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Review

Different methods for hepatic flow measurements: a narrative review

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Abstract

Hepatic blood flow measurement constitutes an essential tool for successful hepatic surgery, especially in situations where graft patency needs to be controlled, such as for instance during and after liver transplantation. In addition, because of its complex intrinsic regulation, the hepatic circulation may be seriously affected in the perioperative setting not only because of systemic hemodynamic alterations but also secondary to the administration of various drugs including anesthetic agents. Unravelling and understanding such effects implies studies involving measurement of hepatic blood flow. Therefore, knowledge and understanding of various tools for estimation of hepatic blood flow is important for correct interpretation of findings from experimental and clinical studies before potential implementation in daily clinical practice. This review summarizes the different techniques, their strengths and limitations, and potential applications in clinical practice and research.

Introduction

HBF measurement constitutes a crucial tool for succesful hepatic surgery, especially in situations where graft patency needs to be controlled, such as for instance during and after liver transplantation. In addition, the hepatic circulation may be seriously affected in the perioperative setting not only because of systemic hemodynamic alterations but also secondary to the administration of various drugs including anesthetic agents. Understanding these effects implies reliable hepatic blood flow measurements.

The aim of the current contribution is to provide a concise overview of the determinants of hepatic blood flow and the technology currently available for its measurement. This knowledge should help the clinician involved in perioperative hepatic surgery to better understand the relevance and implications of findings using various hepatic flow measurement systems[1].

Regulation of the hepatic circulation

The liver, despite its small size of only 2.5% of total body weight, receives a considerable amount of blood supply from both the hepatic artery and portal vein. While the hepatic artery provides only a quarter of the blood supply, it delivers 30-50% of the liver's oxygen requirement due to the arterial blood's higher oxygen content. The remaining 75-80% of deoxygenated blood comes from the stomach, intestine, spleen, and pancreas through the portal vein. The hepatic venous system mixes the blood in the sinusoids and empties it into the inferior vena cava, with the hepatic blood volume accounting for 10-15% of total blood volume. The portal vein is formed by the merging of the inferior and superior mesenteric veins with the splenic vein and carries approximately 75% of total blood flow to the liver, supplying up to 70% of the liver's oxygen requirement. Hepatic blood flow is mainly regulated by the interplay between arterial and portal inflow circuits, rather than extrinsic innervation or vasoactive agents. Evidence suggests that hepatic arterial blood flow increases following a reduction in portal blood flow. The hepatic artery possesses a distinctive mechanism whereby it can respond to changes in portal venous flow by producing compensatory changes in blood flow. In situations where portal blood flow decreases, the hepatic artery dilates, whereas it constricts when portal flow increases. As a result, an increase in hepatic arterial blood flow can mitigate up to

25% to 60% of the reduction in portal flow. This relationship, known as the hepatic arterial buffer response, is regulated by adenosine which plays a significant role in the regulation of hepatic arterial dilation[1].

Overall, the liver's blood supply is complex, with intricate interactions between the hepatic arterial and portal venous circulations.

Measurement of the hepatic circulation

Historically, HBF measurements have been classified into direct and indirect techniques. Direct measurements are usually more reliable, however these techniques are usually also more invasive.

Direct methods

Direct flow measurement

In-continuity systems

The first systems for measuring blood flow were developed in the 19th century and are now only of historical importance. The "Stromuhr" was the first medical instrument capable of measuring flow in major blood vessels. It had to be manually attached to the vessel of interest and a marker was injected into the device to measure the rate of propagation, which was proportional to blood flow. Although measurements were limited to mean flow, an advantage of this method was that vessels could be left unopened[2-4].

Timed collection of hepatic vein output

Blalock et al. described a method in 1936 to temporarily occlude the inferior vena cava above and below the hepatic veins to measure hepatic blood flow. This method is accurate but invasive, causing extreme physiological changes. It is therefore limited to animal studies and used as a reference for calibrating experimental methods[5-7].

Plethysmography

A technique used in rabbits involves completely occluding venous hepatic outflow, causing acute liver volume increase proportional to blood inflow rate. Its invasiveness limits its use in humans[8].

Flowmeters

Metered flow probes are devices that measure the flow rate of a liquid or gas and are used in various applications, including measuring hepatic flow. They are highly accurate and provide continuous readings but require an abdominal incision for direct application to the vessel of interest. The probes rely on electromagnetism or ultrasound, using either transit time or the Doppler effect.

Electromagnetic flowmeters

Hans Christian Osted's observation in 1820 led to the understanding of Faraday's law, which indirectly states that the application of a magnetic field across a vessel with blood flow results in the development of an electric field. Kolin A. developed the first flowmeter in 1936 by applying a magnetic field to a tube of fluid, using the moving liquid as the conductor and introducing two non-polarizable electrodes in the tube. The generated voltage is proportional to the velocity of motion, the strength of the magnet and the length of the moving conductor. In practice the electrodes are placed on the outside of the vessel being studied, at a 90 degrees angle to the vessel. Blood vessel thickness and the ratio of outer to inner diameter can influence readings of electrical current flow through vessels, especially in smaller vessels like the hepatic artery. A film of serous fluid between the vessel wall and probe can create additional barriers. Changes in blood viscosity and tight or loose-fitting probes can also affect readings. The diameter of the portal vein can change as much as 40% due to respiration, resulting in inevitable turbulence. Probes should be calibrated with zero flow and repeated zeroing to avoid drift. Electrical interference, like electrocautery, reduces in vivo accuracy. Electromagnetic flow probes are highly accurate and insensitive to changes in blood temperature and can be used for the measurement of flow rates in any exposed vessel. Disadvantages of these probes include their invasiveness and the need for calibration and correct placement[11-25].

Transit time ultrasound

Transit time ultrasonic flowmeters measure blood flow by emitting an ultrasound signal from a first transducer that crosses the vessel and is received by a second transducer. The travel time in both directions is compared, and the difference is used to calculate flow through the vessel. The preferred transducer configuration depends on the characteristics of the object being measured. The "Z" configuration (Figure 1), with transducers on opposite sides of the vessel, is used for measuring blood flow. The vessel size can easily be determined, and the flow volume is calculated by multiplying vessel cross-sectional area with blood flow velocity. Unlike Doppler flowmeters, transit time flow meters can accurately measure volumetric blood flow. Transit time ultrasound flowmeters are less expensive than electromagnetic probes and can measure absolute flow independently of vessel size. They have been validated in vivo and shown to be as effective as other methods. Advantages include continuous measurements and the possibility of implanting flow probes for longer periods. However,

limitations include the inability to reliably measure simultaneous portal vein and hepatic artery flow, and technical challenges related to vessel diameter changes. Contact temperature, acoustic coupling medium, vessel probe fit, and probe diameter can also significantly influence readings. Additionally, surgical manipulation may result in arterial vasospasm, which can affect measurements[26-30].

Flowmeters based on Doppler ultrasound

Doppler ultrasound emits high-frequency waves that bounce off moving objects, such as red blood cells in the bloodstream, and the change in frequency of the waves is used to calculate the speed and direction of blood flow. These flowmeters require the presence of bubbles or particles to reflect the ultrasonic signals, and in vivo, red blood cells serve as these reflecting particles (Figure 2). The disadvantages of these flowmeters include high interobserver variability due to various factors influencing the obtained measurements. Doppler flowmetry has been successfully used as implantable microprobes in human subjects undergoing orthotopic liver transplantation and for the study of portal hemodynamics in liver disease.

Transabdominal ultrasound is a non-invasive technique that can be used to measure blood flow in the portal vein without exposing vessels. Portal vein flows are easier to measure than hepatic artery flows, yet both flows need to be measured to determine total hepatic blood flow. This total flow is calculated by multiplying velocity by cross-sectional area, which is measured using B-mode ultrasound. However, the portal vein's diameter can vary up to 40% with respiration, leading to potential errors. Paulson et al. found a 69% variability when repeating measurements. While this method is not precise, it is useful for noninvasive, painless measurement of blood flow changes. Again, absolute values may not be reliable[31-37].

Laser Doppler

Laser doppler combines doppler techniques with monochromatic photon emissions to measure blood flow velocity by analyzing the frequency shift of scattered light from red blood cells. Although mostly used for skin blood flow measurements, it has been compared to the hydrogen clearance method for hepatic flow measurement. Its advantages include continuous measurements unaffected by physiological variables, while disadvantages include invasiveness, superficial flow measurement and lack of absolute flow values[38-40].

Echocardiography

Hepatic veins can be visualized with echocardiography and their flow velocities determined using pulsed wave Doppler ultrasound. The flow pattern normally consists of 4 waves: S, D, Ar, and Vr. The S-wave represents anterograde flow from the hepatic veins towards the right atrium during right ventricular contraction, while the D-wave represents anterograde flow from the hepatic veins towards the right atrium when the tricuspid valve opens. The Ar-wave is retrograde flow from the right atrium towards the hepatic veins due to elevated right atrial pressure, and the Vr-wave is ventricular reversal when there is backflow. Left hepatic vein visualization is more challenging, with successful acquisition rates of 18% and 47% using transoesophageal and transthoracic approaches, respectively. Blood flow can be calculated using the formula: blood flow = VTI x π x (D/2)2 x HR, where VTI is the total velocity time integral of one cardiac cycle, π x (D/2) is the cross-sectional area of the vessel, and HR is heart rate. This method is

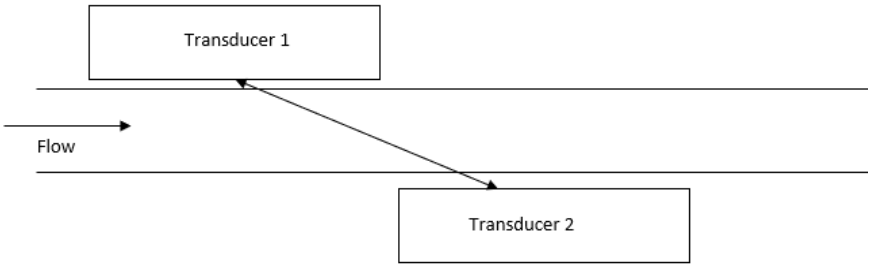

Fig. 1 — Principle of transit time ultrasound.

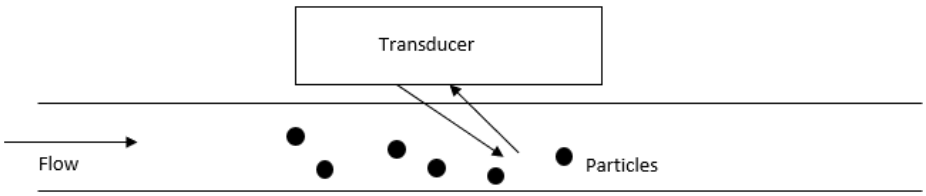

Fig. 2 — Principle of Doppler flowmeters.

low in invasiveness but has limitations, including inaccuracy in determining vessel diameter and assuming a consistent velocity profile. Total hepatic blood flow cannot be determined in most patients due to difficulty in visualizing the left hepatic vein. This method is useful for monitoring changes in hepatic flow during therapeutic interventions[41-45].

Heat exchange techniques

Heat exchange relies on thermocouples, which are made up of two metals welded together to form a junction. When there's a change in temperature, a voltage is created, and when submerged in a fluid, temperature changes are proportional to fluid flow. To measure liver tissue temperature, a thermocouple 2 to 4°C higher than the tissue temperature must be inserted. However, this method only measures relative flow changes and is semi-quantitative due to the location of the thermocouple, probe temperature, and liver metabolic state. Its invasiveness has limited its use in clinical practice[46-48].

Indirect methods

Dye dilution

The indicator dilution technique uses the injection of an inert marker to determine regional blood flow. An indicator dilution curve is constructed based on the injected indicator and indicator concentration at the outflow, and hepatic blood flow is calculated by dividing the indicator dose by the area under the curve. Examples of markers include labeled albumin, labeled red blood cells, cold saline, and para-aminohippurate (PAH). This technique is independent of hepatocellular function, but limited by laparotomy for catheter implantation, blood sampling-induced variation, lack of continuous measurements, and inaccurate readings due to splanchnic-systemic shunts or an aberrant artery in some patients. While useful for research, it has no clinical practicality[49-51].

Clearance methods

These methods are based on the Fick principle, which relates organ blood flow (Q) to the amount of indicator extracted by the organ (R) and the concentration difference of the indicator entering (Ci) and leaving the organ (C0). The equation $Q = R / (Ci - C0)$ is used to determine blood flow. Only indicators with high hepatic clearance can be used and the clearance of compounds with low extraction rates reflects metabolism rather than blood flow. Hepatic vein catheterization is required to determine C0, as the hepatic extraction rate is not always 100% during the first pass. Indicators can be continuously infused or given as a bolus, and dyes and radioactive-labeled substances are commonly used. Calculated plasma flows can be converted to actual blood flow by knowing the hematocrit[52].

Continuous dye infusion

Bradley et al. described this technique in 1945 to analyze hepatic blood flow in humans without surgery. However, determining the concentration of the indicator entering (Ci) and the amount extracted (R) is difficult. Using an indicator with an infusion rate that maintains constant blood levels overcomes this issue. Indocyanine green (ICG) is now commonly used due to its high hepatic extraction rate and ease of measurement. However, ICG contains iodine, which contraindicates its use in thyrotoxicosis or iodine allergy. Transcutaneous devices are available to simplify the standard determination of ICG. Hepatic vein catheterization is necessary, making it a moderately invasive procedure. Markers are not extracted effectively during disease states, since the hepatic extraction ratio is decreased in severe liver disease[53-59].

Bolus dye injection

This method uses a single dose of indicator and calculates blood flow based on a decay curve. After injection, multiple blood samples are taken from the hepatic vein and a peripheral vessel to construct decay curves. The plasma clearance is calculated using the area under the curve of the peripheral artery decay curve (AUCa). The extraction rate can be calculated using (AUCa - AUChv) / AUCa, with AUChv being the area under the curve of the hepatic vein decay curve. This method has some advantages over the continuous infusion technique, such as reduced invasiveness and the ability to determine extraction ratios accurately in patients with limited dye clearance. However, it has been criticized in subjects with liver disease[55].

Dye dilution techniques are simple and have been extensively used, but have several limitations. These include underestimating flow due to extrahepatic shunting, diminished hepatic clearance in liver disease, dilution from backflow, and inaccuracies from dye removal. As a result, the use of this technique has decreased with the development of more accurate methods[60-62].

Radio isotopic methods

Radionuclides can be used to determine hepatic blood flow by using gas tracers or radionuclide angiography. Inert gases like Xenon-133 and Krypton-85 are delivered to the organ and measured using a semiconductor or gamma camera. Flow is calculated using a formula and total hepatic flow can be calculated by multiplying the height/area of the

decay curve by 100 x λ. This method is invasive and has limited uses due to its accuracy and variation. Radionuclides can also be bound to colloids and delivered intravenously, with blood flow calculated using the Fick principle. 99mTc is the most commonly used radionuclide for this method[63-68].

Microspheres / fractional distribution method

This method uses microspheres to measure blood flow by determining the fractional distribution of cardiac output. Microspheres are trapped in capillaries and compared to a reference sample to measure individual organ blood flow. This method brings important limitations, especially for hepatic flow measurements. Microspheres are trapped in capillaries of the gastro-intestinal tract and do not enter the portal system. Consequently, portal flow cannot be measured, it can only be estimated by adding up the measured flows of splanchnic organs draining into the portal vein. Impaction of microspheres may also affect local flow, and therefore the accuracy of measurements. Finally, the main disadvantage is the necessary sacrifice of the study object which makes it impossible to perform it on humans and in clinical practice[67-68].

Radiographic methods

Angiography is useful for obtaining high-quality images of blood vessels, but its role in flow measurements is limited. Angiodensitometry involves looking at contrast medium in a vessel during angiography to calculate blood flow based on the degree of dilution. The technique requires densitometric calibration. Another technique involves measuring the time it takes for a contrast bolus to pass between two sites, but accurate timing is difficult. Angiography for flow measurements is mainly used in cardiac hemodynamics, and liver blood flow measurements are limited to hepatic artery flow. These techniques require direct vascular catheterization and are mainly of historical interest[69-70].

Positron Emission Tomography (PET)

Positrons are charged electrons that, when they react with electrons, produce two gamma photons, which is called the annihilation process. By capturing both photons, the exact location of this process can be determined, resulting in the creation of tomographic images that have better resolution and sensitivity than other nuclear medicine techniques. Organ blood flow can be determined by using a bolus dose of PET tracer, commonly using C11, N13, or O15 tracers. However, few studies have validated hepatic blood flow measurements using PET. Chen et al and Ziegler et al have shown good correlation with radiolabeled microspheres in separate studies, while Shiomi et al reported encouraging results compared to the 99mTc method. Nevertheless, PET techniques remain experimental and are not currently used in daily clinical practice[71-74].

Hydrogen electrode

Hydrogen saturates tissue, then platinum electrodes on the liver measure its clearance polarographically as it is oxidized to hydrogen ions. The generated current reflects perfusion within 5mm of the electrode, mainly studied for cerebral blood flow. Gouma et al found lower flows in porcine liver compared to indocyanine green clearance, concluding mainly arterial perfusion. Advantages include no reported influence on flows, but concerns arise due to inflammability and inability to measure rapid flow changes or heterogeneous perfusion[75-77].

Oxygen electrode

Oxygen electrodes measure tissue oxygen saturation in the liver, and although they cannot determine absolute flow values, they correlate well with changes in local blood flow and arterial pO_2. Studies have shown that oxygen electrode measurements correlate with portal blood flow measured by electromagnetism and may be a reliable and inexpensive way to monitor liver perfusion during transplant surgery[78-80].

Magnetic resonance imaging (MRI)

MRI is used for quantifying blood flow in organs, particularly in the cerebral and cardiac vasculature. It has been found to be more accurate than Doppler ultrasound and has good comparability to perivascular flow probes. However, the MRI method tends to underestimate blood flow compared to transit time ultrasound, and it cannot be used perioperatively due to the immobility of the MRI machine. MRI measurements have advantages of low invasiveness, low variability, and high reproducibility[81-88].

Clinical importance

While studying hepatic flow is important for expanding our understanding of hepatic blood flow, measured hepatic flow also plays a crucial role in clinical practice. The hepatic venous pressure gradient (HVPG), which measures the pressure difference between the portal vein and the inferior vena cava, is the most validated marker for portal hypertension. However, measuring HVPG is invasive and typically involves using a balloon catheter in the right hepatic vein. HVPG is determined by both vascular resistance and blood

flow, and non-invasive measurement of portal blood flow can serve as a useful surrogate marker for HVPG and portal hypertension. In liver cirrhosis, flow is the primary determinant of portal pressure, which is why interventions like transjugular intrahepatic portosystemic shunts redirect blood flow to the systemic circulation. Therefore, measuring portal flow has the potential to quantify the response to treatment. Additionally, hepatic blood flow measurements can play a crucial role during hepatic resections as blood flow may serve as an indicator of liver functional reserve and aid in decision-making. However, organ dysfunction is expected during transplant surgery, and the extent of organ injury is unpredictable. Changes in hepatic blood flow during liver transplant surgery are a crucial factor in predicting liver failure. Studies have shown that hepatic arterial blood flow measured by electromagnetic flowmeters correlates with early graft viability and function. Portal blood flow is the most reliable predictor of early graft dysfunction, as it correlates with bile secretion, bilirubin, transaminase levels, and the coagulation profile. In partial liver transplant, the "small for size syndrome" can be avoided by using a calibrated portocaval shunt with portal vein flow about twice its baseline value. The transesophageal echocardiographic-derived hepatic vein flow index, which is calculated by dividing hepatic vein flow by donor liver weight, has the potential to predict postoperative graft dysfunction.

It's worth noting that while several methods have been used to measure liver blood flow, many of them are of historical importance or are mainly used in research. However, there are some methods that have clinical importance, such as the clearance method, ultrasound, and transit-time flow measurement (TTFM). The clearance method involves measuring the rate at which a substance is cleared from the blood after being injected into the liver, which allows for the calculation of liver blood flow. Ultrasound can provide a non-invasive way to assess liver blood flow, while TTFM is a surgical method that uses an ultrasonic probe to measure blood flow in real-time during liver transplantation or hepatic surgery. These methods have practical applications in clinical settings and can provide valuable information for diagnosing and managing liver diseases[89-94].

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