Gaziantep Üniversitesi Tıp Fakültesi Dergisi, 3:78-93, 1992

REVIEW ARTICLE
MEASUREMENT OF LIVER BLOOD FLOW

Avni GÖKALP, Hayri ERKOL*, Necdet AYBASTI**, İbrahim SANAL***

Anahtar Terimler: Kan akımı, portal kan akımı, hepatik kan akımı, Doppler ultrasound, Doppler laser, anjiyografi.
Key Words:Blood flow, tissue perfusion, portal blood flow, hepatic blood flow, Doppler ultrasound, Doppler laser, x-ray angiography.

SUMMARY

The study of hepatic hemodynamics is of importance in understanding both hepatic physiology and diseases as well assessing the effects of portosystemic shunting and liver transplantation. The liver has the most complicated circulation of any organ many physiological and pathological processes can affect it (1,2). This review surveys the methods available for assessing liver blood flow, examines the different parameters being measured and outlines problems of applicability and interpretation for each technique.
The classification of these techniques is to some extent arbitrary and several so called "different" methods may share certain common principles. The methods reviewed have classified into two groups (Table I):Those primarily reflecting flow thorough discrete vessels or to the whole organ and those used to assess local microcirculatory blood flow. All techniques have their advantages and disadvantages and in some situations a combination may provide the most information. In addition, because of the many factors affecting liver blood flow and sinusoidal perfusion, readings in a single subject may vary depending on positioning, recent food intake, anxiety, anesthesia and drug therapy. This must be borne in mind if different studies are to be meaningfully compared.

ÖZET

KARACİĞER KAN AKIMININ ÖLÇÜLMESİ

Hepatik hemodinamik konusundaki çalışmalar, hem karaciğer fizyolojisi ve hastalıklarının anlaşılması hem de portosistemik şantların ve karaciğer transplantasyonlarının değerlendirilmesi bakımından önem taşımaktadır. Karaciğer, dolaşımı bakımından en karmaşık organ olup birçok fizyolojik ve patolojik olay onu etkileyebilir (1,2).

Bu derlemede halen karaciğer kan akımını değerlendirmede kullanılan metodlar

* *Gaziantep Üniversitesi Tıp Fakültesi Genel Cerrahi ABD. Yrd.Doç.Dr.*
** *Gaziantep üniversitesi Tıp Fakültesi Genel Cerrahi ABD. Doç.Dr.*

ve ölçümündeki değişik parametreler gözden geçirilerek, her tekniğin uygulanabilirliği ve yorumlanmasında karşılaşılan sorunlar üzerinde duruldu.

Bu tekniklerin sınıflaması bir bakıma keyfi olup bazıları aynı ortak temele dayanabilir. Sözkonusu metodlar ayrı ayrı damarlardaki veya organın tümüne gelen akımı yansıtanlar ve yerel mikrosirkülatuar kan akımını gösterenler olmak üzere iki grupta incelendi. Her tekniğin kendisine özgü avantajı ve dezavantajı olduğu gibi bazı hallerde kombine tekniklerin kullanılması ile en çok bilgi sağlanabilir. Karaciğer kan akımı ve sinüzoidal perfüzyon pek çok faktör tarafından etkilendiğinden her olgudaki değerler pozisyon, yeni yemek yemiş olmak, anksiyete, anestezi ve ilaç tedavisi gibi etkenlerle değişebilir. Onun için değişik çalışmalar birbiri ile karşılaştırılırken bu nokta göz önünde tutulmalıdır.

Table I: Hepatic blood flow measurement techniques

METHODS MEASURING BLOOD FLOW
Velocity or Transit Time Methods
Electromagnetic Flowmeter
Doppler Ulkrasound
x-Ray Angiography
Nuclear Magnetic Resonance
Dye Dilution Techniques
Plasma Disappearence Methods
Radiosotope Techniques
METHODS MEASURİNG TISSUE PERFUSION
Radiolabelled Microspheres
Heat Exchange
Hydrogen Electrode
Oxygen Electrode
Laser Doppler

METHODS MEASURING BLOOD FLOW

Velocity or Transit Time Methods

Electromagnetic flowmeter

The measurement of blood flow by electromagnetic induction was first suggested by Fabre (3) and the principle of the technique is based on Faraday's law of electromagnetic induction. If a magnetic fields is applied across a vessel in which blood is flowing then an electric field is induced at right angles both to the induced magnetic field and the flow vector (4,5). The electrical field is detected along its axis from the potential difference across the outside of the

vessel. This potential is primarily determined by the velocity of the flowing blood within the vessel. Accuracy demands attention to detail and proper calibration (6,7) using a pump and saline solution. There is no way of checking calibration in vivo except vessel clamping for zero flow. Interference from other electrical instruments also minimise the accuracy of the technique (8).

In pratice the method involves the placement of the device around the vessel to be assessed. For a good signal, close contact is essential. Drapanas, et al.(9) and Price et al. (10) compared electromagnetic flowmetry with the bromsulphalein clearence method (11) for measuring hepatic arterial and portal vein flow in the dog and found a good correlation between the two methods. Because of the invasive nature of the technique, it is more applicable to animal studies and on the patients at the time surgery. These devices are, however, still regarded as the "gold standart" against which all other methods of measuring flow must be compared. They are able to measure instantaneous and mean blood flow in an exposed vessel. They can detect forward and reverse flow and the temporal resolution is fast enough for flow to be studied during the cardiac cycle. Other advantages of the method are its insensitivity to changes in blood temperature and viscosity.

Doppler Ultrasound

The first attempted use of Doppler ultrasound for the measurement of blood flow from the surface of the body was reported by Satomura in 1959(12) but compared to ultrasound imaging the role of Doppler ultrasound has evolved slowly and has largely been restricted to a relatively few well defined indications in cardiac diagnosis, evaluation of carotid and peripheral vascular disease, and more recently in obstetrics and the abdomen (13,14). The combination of real time B-mode ultrasound imaging and a pulsed Doppler flowmeter is referred to as a duplex scanner (15). Using these machines the diameter of the vessel, peak velocity, mean velocity, volume flow rate and pulsatility of blood flow waveforms can be measured (16). A recent refinement is the development of colour flow mapping where the image provides flow information concerning all structures in the image field rather than just at one selected site.

Duplex ultrasound offers the best non-invasive way of assessing portal vein patency (17) and can demonstrate cavernous transformation and whether portal flow is hepatopetal or hepatofugal. Doppler has also been used in quantitative measurement of portal blood flow (18), but it needs calibration against a flow model. Doppler might be of more use for assessing relative changes in portal flow rather than for giving absolute flow values (19). Ackroyd et al. (20) stated that raw flow values vary from person to person according to different body conditions and suggested that the use of standardised conditions could improve accuracy. One further reason for not relying on portal velocity measurements in studying cirrhotic patients is that portal flow is well maintained by portal vein

dilatatiton until portal hypertension is severe (21). For this reason a portal congestion index, which is the cross sectional area divided by the mean velocity, has been suggested by Moriyasu et al. (22) as being more useful than absolute flow.

The Duplex scanner can also be a useful non-invasive tool for assessing patients with portosystemic shunts. Nelson et al.(23) studied patients before and after portosystemic shunting with both duplex scanning and angiography. They concluded Duplex was accurate in determining the direction of flow if an adequate tracing was obtained. Preoperatively it allows the determination of portal vein patency and direction of flow. Postoperatively most portocaval and mesocaval shunts can be visualised as well as some Warren type shunts (17).

Duplex is less useful in the assessement of hepatic and splanchnic arterial flow (24). The vessels are relatively short, tortuous and deeply situated, making them difficult to image and the hepatic arterial supply is frequently multiple. Post liver transplantatiton the anatomy may be even harder to demonstrate and scanning of the hepatic artery is currently too time consuming and inaccurate to make it clinically useful in detecting hepatic arterial thrombosis. Intra-arterial Doppler flow probes are now being developed and combined with angioraphy may ultimately provide the best way to quantitatively measure hepatic and splanchnic arterial flow (24).

In summary, Duplex scanning potentially provides a non-invasive way of assessing liver blood flow in many clinical situations including of assessment of portal vein patency, direction of flow, surgical porto-systemic shunting and liver transplantation. Its accuracy has been validated in vitro and in experimental animals (25,26), but problems do exist in using this technique in clinical practice. It offers one of the best approaches to the noninvasive assessment of portal flow but it is not yet capable of reliably assessing hepatic arterial flow.

x-Ray Angiography

Angiography, or radiographic imaging of blood vessels, has a well established role in the diagnosis of liver disease and portal hypertension and is widely used in clinical practice for obtaining high quality vessel images (27). As well as anatomical information, however, information on blood flow is also potentially available.

The techniques available for measuring flow using angioraphy are based on one of two principles. The first approach uses the principle that when an indicator is injected at constant rate into a blood vessel, the degree of dilution is proportional to blood flow, and the concentration in blood after mixing will be lower with higher flow and vice versa (28). The main problem with this technique is accurate densitometric calibration. The second technique involves the measurement of the time taken for the passage of a bolus of contrast

material between two sites but unfortunately precise timing of the passage of a dispersing bolus is often difficult to achieve (29). In a new approach to this problem flow is determined by computer analysis of contrast concentration profiles as a function of time and distance along a vessel segment (29,30). Another solution has been to asses relative flow by using two injections and measuring superior mesenteric, hepatic and splenic arterial flow relative to cardiac output (31,32).
The measurement of liver blood flow by angiographic techniques has largely been limited to hepatic arterial studies because catheter access to portal system is not a routine procedure. Indirect portography, where contrasts is injected into either the superior mesenteric artery or coeliac artery and imaged as it passes out into the portal system results in generally poor images unsuitable for flow analysis. Following direct insertion of a catheter into the portal system, Sovak et al. (33) and Iwanaga et al.(34) used this method with a computer to calculate the displacement of lipoidal droplets per frame. They found this technique quite useful for the measurement of liver blood flow (34,35).

Altougth it requires vascular catheterisation x-ray angiography is still the modality of choice for critical morphological vascular studies. That x-ray angiography has not been widely used for measuring blood flow is probably due to the use of inappropriate algorithms for processing the image data (29,36). The method does, however, have great potential especially when combined with lower dose Digital Subtraction Angiography and new low osmolarity non-ionic contrast agents (37). Mini puncture needles and catheters (38) have led to increased safety of the technique and equipment and expertise is potentially available in many centers.

Nuclear Magnetic Resonance

Nuclear Magnetic Resonance (NMR) imaging is a noninvasive imaging modality that is rapidly gaining clinical acceptance, although widespread introduction has been delayed by expense. Flow detection with NMR spectroscopy has been explored for more than 30 years (39-41). When NMR imaging was first performed in the late 1970s signal loss was noted within arteries and attributed to high flow rates (42). In the early 1980s, several causes of increased signal intensity were described, generally associated with slow flow in veins and dural sinuses (43,44). Understanding these flow phenomena has provided the basis for the development of specialized NMR imaging sequences intended to quantitate blood flow measurements. Several methods have been proposed to quantify blood flow (45-47) but at this stage their relative merits have not been completely evaluated. However, it seems that this will be an area of great development in the future.

Dye Dilution Techniques

Plasma disappearence methods

Attemps have been made since the middle of this century to measure liver blood flow by dye infusion methods (48). Certain organic dyes are extracted by the hepatocytes and if the rate of extraction is measured, liver blood flow can be calculated using Fick's Principle (49).

The first dye used was bromsulphalein (50) but indocyanine green is now used more commonly as it is more specifically extracted by the liver (51). The first measurements made using this substance employed the constant infusion method but Caesar et al.(51) have shown that analysis of plasma disappearence curves after a bolus injection gives nearly identical results. Hepatic extraction is usually measured by hepatic vein sampling, however, a method requiring only peripheral vein sampling and utilising pharmacokinetic modelling has been described and validated in normal subjects (52). This method has, however, been criticised when applied to patients after liver transplantation (53) and it may be unreliable in patients with liver disease (54). Pirttiaho et al.(55) estimated liver blood flow by fast intravenous injection of indocyanin green.

The advantage of dye clearence techniques is that they are relatively simple. Inaccuracies arise, however, when extrahepatic removal of the dye occurs (50) or when it is used in patients with liver disease (54). For this reason, dye clearance methods being used less commonly nowadays. For many years, however, they were the best tecniques available and much pioneering work was done using them.

Radioisotopic methods

Three basic groups of techniques have been described.

A. Diffusible Gas Tracers

Kety (56) introduced the principle of "local tissue clearance" or "washout" of rapidly diffusing isotopes as a way of measuring blood flow. Initially small amount of radioactive ^{24}Na was used but later inert and lipid-soluble gases such as ^{85}Kr and ^{133}xe (57) were found to be more valuable with the cellular membrane not constituting a barrier to diffusion (58).

Following injection of an arterial or portal venous bolus of gas dissolved in saline the elimination of this elements is in most situations limited by the rate of capillary blood flow. Externally placed scintillation detectors are used to record the clearance curve. Fick's Principle is then used in the analysis of the data and from a series of washout curves liver blood flow can be calculated.

B. Radio-labelled Colloids

In this technique colloid-bound radionuclides are administered intravenously and the rate of liver uptake is measured either by multiple blood sampling or external scintillation counting. The Fick's Principle is then applied to calculate blood flow, with assumption that extraction efficiency is 100%. ^{32}P labelled chromic phosphate and colloidal ^{198}Au have been used before (59-62). Now, ^{99m}

Tc-labelled sulphur colloid is most frequently used as it has a high extraction efficiency and can be counted externally. Dynamic images are acquired via a gamma camera and an on-line computer system and assumption is made that the liver and spleen have an equal extraction efficiency for colloidal particles (63) and that this is close to 100%. Unfortunately, although these assumptions are probably valid in normal subjects, they may not be true in patients with liver disease (64). Analysis of the time variation in liver activity is perfomed bolus intravenous injection. The arterial and portal components are separated by their times of arrival at the liver. Several different methods have been described to estimate fractional hepatic arterial flow using hepatic artery, portal vein, and reference organ time activity curves (63-67).

C. Hepatosplenic Radionuclide Angiography

This tecnique is based on the use of ^{99m} Tc-pertechnetate which is not extracted by the liver. A bolus injection is given intravenously and dynamic images are acquired during its first pass phase (68). The original technique (69) has been modified (70) and is now reported to be more reproducible (68). Sarper et al.(68) generated first-pass radioactivity versus time curves by following a rapid intravenous injection of 740 MBq of ^{99m} Tc-pertechnetate. Hepatic perfusion can be calculated analysing these two curves.

Advantages and Limitations of Radioistope Methods

The use of radiolabelled diffusible gas tracers is not as accurate for measuring liver blood flow and the washout curves are frequently not monoexponential (71), perhaps due to recirculation of the tracer, the fact that liver tissue may not be homogenously perfused or because there is incomplete clearance of tracer during its first passage (72). In addition, the need to catheterise either the hepatic portal or arterial system is a major disadvantage and one of the reasons why the technique has failed to gain widespread popularity in hepatic studies.

Colloid bound tracers and radionuclide angiography can not provide absolute values for flow but they can provide valuable information about the relative contribution of the hepatic arterial and portal venous systems. Such an index may be of more interest than absolute flow values in certain disease states such as cirrhosis. However, the background scatter of tracer and affinity to fat which many tracers have, makes the measurements difficult to evaluate. Colloids also have a range of particle sizes and hence a range of values of extraction efficiency.

METHODS MEASURING TISSUE PERFUSION

Radioactive Microspheres

If a bolus of tracer is well mixed in the afferent blood supplying an organ, then it will be distributed to different parts of the organ in exactly the same way as the blood which is transporting it. This is called the indicator fractionation principle. This principle has been used to quantify regional blood flow

distrubution using radio-labelled particles, diffusible indicators and autoradiography (73,74). Microspheres are chosen to be of a size (10-15μm) which will just lodge in the capillary circulation.

Using this technique Greenway et al.(75) studied the regional distribution of portal and hepatic blood flow in the liver by injecting ^{14}C and ^{51}Cr microspheres into the portal vein and hepatic artery of experimental animals. They found the liver homogenously perfused from both systems in contrast to other work using different techniques (76,77). The technique has also been used to study the vascularity of experimental liver tumors and in particular the relative role of portal and arterial blood supply to these tumors (78-81).

The microsphere method is useful for providing values of blood flow in a studies where sacrifice of the animal occurs. So it can not be used clinically.

Heat Exchange Methods

The concept of measuring tissue blood flow using heat clearence techniques was first suggested by Gibbs (81). This method requires a heated thermocouple, maintained at a certain temperature (2-4°C) above that of the surrounding tissue, to be either placed onto the liver surface or inserted into the liver tissue. The temperature of the needle is dependent on local blood flow. Increased perfusion tends to cool the needle, whereas reduced perfusion allows it to heat up. Measurement of the energy required to maintain the temperature increment constant therefore can be regarded as giving an indirect measurement of flow (82-85). However, values will depend on the exact position of the probe and the metabolic state of the liver (86). The method is, therefore, only a semiquantitative approach to flow and because of its invasiveness has not yet found widespread favour for liver studies.

Hydrogen Electrode

This method was introduced by Auckland and Bower (87) and further developed by Fieschi et al.(88,89) and Bozzao et al.(90). Molecular hydrogen is administered with the respiration gas until the tissue reaches saturation. The hydrogen supply is then turned off and its clearance rate is determined polarographically through platinum electrodes placed on, or into, the liver. A current is generated at the electrode surface by oxidation of molecular hydrogen to hydrogen ions. This current declines as hydrogen is removed and the steepness of the clearance curve correlates directly with the magnitude of the total liver blood flow and reflects perfusion within a radius of approximately 5 mm of the electrode. The calculation of the tissue blood flow from hydrogen clearance curves is based on theory developed by Kety, (91) and the method has been reviewed and simplified by Young (92).

Gouma et al.(77) applied this technique to the porcine livers and found that blood flow fell by over 90% if the hepatic artery was ligated. They concluded

from this experiments that the surface of the liver is mainly supplied from the arterial system. Nishiwaki et al.(93) used the hydrogen clearance method and transit-time ultrasonic blood flowmetry to investigate blood flow after liver transplantation in 40 mongrel dogs and found reductions in both hepatic arterial and portal venous flow after liver transplantation. The advantages of this method are that it can provide unlimited measurements of liver blood flow without significant alteration in physiological variables. There is no evidence that the administiration of the hydrogen itself significantly alters flow. Despite this, most investigators have not used the technique, mainly due to concern over the inflammability and explosiveness of pure hydrogen gas. In addition the method is not continuous, can not handle rapid changes of flow and may reflect arterial rather than venous inflow(77). It may also be inaccurate if the liver is not homogenously perfused.

Oxygen Electrode

An oxygen electrode consist of a noble metal cathode maintained at a negative potential with respect to a reference electrode. It is placed on the surface of the organ to be studied and oxygen diffusing from the tissue to the cathode surface is reduced when the potential is applied, giving rise to a current (94). A naked electrode is subject to "poisoning" by electrophoretic deposition of tissue protein on its surface but this can be prevented by covering the electrode with a gas permeable membrane (95). When the oxygen consumption of the electrode is low, tissue oxygen is not disturbed and so a direct measurement of the partial pressure (pO_2) is obtained. However, if the oxygen consumption of the electrode is high the electrode will measure the rate of supply of oxygen to the tissues and this is depended on local blood flow (97,98).

Ji et al.(99) applied a microneedle electrode to rat liver and found that tissue pO_2 values were different at periportal and perihepatic sites. Kram and Shoemaker (100) applied a miniature oxygen electrode in a single illustrative case to human cirrhotic liver to measure tissue pO_2 and their instrument responded to both changes in local organ blood flow and arterial pO_2. Piasecki et al.(101) used this technique in rabbits and measured portal blood flow.

This technique can give a continuous and instantaneous measurement of portal venous inflow when hepatic arterial inflow is undisturbed. However it is invasive as the electrode must be applied directly onto the liver surface. In addition it only gives a measure of flow in the tissue immediately below the electrode and no absolute value for flow can be calculated. Potentially, however, it can be used on human liver either at laparatomy or laparascopy.

Laser Doppler

Laser Doppler is a relatively new technique (I02) for measuring local blood flow. The device consist of helium-neon laser and an optic fibre which transmits this

light to the surface of the tissue to be studied. Light that is scattered by red blood cells undergoes a frequency shift and a portion of this spectrally-broadened light is transmitted back by a fibre light-guide to two photodetectors. This signal is analysed and the relative portion of light which has undergone Doppler shift is proportional to velocity of blood flow. The microvascular bed consists of an intricate network of small blood vessels and hence the angle between the red cell velocity vectors and the beam propagation vectors of the scattered light can be regarded as random (103).

This technique gives a continuous measure of red cell motion in the outhermost layer of the tissue under study with little or no influence on blood flow. The depth which the beam penetrates varies with the tissue being studied (103,104,76) and flow is likely to be measured in a volume of approximately 0,6-1,3mm^3 when the probe is applied to the liver surface.

Laser Doppler has been studied in vitro by measurement of liquid flow through small-bore tubes and a coefficient of variation for readings of 6% confirmed its accuracy. In vivo it has been used extensively to measure skin blood flow (106) but less has been written on its use and limitations for estimating liver blood flow (76,107).

Arvidsson et al.(76), using Laser Doppler flowmetry in pigs, investigated liver blood flow and confirmed previous work (77) with hydrogen clearance methods that the liver surface is mainly supplied from the arterial system. Laser Doppler has also been used to study blood flow to experimental liver metastasis (108).

The advantages of the method are that it can provide an instantaneous and contunious measurement of microcirculatory flow in a way that does not alter flow. Its disadvantages are that the probe must be applied directly onto the liver, flow can not be measured in absolute units, the absolute volume of tissue measured is not known and only surface flow is assessed (needle probes have not been used in the liver as hematoma formation around the probe tip would make readings unreliable).

CONCLUSION

Currently the measurement of hepatic blood flow and perfusion is fraught with diffuculties. There are often large variations in both flow and perfusion measurements not only between techniques but also between different groups using the same technique. Some of these differences may be due to the methods and conditions used and others are undoubtedly caused by complexities of liver circulation.

Duplex Doppler Ultrasound offers a good way of assessing portal vein flow but its many inaccuracies should be borne in mind. Clinical measurment of hepatic and splanchnic arterial flow is more difficult and duplex does not have the

accuracy to perform this function reliably. Intraarterial Doppler flow probes, flow analysis of digital x-ray angiograms and NMR may have a role in the future. Radiolabelled colloids or hepatosplenic radionuclide angiography can provide valuable information abouth the relative contribution of the portal and arterial system but are still largely research tools and are less accurate in the presence of pathology. Currently, investigators are best advised to familiarise themselves with a range of techniques as it is apparent that no single method is able to fulfill all the requirements of either basic research or routine clinical practice.

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