutaneous tissue of the animal's flank for repeated access during chronic experimentation. It is also possible to place two probes in the same vicinity (i.e., hepatic artery and portal vein) and record both simultaneously, provided each is zeroed while the other is operating [24]. These measurements can also be made in human subjects during operative procedures [29]. Prior to portacaval shunting, the effect of portal vein clamping on hepatic artery flow can be assessed [30]. Electromagnetic flow probes, once calibrated, provide accurate data which serve as standards by which other methods are measured. The disadvantages of this technique involve the implantation of the probes and the expense of both the probes and the recording equipment.

b. Ultrasonic. Three basic types of ultrasonic flow probe devices are available. The pulsed ultrasonic probe uses two piezoelectric transducers attached to opposite sides of the vessel at 45 degree angles to the vessel's long axis. Each probe transmits and receives alternatively signals sent at 800 times per second; flow is calculated from the time difference between the upstream and downstream signal velocities. The Doppler frequency shift [31] flowmeter is similar to the pulsed instrument, however one transducer is the transmitter and the other is the receiver, making the signal unidirectional. These devices have been used to measure relative changes in flow, while absolute flow determinations remain difficult without accurate *in situ* calibration. A more practical device has recently been tested in dogs. A totally implantable and telemetered pulsed Doppler ultrasonic probe is placed at operation and the awake animals studied following recovery [32]. The singular probe acts to both transmit and receive the signal, as well as estimate vessel size. The flow volume is estimated by multiplying the vessel cross-sectional area by blood flow velocity. This device does not demonstrate the zero drift that is common with the electromagnetic probes. Accurate portal vein flow measurements have been made by this approach, but the simultaneous measurement of portal vein and hepatic artery flow is impossible because of signal interference. This problem may be circumvented by nonsimultaneous measurements

performed at alternating intervals [33]. The equipment cost is much less when compared to the electromagnetic technique (probe cost is approximately 1:15), hence probe depreciation during chronic animal experiments is more economical using ultrasonic probes. With chronic implantation, however, calibration of ultrasonic probes is performed at the end of the study. The assumption that probe function was constant over the course of the experiment is necessary to convert the signals to accurate absolute flow values.

V. Heat Exchange Techniques

Heat exchange methods rely on the theory that changes in the temperature of a heated thermocouple are directly proportional to the rate of blood flow bathing the thermocouple. The thermocouple can be implanted in the liver or hepatic vein [34, 35]. Placement of the probe into the hepatic parenchyma has practical use in humans as the thermocouple can be implanted by percutaneous needle, peritonoscopy, or at the time of operation [28, 36]. This method detects only relative changes in hepatic blood flow. Baseline differences are dependent on the position of the device in the liver [37]. Probe temperature may also be affected by the metabolic state of the liver and hence this method is only a semiquantitative approach to measuring blood flow.

B. INDIRECT METHODS

The indirect methods in this classification include all techniques which involve the injection of metabolized or nonmetabolized dyes, other markers, and radioisotopes.

I. Dye Dilution Technique

The dilution of a nonmetabolized marker such as the inert organic dye *para*-aminohippurate (PAH) is a valuable method for measuring blood flow to an organ or regional bed. The method proposed by Katz and Bergmann studied regional flow in the sheep and dog following placement of indwelling catheters [38]. Laparotomy was required for placement of the infusion and sampling catheters, although the hepatic vein catheter can be positioned percutaneously under fluoroscopic control [39, 40]. Following recovery, the dye was infused continuously through a catheter placed in a small tributary of the mesenteric vein until steady state was achieved. Sample catheters, placed in the portal and hepatic veins, and an artery were used for simultaneous withdrawal of blood for substrate and dye analysis. The blood flow was calculated from

$$F_{pv} = I/(C_{pv} - C_{art})$$

where F_{pv} = rate of blood flow (in ml/min) in the portal vein, I = perfusion rate of PAH (in mg/min), C_{pv} = conc. of PAH (in mg/ml) in the portal vein, and C_{art} = conc. of PAH in the arterial blood. Similarly flow in the hepatic vein was determined by

$$F_{hv} = I/(C_{hv} - C_{art}).$$

Hepatic artery flow was calculated by subtracting portal from total hepatic flow. Simultaneous blood samples can be obtained for substrate analysis in studies in awake animals, studied during steady state, and possibly non-steady-state conditions. The Bromosulphthalein (BSP) extraction method (discussed later) compares favorably with this technique (BSP values are 95 ± 4% of PAH measurements when both methods were used in the same preparation [41]). The disadvantages of the dye dilution technique include the need for catheter implantation, the variation that may occur during blood sampling, and the inability to make continuous non-steady-state measurements. This technique is almost exclusively confined to laboratory animals.

II. Clearance Methods

Certain substances introduced into the bloodstream are cleared by the liver and the rate of disappearance from the blood stream is used to estimate hepatic blood flow. Dyes and radioactive-labeled substances are utilized in these methods and can be continuously infused or administered as a bolus.

a. Continuous infusion. This method described by Bradley [42] is based on the Fick principle: under conditions of constant flow, the volume of blood moving through an organ

per unit time (Q) can be calculated by determining the amount of indicator extracted (R) over that time and the concentration difference of the indicator entering (C_i) and leaving (C_o) the organ. The equation for this relationship is:

$$Q = R/(C_i - C_o).$$

Under steady-state conditions, the intravenous infusion rate (I) of an indicator removed exclusively by the liver equals the rate of hepatic removal ($R = I$). C_i is determined from blood obtained from a peripheral vein or artery (since the dye concentrations are the same) and C_o is measured in hepatic vein blood drawn from a previously placed catheter. Because most indicators currently used are distributed only in plasma, the calculated plasma flow can be converted to blood flow by knowing the hematocrit:

Q(blood flow in liters/min)

$= Q$(plasma flow in liters/min)

$\times 1/1 - \text{Hct}.$

The indicators used for continuous infusion methods include indocyanine green dye (ICG), Bromosulphthalein, and ^{14}C-labeled taurocholate. Compared with ICG, the ^{14}C-taurocholate method yields a 22% higher blood flow, but the two techniques correlate well [43]. ICG is the preferred substance as it has a high hepatic extraction ratio, extrahepatic uptake is absent, toxicity is low, and the measurement is easy (analytical error of ICG determination is less than 2%) [44]. With BSP, extra-hepatic uptake and recirculation via the entero-hepatic route occur [28]. When compared to values obtained by pump-generated flow via the hepatic artery and portal vein, the ICG values were equivalent and correlated linearly [45]. There is also good agreement between electromagnetic flow and constant dye infusion values.

There are several disadvantages to this technique. The procedure requires hepatic vein catheterization, a moderately semi-invasive procedure using percutaneous techniques. Position of the catheter tip is important for it must be deep in the hepatic vein but short of wedged position [46]. Backflow of blood from the inferior vena cava can occur during sampling and such dilution of the hepatic venous sample introduces error. Either the left or right hepatic vein is acceptable for sampling, but the major right hepatic vein is usually larger and generally more suitable [44, 47]. While the hepatic extraction ratio (ER) (estimated by $(C_i - C_o)/C_i$) is usually greater than 90% in normals, it is much lower in patients with severe liver disease. Moreover, the back-diffusion of dye from the hepatocyte into the hepatic vein may occur in the septic patient [48]. Poor extraction and back-diffusion result in narrow arterial-hepatic vein dye concentration differences and an overestimation of blood flow.

Until recently, estimation of hepatic blood flow from first-order galactose clearance by the liver has been limited by the method used to assay galactose [49, 50]. With a more sensitive determination (coefficient of variation = 8.6% at 0.01 mg/ml), galactose can be infused at a constant rate to attain the low steady-state concentration required to measure disappearance. The high hepatic extraction ratio of galactose makes blood flow the primary determinant of clearance. The ER has been measured as 94% in normals and 79% in cirrhotics [49]. By measuring arterial and hepatic vein concentrations of galactose, an accurate ER can be calculated which allows the determination of hepatic blood flow. Alternatively, clearance can be measured without hepatic vein determinations and ER estimated from liver function [51].

b. Single injection (bolus method). The clearance of a bolus of dye will allow calculation of hepatic flow. A single dose of ICG (or BSP) is given and frequent and simultaneous blood samples drawn at timed intervals (every 3 min) from a peripheral artery (or vein) and hepatic vein. Plasma dye concentrations are determined and whole blood dye clearance (BC) is calculated as [44]

$$\text{BC} = \text{Dose}/\text{AUC}_a \times (1 - \text{Hct})$$

where AUC_a is the area under the peripheral artery decay curve. The extraction ratio is calculated by

$$\text{ER} = (\text{AUC}_a - \text{AUC}_{hv})/\text{AUC}_a$$

where AUC_{hv} is the area under the hepatic vein curve. The hepatic blood flow is

$$HBF = BC/ER.$$

This estimation correlated very well with values from the continuous injection ICG method in patients with liver disease who were studied by both methods [44]. A noninvasive method for estimating HBF using a single injection, time curves for plasma clearance, $t_{1/2}$, and volume of distribution has also been used in normal human volunteers. This particular method yields reproducible values which correlate well with known values of hepatic blood flow [52].

One advantage of the single injection method is the speed with which the test can be performed. Timed samples drawn over a 15- to 20-min period after bolus injection make this technique applicable to repeated tests in volunteers and patients. The bolus technique allows more precise determinations of ER in patients with liver disease and limited capacity for dye extraction, because dye saturation and back-diffusion do not occur in the early period following bolus administration. If an ER is assumed, hepatic vein sampling is not required and this approach may have advantages in certain clinical situations. Assumed values for extraction ratio have been used in certain studies [53, 54]. ER for ICG has been reported between 0.6 and 0.9 [1] and as low as 0.1 [55] in severe liver disease. The assumption of ER = 1 leads to an underestimation of liver flow in patients with liver disease.

A variety of radioactive-labeled colloid substances have also been used for estimating hepatic flow following their bolus injection. The colloids are taken up by the Kupffer cells of the liver's reticuloendothelial system at a rate that is proportional to blood delivery. Plasma disappearance and hepatic uptake are measured by external counting and blood flow is calculated from the elimination rate constants for colloid clearance. In early studies ^{131}I-albumin was introduced into the portal system via splenic pulp injections [41, 56–58], but now colloids are more commonly administered via a peripheral vein, making the procedure less invasive. Radioactive-labeled gold, phosphorus, and technetium colloids have all been used to measure liver blood flow [;59–62] Tc-99m-sulfur-colloid is commonly used in functional liver scintigraphy and has been used for estimating portal fraction and total hepatic blood flow measurements [63]. ^{51}Cr-labeled red blood cells have been injected and when this method was compared to electromagnetic flow probe measurements in the same animal, comparable values were obtained [41]. The chromium method is undesirable in humans due to excessive radiation exposure.[3] All colloids are subject to extrahepatic uptake (notably in the spleen), introducing methodological error. However a new noncolloidal, liver-specific compound (Tc-99m-galactosyl-neoglycoalbumin) has been developed which may have valuable practical applications in human liver blood flow measurements [64].

c. Tc-99m-pertechnetate uptake. The technetium-99m-pertechnetate hepatic uptake is a single injection, clearance method. However this technique deserves separate discussion because of the relevance of the technique to clinical medicine. A ratio between hepatic artery and portal vein flow can be measured although absolute values for blood flow are not obtained [65, 66]. The time–activity curve of the uptake is monitored externally over the liver and two separate slopes are plotted which correspond to hepatic artery and portal vein activities. The hepatic artery activity corresponds to the arterial phase in other visceral organs (i.e., the kidney), which can be measured separately and superimposed on the liver curve [66]. More recently, the Hepatic Perfusion Index (HPI) has been described for normals and cirrhotic patients. The HPI is basically a ratio of portal flow to total liver blood flow and the flows are expressed in the form of slopes of liver uptake curves generated by hepatic artery and portal vein activity [66]. Lung activity is also measured and subtracted

[3] Both the ^{131}I-albumin method and the ^{51}CR-labeled red blood cell technique utilize indicator-dilution methodology for the determination of hepatic blood flow. All other techniques utilizing radioactive colloids involve clearance calculations.

from the liver activity. Original methods underestimated HPI in patients with decreased portal perfusion. A new method which subtracts hepatic artery washout (estimated from splenic washout) yields a true portal slope on the biphasic curve. This method is reproducible and correlates with angiographic grades of hepatic perfusion [67].

The HPI is approximately 66% in normals and decreases with varying severity of liver disease. This value compares with a mean of 71.9% in normals measured under anesthesia with electromagnetic flow probes [30]. Problems with this index are encountered in patients with small livers and in post-op patients where contributions from portacaval shunts cannot be eliminated. While the method does not provide absolute values for hepatic flow, a technique is provided whereby cirrhotics can be followed for deteriorations in flow.

III. Inert Gas Washout

Inert radioactive gases like xenon-133 and krypton-85 have an instantaneous distribution between tissue and blood according to a specific partition coefficient (λ). These gases can be delivered to the liver directly by intraparenchymal injection [68, 69], intrasplenic injection [70], bolus injection into the portal system [71, 72], or by inhalation and vascular transport [73]. These injection methods are invasive or semi-invasive and are limited to animal studies. The method relies on the principle that, following injection, equilibrium between blood and tissue is reached. The tag is then washed out from the tissue and the rate of disappearance equals the rate of blood flow. Disappearance is measured by external counting devices and the flow is estimated by [74]

$$\text{flow} = (\lambda \times \log 2 \times 60)/t_{1/2}$$

where $t_{1/2}$ is the time for the radioactivity to decrease by half the initial value. The decay curve is bi-exponential [68] and the $t_{1/2}$ is measured from the fast component. Another method uses the height/area of the curve multiplied by $100 \times \lambda$ to estimate total hepatic flow [45]. This height/area calculation yields values which correlate well with controlled pumped flow and ICG clearance methods in isolated pig livers. Good correlation between intraportal or intrasplenic injection and electromagnetic flow measurements has been demonstrated in dogs [70].

These methods are reproducible in the same individual within a 3–5% range [73, 75]. With portal injection the coefficient of variation ranges between 12 and 22% when multiple studies were performed in the same animal [74]. Errors in the method are introduced when the partition coefficient (assumed to be 0.72 between liver and blood) is influenced by hepatic fat, drugs, and liver disease. λ must be corrected for hematocrit or the liver flow is underestimated [45]. Background radioactivity from the lung interferes with liver washout counting. This can be eliminated by subtracting lung background or limiting hepatic counting to the lower edge of the right lobe of the liver (which may not be representative of the total liver with respect to blood flow and fat content).

IV. Microspheres/Fractional Distribution Method

Radioactive and nonradioactive-labeled microspheres have been used to measure gastrointestinal blood flow but this method has limited use in hepatic blood flow measurements. Only the arterial blood supply can be measured by this technique for the microspheres are trapped in the capillaries of the gastrointestinal tract and do not enter the portal system. Arterial inflow can be assessed in animals after portacaval shunting [76]. Sacrifice of the animal is required after microsphere injection.

The fractional distribution method is quite similar to the microsphere technique. Radioactive substances (^{42}K, ^{86}Rb, ^{131}I) are injected intravenously and all organs are counted to detect which fraction of the cardiac output each has received [77].

V. Radiographic Methods

Radiographic methods have been developed which allow quantitative summation of contrast medium over a cross section in a vessel during angiography [78]. The results are displayed in a time–density curve which can be

analyzed along with the vessel volume to calculate blood flow [78, 79]. Angiodensitometry has been utilized to investigate cardiac hemodynamics, but the measurement of liver blood flow by this method has been limited to specific laboratories [78, 80, 81]. These methods are limited to hepatic artery flow because catheter access to the portal system is difficult. However a unique method of umbilical and portal vein catheterization has been used to isolate portal blood flow in patients with normal and diseased livers [82, 83]. The catheters are placed during laparotomy or extra-peritoneal dissection through a small midline incision and flow is subsequently measured by cineradiography of injected radioopaque lipiodol droplets. The product of the measured velocity of the droplets and the cross-sectional area of the portal vein yields the blood flow. While being invasive, this method provides accurate portal flow measurements in unanesthetized individuals.

CONCLUSION

A variety of techniques exist for the measurement of hepatic blood flow. There are direct and indirect and invasive, semi-invasive, and noninvasive methods which have been outlined; each have their inherent strengths and weaknesses. It is critical to select a technique which yields desired accuracy without interfering with the physiologic conditions under study.

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