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The Measurement of Liver Blood Flow: A Review of Experimental and Clinical Methods

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Changes in hepatic blood flow reflect adaptive responses of the liver to injury, regeneration, and the development of disease states. The measurement of hepatic blood flow is, however, technically challenging and although theoretically useful has not become routine in clinical work. The different techniques that have been developed for quantitative measurement of hepatic blood flow require careful interpretation of the results obtained but are frequently applied without careful considerations of their technical limitations. In particular, many noninvasive techniques depend on good hepatocellular function and are thus irrelevant under most clinical conditions. Many other potentially useful techniques are poorly validated and standardized and there is a need for further research into methodology.

This review summarizes the salient technical features of the different techniques for quantitative measurement of hepatic blood flow. The techniques are divided into invasive, minimally invasive, and noninvasive categories and the relevance of each technique to both routine clinical application or research is discussed.

Key Words: **liver blood flow; experimental method; clinical method; functional liver blood flow; clearance; first-pass; Doppler ultrasound; radionuclide; flowmeters; indicator fractionation.**

INTRODUCTION

Hepatic blood flow (HBF) is an important physiological parameter of liver function and disease and reflects adaptive responses to injury, regeneration, and the development of malignancy [1–4]. However, the technical challenges to accurate HBF measurements are considerable, with the main ones being a dual blood supply, difficult direct access, and the inconstant ratio of portal venous to hepatic artery blood flow [5, 6]. In addition, many noninvasive techniques for measuring liver blood flow depend on good hepatocellular function and are thus irrelevant under most clinical conditions. Thus, although measuring HBF is relevant to the management of many clinical conditions, this has not become routine.

Many techniques for measuring HBF are nonquantitative, but more clinically useful quantitative techniques are available. The technical limitations of the currently available quantitative techniques require careful interpretation of results but are frequently applied in the clinical or research settings without taking these limitations into account. This paper reviews existing methods that measure HBF in quantitative terms and classifies them according to their relative potential for routine clinical application or research (Table 1).

INVASIVE TECHNIQUES

Direct Flow Measurements

Direct flow measurements are essentially timed collection of hepatic venous outputs and involve suprahepatic inferior vena cava (IVC) cannulation, ligation of the infrahepatic IVC, and diversion of infrahepatic IVC blood to the jugular vein using long cannulae or double-lumen balloon catheters [7]. Extreme physiological and anatomical disturbances are caused and their only application is in experimental work as reference methods.

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TABLE 1

Classification of Methods for Measuring Liver Blood Flow

Invasive methods: require surgical placement of measuring devices in the peritoneal cavity, or methods are sacrificial in nature, i.e., requires postmortem analysis.
1. direct flow measurement
2. electromagnetic and ultrasonic flowmeters
3. reference sample (microspheres)

Minimally invasive methods: require cannulation of central vessels, e.g., transjugular cannulation of hepatic vein, transfemoral cannulation of hepatic artery
1. indicator dilution
2. hepatic clearance
3. inert gas washout
4. radiographic imaging

Noninvasive techniques: include those that require peripheral venous access
1. transabdominal Doppler-duplex ultrasonography
2. first-pass analysis of nondiffusible intravascular tracers
3. MRI/PET scans

Electromagnetic and Ultrasonic Flowmeters

Electromagnetic (EMF) and ultrasonic (USF) flowmeters require surgical placement and may be chronically implanted. Relative movement between the probes gives rise to errors and calibration and repeated zeroing must be carried out to avoid drift from baseline [8]. With both of these flowmeters, the diameters of the probes must be 5–10% less than that of vessel diameter to fit snugly without constriction and flow turbulence [9] but under physiological conditions, the portal veins in particular vary in size with the phase of respiration by as much as 40% in human subjects [10] and constriction and turbulent flow are inevitable. Changes in portal pressure after hepatectomy also greatly influence portal vein diameter and can be increased by up to one third [11]. Changes to blood viscosity also alter conductivity [12]. With EMF, the ratio of the inner to the outer diameters of the blood vessel significantly influences the sensitivity of the method, especially in small-caliber vessels such as the hepatic artery [13]. Measuring flow in both the portal vein and the hepatic artery simultaneously is possible with EMF (giving real-time HBF), although significant signal interference renders this impractical with USF.

The widest application of EMF and USF is in large animal research, although the technique has been used in human subjects after liver surgery [14] in patients with liver cirrhosis [15], and in the early period after transplantation [16].

Indicator Fractionation or Reference Sampling Method

The measurement of regional blood flow by determining the fractional distribution of cardiac output was first reported by Sapirstein in 1958 [17] and was subsequently applied to the liver. A known amount of radioactive microspheres is injected into the left ventricle and a reference sample is simultaneously withdrawn from a peripheral artery at a known rate using a pump. The injected radioactive microspheres are extracted with 100% efficiency, being trapped in the various vascular beds in the body in proportion to the fraction of the cardiac output that supplies the individual vascular beds. The experimental animal is subsequently sacrificed, the organs removed, and the amount of microspheres trapped within the organs determined by the amount of radioactivity present and compared to the reference sample to arrive at organ blood flow. Radioactivity in individual organs is determined by a gamma scintillation counter and defined as radioactive counts per minute (CPM). Examples of radioactive nuclides used to label microspheres are ^{57}Co and ^{51}Cr [18, 19].

$$\text{CO (cardiac output)} = \frac{\text{injected radioactivity}}{\text{reference blood radioactivity}} \times \text{reference blood flow (ml/min)}$$

similarly:

$$\text{organ blood flow} = \frac{\text{organ radioactivity}}{\text{reference blood radioactivity}} \times \text{reference blood flow}$$

The liver presents special problems because it has a dual blood supply. Only hepatic arterial blood flow (HAF) can be measured directly by this method and portal venous flow (PVF) is estimated by adding the separate flows to the splanchnic organs that drain into the portal vein. Portal-systemic shunting (PSS) can be estimated by injecting a second radioactive microsphere directly into either the splenic or mesenteric vein [20]. Microspheres shunted into the systemic circulation will be trapped in the lungs and shunts can be quantified. The calculation of PSS will differ depending on whether microspheres are injected into the splenic (overestimates shunting) or mesenteric vein (underestimates shunting).

Uniform mixing of the microspheres with blood is assumed. Significant reduction in organ blood flow can occur when large numbers of microspheres are injected [18] and blood loss from reference sampling should be $<1\%$ of the cardiac output to maintain normal hemodynamics [21]. The rate at which the microspheres are injected also influences the measured blood flow [18]. This method, however, has little impact on circulatory physiology if used judiciously and is accurate and reproducible. The radiation involved mandates special precautions on the part of the researcher and the co-

loured microsphere technique was developed to overcome this limitation [22].

Postmortem removal of the organs is necessary and the method has no clinical application, although it is a good research tool.

MINIMALLY INVASIVE METHODS

Clearance Method

In principle, the rate of disappearance from the bloodstream of an indicator substance exclusively cleared by the liver is proportional to the rate of hepatic blood flow. This derivation of the Fick principle was first used by Bradley to measure liver blood flow in 1945 [23].

$$E = HBF \times (Ci - Co)$$

Where

E = rate at which indicator is extracted
Ci = concentration of indicator entering the liver
Co = concentration of indicator leaving the liver

thus

$$HBF = \frac{E}{Ci - Co}$$

Because clearance is never purely flow-dependant and the indicator is never totally extracted by the liver during first pass (i.e., Co is never 0), in practice, hepatic vein catheterization is mandatory especially in patients with hepatic diseases or the results become highly inaccurate [24]. The indicator is usually introduced intravenously via a peripheral vessel by either continuous infusion or by a bolus dose.

With continuous infusion and under steady-state conditions, the amount of indicator extracted exclusively by the liver is proportional to the volume of blood moving through the liver. Inflow indicator concentration (Ci) is obtained indirectly by varying the infusion rate to maintain constant peripheral blood concentration on the assumption that infusion rate (I) then equals hepatic extraction rate (E) and Ci equals peripheral concentration.

Thus

$$HBF = \frac{I}{Ci - Co}$$

Co is determined by hepatic vein catheterization.

The indicator may also be introduced into the vascular system by a bolus dose, followed by frequent, timed, and simultaneous blood sampling from both a peripheral vessel (artery or vein) and the hepatic vein. Hepatic extraction efficiency is determined by analysis of the clearance curve derived from peripheral blood samples [25]. The bolus injection method allows measurements to be completed within 15–20 min and repeated measurements are possible.

The clearance technique has many practical limitations [26]. Most indicators have some degree of extrahepatic clearance [27] and single hepatic vein sampling is representative of total liver efflux only when no aberrant arterial supply exists [28]. Extrahepatic shunting, which is common in liver disease, artificially decreases indicator concentration in the hepatic venous blood and underestimates flow. Most importantly, hepatic clearance diminishes rapidly and in a variable manner in the diseased liver [29]. Technical problems with the wedging of catheters and backflow of blood from IVC also give rise to dilution.

Examples of indicator substances used in the clearance method are indocyanine green (ICG) [27], bromosulpthalein (BSP) [23], Rose Bengal [30], sorbitol [31], galactose [32], and radiolabeled imino acid analogs [33, 34]. ICG has little extrahepatic uptake, negligible extrahepatic metabolism, and is the indicator substance normally used in the clearance method.

The term "functional hepatic blood flow" (FHBF) is frequently used in relation to the measurement of HBF by the clearance method and conceptually explains the discrepancy in values obtained by clearance methods versus clearance-independent methods especially when relative hepatocyte insufficiency exists [26]. That component of HBF directly perfusing hepatocytes and leading to metabolic activity (as opposed to blood shunted away via intrahepatic or extrahepatic shunts) is presumed to be equivalent to the flow obtained by the clearance method and is termed FHBF. This assumes the validity of the "intact hepatocyte theory," which attributes reduced clearance in hepatocellular disease (specifically cirrhosis) to reduced perfusion of otherwise functional hepatocytes caused by portosystemic shunting [35]. Direct evidence to support the practice of attributing values obtained by clearance methods to FHBF in the context of heptocellular insufficiency is scanty, however.

Adaptations of the Clearance Method

Adaptations of the clearance principle to obtain accurate data without the need for hepatic vein (HV) catheterization conceptually offer the possibility of wider clinical applications. These may be divided into two broad categories, namely, the use of highly extracted radiolabeled indicators and the use of indicators taken up by the hepatic reticuloendothelial system (RES).

The rate of extraction of small amounts of radiolabeled iminodiacetic acid anions injected via a periph-

eral vein (mebrofenin [36], 99mTc-diethyl-IDA [33] by the liver and the consequent disappearance of radioactivity in the bloodstream can be measured by elimination kinetics via either external monitoring of radiation of a region of interest (ROI) drawn over the liver by means of a gamma camera [37] or by plotting a radioactivity-disappearance curve from serial samples drawn from a peripheral vein after correction for natural decay [38]. Because only minute quantities of radiolabeled iminodiacetic acid anions is required, in healthy livers, extraction approximates unity [39] but this is no longer true in the presence of hepatocellular dysfunction [40].

The intravenous injection of a particulate matter (colloid) via a peripheral vein leads to the removal of that matter by the hepatic reticuloendothelial cells (Kupffer cells) at a rate proportional to HBF and leads to the accumulation of that colloid in the liver. If radiolabeled colloids were used, plasma disappearance and hepatic uptake could be measured by external counting and blood flow is estimated from elimination rate constants for colloid clearance [41] without the need for hepatic vein cannulation.

In practice, however, the extraction rate is low and the results are disappointing. In addition, although approximately 90% of cells in the RES in the body can be found lining the sinusoids of the liver under normal condition, all colloids (with the exception of Tc99m-galactosyl-neoglycoalbumin) are subject to extrahepatic RES uptake especially by the spleen [42]. The disappearance constant k is thus a composite of all RES extraction and not that of the liver alone. Under conditions of hepatic dysfunction, clearance by hepatic RES is theoretically better than clearance by hepatocytes because reticuloendothelial cell function was assumed preserved under such conditions. Existing data, however, suggests that RES function is reduced in the face of significant hepatocellular disease [43]. Failure of phagocytosis amounts to an "intrahepatic shunt" unrelated to blood flow. The clinical application of this method is thus limited.

Examples of radiolabeled colloids used are ^{32}P-colloidal chromic phosphate [41], ^{125}I-labeled albumin microaggregates [43], ^{198}Au-colloid [44], and ^{99m}Tc-sulphur colloid [45].

Indicator Dilution Method

The indicator dilution method is an application of the Stewart-Hamilton method [46], derived from the Fick principle. In principle, HBF is proportional to the amount of hepatic blood that has diluted an introduced indicator.

$$I = HBF \times \Sigma C$$

where

I = total amount of indicator injected

C = concentration of indicator per unit time

Thus,

$$HBF = \frac{I}{\Sigma C}$$

Or

$$HBF = \frac{\text{dose of indicator}}{\text{area under the indicator dilution curve (IDC)}}$$

Thus, only knowledge of the amount of indicator injected and determination of the concentration of the indicator at the outflow is required. The IDC is constructed from outflow indicator concentrations (measured sequentially or continuously) and extrapolation of the downslope to baseline to correct for recirculation. In practice, a bolus injection of the indicator is introduced into the superior mesentery artery (or its equivalent in animal models) or the portal vein, and the indicator concentration in a hepatic vein is measured. A percutaneous approach to these vessels avoids open surgical cannulation. Catheter blockage and displacement are important technical drawbacks. The presence of splanchnic-systemic shunts, which is common in clinical practice, renders the method inaccurate.

This method is independent of hepatocellular function and is reliable and reproducible under the following conditions. The indicator must remain within the vascular space and must be neither metabolized nor excreted prior to sampling. Fick's principle also presupposes a steady state otherwise either flow or marker concentration must be equal on both sides of the organ at each instant in time [47]. Sampling must also be at a rate that does not give rise to changes in the hepatic circulation, e.g., not more than 30 ml/min in dogs [48]. Complete mixing of indicator with blood at the sampling site is essential and, in the dog, blood from any hepatic vein has been shown to be representative of total hepatic venous blood after cranial mesenteric injection of the indicator [28]. However, in 30% of patients, one or more lobes derive its arterial supply from an aberrant artery and blood fails to mix thoroughly after injection into one hepatic artery [29]. To account for extrahepatic shunts, separate injections have to be made into the splenic artery, the superior mesenteric artery, and the hepatic artery to calculate the amount of blood shunted in each bed [49].

Examples of indicators that have been used are ^{131}I-labeled albumin [48], ^{51}Cr-labeled red blood cells [28], amino-hippurate para-amino-hippurate (PAH) [50],

and cold saline by thermodilution [51]. With PAH, the indicator may be introduced by continuous infusion after a priming injection until steady state is achieved. PAH is efficiently excreted by the kidneys and at steady state the rate of infusion equals the rate of renal excretion and the problem of recirculation is avoided. The indicator dilution method is a useful research tool, but there is little practical application of this method in routine clinical work.

Inert Gas Washout

Radioactive gases such as krypton-85 (^{85}Kr) and xenon-133 (^{133}Xe) distribute instantaneously and reach equilibrium between tissue and blood according to a specific partition coefficient (λ). The gas is then washed out from the tissue, and the rate of disappearance equals the rate of tissue perfusion [52, 53]. Hepatic tissue perfusion (expressed as perfusion per unit mass of liver) rather than blood flow is measured, and HBF is thus estimated indirectly. The inert gas can be introduced into the vascular system through many routes, e.g., hepatic intra-parenchymal injection [54], intrasplenic injection [55], bolus injection to the portal system [56], inhalation [57], and per rectal [58]. Because of a variable and uncorrected delivery of isotope via the portal vein, true perfusion rate is underestimated unless direct injection of the gas into the portal vein is carried out. Beta emission from ^{85}Kr is measured by a semiconductor detector over the exposed liver surface but gamma emission from ^{133}Xe may be monitored transcutaneously by a gamma camera

The method is independent of the clearance ability of the liver and thus not influenced by hepatocellular diseases or nonperfusion shunts. The coefficient of variation, however, ranges between 12 and 22% within the same subject (with portal injection) when multiple studies are performed [59]. The method has limited clinical and research applications.

Radiographic Imaging Methods

These methods are only of historical interest and are based on the summation of contrast media over the cross-section of a vessel by cinematography during angiography [60, 61]. Access to the hepatic artery is obtained via percutaneous femoral artery cannulation but access to the portal vein may be achieved by cannulation of the umbilical vein [61].

NONINVASIVE METHODS

Truly noninvasive methods for measuring HBF have been developed over the last 15 years and although ultrasound is easily available and thus most widely used, the less accessible nuclear medicine techniques are far more robust and reproducible.

Transabdominal Doppler-Duplex Ultrasound

Transabdominal Doppler-duplex ultrasound (TDDU) is perhaps currently the most widely used technique for measuring HBF in clinical research and has found applications in the assessment of portal hypertension [62] the diagnosis of occult liver metastases [63], and the postoperative monitoring of patients after hepatectomy [3]. THBF is obtained from the equation:

$$Q = V \times CSA$$

where

Q = volume of blood flow

V = velocity of erythrocytes flowing in vessel

CSA = cross-sectional area of vessel

The assumptions are 1) the velocity of red blood cells moving in the bloodstream approximates the velocity of blood flow, 2) blood flow is parabolic and nonturbulent, and 3) the cross-sectional area (CSA) of the vessel remains a constant. The velocity and CSA are obtained separately by the Doppler and B-mode functions of the ultrasound machine, respectively, and then multiplied to obtain the flow. Portal venous and hepatic arterial blood flow are measured separately and then added up to obtain HBF. Aberrancy of arterial supply must be accounted for and each arterial in-flow should be individually measured.

This technique appears ideal because it is completely noninvasive, gives real-time measurement of HBF, and allows repeated measurements to be carried out over time. It is, however, not always possible to visualize all hepatic vasculature adequately [64]. A substantial amount of subjective judgment is required and it is significantly operator- and machine-dependant [65]. The CSA of the portal vein *in vivo* varies significantly with respiration, and the respiratory index of the portal vein (ratio of maximal to minimal CSA) in man is as high as 1.4 [10, 66]. In a validation study on TDDU carried out in a large animal model, differences in the CSA of the portal vein caused by respiration gives rise to values of portal flow that differ by 53% [11]. There is currently no agreed upon standardization of the methodology for measuring the CSA of the portal vein by TDDU that takes into account of the impact of respiration on this parameter.

Although TDDU is a useful technique for monitoring large changes in HBF occurring over a short period of time [65], it has low precision and interpretation of HBF obtained by this technique requires circumspection.

First-Pass Analysis of Non-diffusible Radioactive Intravascular Tracer

Peters described a general method of calculating absolute blood flow through any organ based on analysis

of the first-pass time-activity curve (TAC) of a nondiffusible intravascular tracer and fractionation of the cardiac output based on the same principle underpinning the microsphere technique [67]. Although transit time of microspheres through an organ may be considered infinite, transit time of an intravascular radioactive tracer is finite and the integrated TAC over an organ or ROI can be used to predict blood flow to that region if the tracer behaves like a microsphere. The TAC is constructed by monitoring the appearance of radioactivity over the ROI using a gamma camera. An appropriate scaling factor must, however, be determined and correction made for recirculation and Peters' technique uses the ratio of the maximum upslopes of the aortic and organ TAC to calculate the scaling factor. Because the cardiac output is known by first-pass analysis of the TAC over the left ventricle, blood flow in virtually every solid organ can be determined.

The liver is, however, an organ with a dual blood supply whereas the technique developed by Peters *et al*. is based on the assumption of a single blood supply. Modification to the technique is thus necessary for quantification of HBF to account for its dual blood supply.

Scaling by Constrained Deconvolution

To address the dual blood supply of the liver, Tindale *et al*. adopted a novel approach to the determination of HBF by measuring HAF and PVF separately. Tindale's method used a model of liver impulse retention function (IRF) obtained by a constrained deconvolution technique from which best-fit hepatic arterial and portal venous signals can be determined as separate components [68, 69]. The assumptions are 1) there is temporal separation between the arrival of the radioactive tracer via the hepatic artery and portal vein and 2) the liver is homogenous throughout with respect to the two components of in-flow. The fraction of the cardiac output passing along the hepatic artery is given by:

$$\frac{ABF}{CO} = \frac{h \int B(t)\,dt \times C_B}{D \times S}$$

where

ABF = hepatic arterial blood flow
B (t) = re-circulation time
D = injected dose
S = detector sensitivity
C_B = attenuation correction factor

The height h of the hepatic artery IRF represents the scaling factor between the integrated blood concentration and the hepatic artery signal.

$$CO = \frac{D \times S}{\int B(t)\,dt \times C_c}$$

where

Cc = calibration factor that converts amplitude of blood conc. curve to cps/ml

$$ABF = h\,\frac{C_B}{C_c} \quad \text{and} \quad HBF = (h + p)\,\frac{C_B}{C_c}$$

The ratio of h to the sum of the heights of the two components of IRF (h + p) represents the arterial–total blood flow ratio. C_c is determined by relating the rate count from a venous blood sample taken at any time t after equilibrium of the tracer to the count rate at time t, H(t) over the region (e.g., heart) used to define the shape of the blood concentration curve.

Thus, for a blood sample of volume V with count rate T:

$$C_c = \frac{H(t) \times V}{T}$$

C_B is the ratio of the total activity in the liver to the count rate from the liver for a particular view employed and theoretically depends on the assumption of negligible activity in the tissues overlying the organ that can not be realized in practice. A second study employing colloids (which accumulate in the liver with minimal background contribution) is thus required. In practice, a standard liver scan is first performed using intravenous Tc-99m-tin-colloid followed by a dynamic scan using intravenous Tc-99m-human albumin serum (HAS). This method has not been validated against an independent technique.

Scaling by constrained deconvolution is demanding and makes the technique difficult to use for the nonspecialist researcher. Few researchers are familiar with the mathematics of deconvolution analysis.

Scaling by Hepatic Perfusion Index

Yu *et al*. used a more convenient method of measuring HBF by first-pass analysis that does not require constrained deconvolution [38]. This technique untilizes the hepatic perfusion index (HPI), the ratio of the HAF to HBF, which is a sensitive and independent index of liver perfusion. The HPI is derived from first-pass analysis [70, 71] and another advantage of this technique is thus that all hepatic haemodynamic parameters (HPI, HAF, HBF, and PVF) as well as cardiac output can be obtained in a single study.

From first-pass analysis of the TAC over the liver ROI (Fig. 1),

$$\text{HPI} = \frac{\text{H1}}{\text{H1} + \text{H2}}$$

where

H1 = slope of the arterial portion of the TAC
H2 = slope of the portal venous portion of the TAC

The HAF is determined by analysis of the integrated liver TAC and the integrated left ventricular TAC according to Peters' method [67].

$$\text{HAF} = \frac{(gk/ga)}{(\alpha/\gamma)}$$

where

gk = maximum gradient of the arterial component of the liver time-activity curve
ga = maximum gradient of the integrated time-activity curve of left ventricle
γ = conversion factor that converts count rate of the left ventricle ROI to MBq/ml
α = correction factor for detector sensitivity, organ depth, and photon attenuation

and thus

$$\text{PVF} = \frac{\text{HAF}}{\text{HPI}} \times (1 - \text{HPI})$$

$$\text{HBF} = \text{HAF} + \text{PVF}$$

Taking recirculation into account is unnecessary because only the initial portion of the TAC is required for the analysis. This approach requires only a single study and combines ease of application with the elucidation of all hepatic hemodynamic data. The principles underlying changes to the HPI has already been applied to the early detection of metastases to the liver [72] and the monitoring of deterioration in liver cirrhosis [71] and the application of this method based on first-pass analysis is potentially useful in clinical work.

Positron Emission Tomography

Positrons are highly unstable positively charged electrons that react immediately with the electrons of the surrounding atoms. This annihilation process results in the destruction of both the positrons and electrons and the production of two gamma photons with energies of 0.511 MeV each traveling at an angle of 180 degrees to each other. By capturing the two photons simultaneously using a ring detector, the position at which the annihilation has taken place may be determined. Positron emission tomography (PET) makes use of this mechanism to produce tomographic images with resolution and sensitivity better than those of conventional nuclear medicine images. Because most commonly used positron emitting radionuclides are radioisotopes of physiological atoms, e.g., C^{11}, N^{13}, O^{15}, many physiological parameters such as organ blood flow may be estimated.

Organ blood flow may be estimated using a continous infusion or intravenous bolus of PET radiotracers [73]. In measuring HBF, the continous infusion method is not appropriate because the input radiotracer concentration cannot remain constant because of the dual blood supply of the liver and the radiotracer concentration in the portal supply will be lower because of the physical decay of the radiotracer passage through the mesenteric and splenic vascular beds [74]. Hence, an intravenous bolus injection is recommended. When wash-out and recirculation of the radiotracer is taken into consideration, the equation to determining organ blood flow can be written:

$$\frac{Q}{V} = \frac{\int \text{Cr}(t) \cdot dt}{\int\{\int \text{Ca}(t) * e^{-(Q/\lambda V)t} \cdot dt\}dt}$$

where the symbol * denotes the process of convolution.

Ca is the arterial radioactivity concentration
Cr is the venous radioactivity concentration
λ is the partition coefficient of the radiotracer between plasma and the organ
Q is the blood flow of the organ
V is the volume of the organ

Cr can be measured from three-dimensional images of the organ of interest. Ca is measured by drawing an arterial blood sample or placing a region of interest over the cardiac chambers or a larger artery.

There have been very few studies validating measuring HBF using PET and no satisfactory method for measuring HBF by PET has been established. Chen *et al*. measured hepatic arterial blow flow [75] using a two-compartment model and N^{13} labeled ammonia. THBF was estimated using the following equations:

$$(E)(\text{rHABF}) = Q(T) / \int_0^T \text{Ca}(t)\, dt$$

where

rHABF was the regional hepatic blood flow (ml/min/gm)
Ca(t) was the arterial radioactivity of N-13 ammonia (cpm/pixel)
P was the specific gravity of blood (approximately = 1)
t was time (min)
E was the tissue extraction ratio of N-13 ammonia

By using mongrel dogs as the animal model and nu-

merous assumptions, the authors demonstrated close regression between HBF measured by PET and that measured by radiolabeled microspheres (MS) as described by the following equation

$$\text{rHABF} = 0.95 \times \text{MS} + 0.04 \ (\text{R} = 0.97)$$

Using a one-compartment model and O^{15} water, Ziegler *et al*. [76] measured HBF in dogs and compared the results of the HBF measured using radiolabled microspheres. The investigators studied two different conditions, one with a dual blood supply (hepatic and portal input) and the other with a single blood supply (hepatic input with an extra compartment of gut radioactivity). However, the investigators were not able to establish a correlation between HBF measured by PET and that measured by microspheres.

Taniguchi *et al*. [77] developed a model consisting of liver and a portal system components and a coefficient of circulation time was introduced. The researchers studied the arterial and portal flows in 52 patients. The results were reported as encouraging. Shiomi *et al*. [78] measured HBF using O^{15} water and the same analysis technique in patients with liver cirrhosis. The results were reported as satisfactory but the technique has not been fully validated.

Although PET remains a potentially useful clinical method for measuring HBF, it suffers from several serious limitations. Most positron-emitting radioisotopes have very short half-lives (the half-lives of O^{15} and N^{13} are 10 min and 2 min, respectively) and have to be produced on site immediately before being injected into patients. A cyclotron with all its attendant financial investment is therefore a prerequisite. The operation and maintaince of a cyclotron and PET scan are far more complicated than routine nuclear medicine imaging and requires a team of highly trained professionals including a radiopharmacist, radiation physics, and engineers.

The dual blood supply of the liver has added significant difficulties in the modelling and kinetic analysis of HBF. Although several models have been developed, none of them can adequately describe or reflect the complexity of blood flow in the liver. Until a better model is developed and the cost of PET becomes more attractive, the use of PET for the measurement of THBF remains a purely research technique.

DISCUSSION: INDICATIONS AND CHOICE OF METHOD

An ideal method for measuring HBF must fulfill a number of requirements [26]. The method must be independent of hepatocellular function and should account for both total hepatic blood flow and shunt fraction. It should be noninvasive, safe, be simple in concept, and give accurate, real-time, and repeatable measurements. It should not require highly specialized or expensive equipment and should not be operator-dependent. Such a method does not currently exist.

Measuring HBF remains necessary for various experimental situations and useful in many clinical conditions. The choice of appropriate methods to achieve this thus becomes important in the absence of an ideal and universally accepted standard method.

Experimental Research

HBF is an important parameter in experimental research on the pathophysiology of liver resection and liver transplantation, trauma, systemic sepsis, liver parenchymal disease, and drug metabolism and pharmacokinetics. Some degree of liver impairment exists under most of these experimental conditions and changes in many of the other research parameters (e.g., liver viability and regeneration, multiorgan failure, metabolism) can be interpreted in meaningful ways only in conjunction with HBF. The choice of an appropriate method for measuring HBF is therefore crucial.

The reference sampling method using radioactive microspheres is robust and accurate for experimental research using animal models. Reference sampling is independent of hepatocellular function and has little impact on circulatory physiology if used judiciously (e.g., withdrawal of $<1\%$ of cardiac output for reference sampling). The disadvantages are that repeated measurements are not feasible and the animal under investigation can not act as its own control. The cost of using this technique in large animal models is however prohibitive and thus impractical.

The application of clearance methods is only meaningful under conditions where there is absence of hepatic impairment such as in studies of physiological responses to nonmetabolic and nontoxic stress. The need for hepatic vein cannulation makes the method impractical for follow-up studies. This drawback may be circumvented by the use of highly extractable radiolabeled susbstances such as radiolabeled iminodiacetic acid anions. These may be injected via a peripheral vein (mebrofenin [36], ^{99m}Tc-diethyl-IDA [33]) and the subsequent disappearance of radioactivity in the bloodstream can be measured by elimination kinetics either through external monitoring of an ROI drawn over the liver by means of a gamma camera [37] or by plotting a radioactivity-disappearance curve from serial samples drawn from a peripheral vein after correction for natural decay [38]. Minute quantities of radiolabeled iminodiacetic acid anions are required and thus in healthy livers, extraction approximates unity [39] but this is not applicable in the presence of relative hepatocellular dysfunction [40].

In large animal models, a more robust and suitable

technique is first-pass analysis using an HPI scaling method. Although the method is accurate and independent of hepatocellular function, it requires nuclear medicine facilities including access to a gamma camera [38]. This may not be a viable option for many researchers. Transabdominal duplex-Doppler ultrasonography is feasible in large animals, but the method is operator- and machine-dependent and there is low precision. Prior validation at both the individual and institutional levels is necessary if the results were to be interpreted with any degree of confidence [11].

There are few useful indications for the other methods, which have been superceded by the methods discussed above. Although the indicator dilution method, for example, is independent of hepatocellular function, the high incidence of aberrant vasculature in most animal models render it inaccurate and more reliable methods are available.

Clinical Applications

There is increasing evidence that HBF is an important marker of disease processes in the liver. Analysis of the transit time of a bolus of contrast in the liver has been demonstrated to discriminate between patients with cirrhosis from controls and from patients with noncirrhotic diffuse liver disease. Changes in the perfusion index of the liver have been shown to predict colorectal metastases [80] and changes in hepatic blood flow predict liver dysfunction after major hepatectomy [3]. Invasive methods of measuring HBF have no place in routine clinical practice. A good clinical method must be minimally invasive, but truly noninvasive methods of measuring HBF that are accurate, reproducible, and accessible are few. The choice of appropriate methods for measuring HBF in clinical practice is thus limited. HBF measurement has thus not become routine in clinical practice outside of research protocols.

Transabdominal Doppler-duplex ultrasonography is inaccurate and operator-dependant and has limited usefulness. When properly validated at the operator level, however, it remains useful if the limitations of the method are understood. PET is potentially useful, but no model currently describes HBF adequately and further research on the methodology is required. Methods based on first-pass analysis are robust and useful. Although simpler in concept and execution and cheaper than the PET scan, first-pass analysis methods still require the use of a gamma camera and can thus only be carried out in tertiary institutions. Their potential for widespread use is limited. There are few indications for using the other minimally invasive or noninvasive methods. Methods based on hepatic clearance especially have poor accuracy and even with hepatic vein cannulation are still dependent on good hepatocellular function.

The measurement of HBF as routine clinical investigation currently remains feasible only in specialized institutions. There is thus need for further research on the methodology of measuring HBF before this can be used as routine investigation. In the interim, a clear understanding of the limitations of existing techniques is required to allow careful selection of methodology and appropriate interpretation of results.

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