Research Article

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Reliability of the estimation of total hepatic blood flow by Doppler ultrasound in patients with cirrhotic portal hypertension

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Background & Aims: Hepatic blood flow (HBF) is best estimated by the Fick's method during indocyanine green constant infusion (ICG-HBF) on hepatic vein catheterization. We investigated the consistency and agreement of HBF measured by Doppler ultrasound (US-HBF) as compared with ICG-HBF in portal hypertensive patients with cirrhosis.

Methods: In 50 patients observed for HVPG measurement (56% compensated; Child score 7 ± 2; HVPG 16.6 ± 6.0 mmHg; varices in 75%) US-HBF (Sequoia-512-Acuson; 4.5–7 MHz convex probe; US-HBF = hepatic artery blood flow + portal vein blood flow) and ICG-HBF (Fick's method after an equilibration period of at least 45 min of ICG bolus of 5 mg + constant rate infusion of 0.2 mg/min). Intraclass correlation coefficient (ICC) for consistency and absolute agreement between US-HBF and ICG-HBF were calculated.

Results: Mean ICG-HBF and US-HBF were similar, being respectively 1004 ± 543 ml/min and 994 ± 494 ml/min ($p = 0.661$ *vs.* ICG-HBF). However, results in individual patients disclosed marked differences between the two methods (386 ± 415 ml/min) and showed only moderate consistency (ICC 0.456; $p < 0.0001$), absolute agreement (ICC 0.461; $p < 0.0001$) and linear correlation ($R = 0.464$; $p < 0.0001$). The discrepancy between the two methods was maximal in patients with poor liver function, high HBF by any technique and more arterialized liver circulation. Hepatic artery blood flow $\geqslant$40% of US-HBF indicated, with 90% specificity, a discrepancy $\geqslant$20% between US-HBF and ICG-HBF.

Conclusions: HBF estimations by Doppler-ultrasound and ICG are significantly correlated, but their discrepancy in individual cases is high. Estimation of HBF by Doppler-US should be considered unreliable in patients with poor hepatic function and large liver arterialization.

Keywords: Non-invasive methods; Portal hypertension; Hepatic veins; HVPG.
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Introduction

In patients with cirrhosis and portal hypertension, the goal of therapy is to reduce portal pressure without deteriorating hepatic perfusion [1]. While hepatic venous pressure gradient (HVPG) measurement is a consistent and reproducible surrogate of portal pressure in cirrhosis [2], there is an unmet need for reliable techniques to assess total hepatic blood flow (HBF) in clinical practice.

The indocyanine green (ICG) constant infusion technique [3] has been widely used to estimate HBF by Fick's method in healthy subjects [4] and in patients with cirrhosis [5,6]. This method is objective and reproducible, and is currently considered the gold standard for HBF quantitative measurement. However, this technique requires hepatic vein catheterization, and cannot be used routinely.

Given the limitations of ICG-based HBF measurement (ICG-HBF), non-invasive methods to estimate HBF have been investigated. Doppler duplex ultrasonography (DUS) allows a non-invasive study of abdominal organs and abdominal circulation in real time, and has been widely used to assess the circulatory abnormalities occurring in patients with cirrhosis and portal hypertension [7,8]. DUS allows evaluating separately the two components of total HBF, namely portal vein blood flow (PBF) and hepatic artery blood flow (HABF) [9], but while DUS has been proved reliable for PBF estimation [10], very limited and inconclusive data exist on DUS-based measurement of total HBF in patients with cirrhosis [11].

The aim of this study was to assess the consistency and agreement of Doppler ultrasound for the assessment of hepatic blood flow in patients with cirrhosis by comparing this method with HBF estimated by the gold standard (HBF by ICG by Fick's method during hepatic vein catheterization).

Materials and methods

This study was approved by the Ethics Committee of Hospital Clinic. The nature of the study was explained to the patients, and a written informed consent was obtained in each case, according to the principles of the Declaration of Helsinki (revision of Edinburgh 2000).

Patients

Fifty patients with liver cirrhosis and hepatopetal portal blood flow, with valid measurements of ICG-HBF and valid measurements of both PBF and HABF by DUS, admitted to our laboratory for hepatic venous pressure gradient measurement, were included in this study. Exclusion criteria were the following: age <18 or >80 years; pregnancy; hepatocellular carcinoma; portal vein thrombosis; extraction index of ICG <0.1 [5]; insufficient visualization of the portal vein and hepatic artery. This last criterion led to the exclusion of 9 patients.

Table 1 shows the main clinical and laboratory characteristics of the studied population.

Hepatic venous pressure gradient and HBF by indocyanine green (ICG-HBF) measurement

Patients underwent hepatic vein catheterisation in the morning after at least 8-h fasting. Under local anaesthesia, with ultrasonographic guidance (SonoSite Inc, Bothell, WA), a 8F venous catheter introducer (Axcess; Maxxim Medical, Athens, TX, USA) was placed in the right internal jugular vein using the Seldinger technique. Thereafter, a 7F balloon-tipped catheter (Edwards Lifesciences, Irvine, CA, USA) was advanced into the right hepatic vein to measure wedged and free hepatic venous pressures (WHVP and FHVP, respectively) by the connection to external electro-mechanical transducer and polygraph (Mac-Lab®, GE Healthcare, Freiburg, Germany). HVPG was calculated as WHVP − FHVP [2].

Preceded by a priming dose of 5 mg, a solution of indocyanine green (Pulsion Medical Systems, Munich, Germany) was infused intravenously at a constant rate of 0.2 mg/min. After an equilibration period of at least 40 min to achieve a steady-state, 4 separate sets of simultaneous samples of peripheral and hepatic venous blood were obtained for the measurement of hepatic blood flow according to the Fick's method, as previously described [12]. To avoid interferences from differences in plasma turbidity, the Nielsen's correction was used [5] at the moment of reading ICG concentration in the samples by spectrophotometry (SP-830, Turner Biosystems, Sunnyvale, CA, USA).

Briefly, ICG clearance was calculated as ICG constant infusion velocity/mean concentration of ICG in the peripheral venous blood. ICG extraction index was calculated as: (concentration of ICG in the peripheral venous blood – concentration of ICG in the hepatic venous blood)/concentration of ICG in peripheral venous blood. Hepatic plasma flow was estimated as ICG clearance/ICG extraction index. Finally, hepatic blood flow was estimated as: hepatic plasma flow/(1 − hematocrit).

HBF by Doppler ultrasound (US-HBF)

Patients underwent DUS examination on the same morning of hepatic vein catheterization, after an overnight fast, before undergoing the invasive procedure. They were invited to lie supine for 10 min. Thereafter, Doppler measurements were performed using a Siemens ACUSON Sequoia™ 512 (Acuson, Mountain View, CA, USA) ultrasound system, by the same physician, in order to avoid inter-observer variability. A 3.5–5 MHz convex probe provided by a color, power and pulsed Doppler software was used. Following current recommendations [7,8], portal vein and hepatic artery were imaged by B-mode. The gain was reduced and the image size made as large as possible to improve resolution. Diameter and flow velocity were measured in both vessels during short-time suspended normal respiration, using an oblique scan in the epigastrium in a standardized site (crossing of hepatic artery and portal vein). Insonation angles of 50–55° were used for these measurements. The Doppler sample was positioned in the center of the lumen, setting its dimension as wide as ⩾50% of the vessel diameter. Measurements were taken in triplicate, and the results were expressed as the mean value. Variability between different measures was <10%. Intraobserver variability was previously assessed and was <10%.

Time averaged maximum velocity in the portal vein and in the hepatic artery was obtained from delineation of the Doppler spectral signal. Portal blood velocity was calculated as time averaged maximum velocity multiplied by 0.57, assuming the portal velocity profile as parabolic, as previously reported [13,14]. Similarly, hepatic artery velocity was calculated as time averaged maximum velocity multiplied by 0.62, as previously reported [7,8].

Portal blood flow (PBF) and hepatic artery blood flow (HABF) were obtained by multiplying the portal vein cross-sectional area, assuming a circular shape of the portal vein and hepatic artery section, by the mean velocity of blood flow in the vessel [10,13,14], according to the following formula:

$$\text{Blood flow (ml/min)} = \text{cross sectional area of the vessel} * \text{mean flow velocity (cm/s)} * 60$$

Total hepatic blood flow (US-HBF) was then calculated as PBF + HABF.

Table 1. Main clinical, laboratory and hemodynamic features of the studied population (n = 50).

Characteristic	
Age (yr)	56 ± 9
Sex, n (M/F)	33/17
Body surface area (m^2)	1.81 ± 0.16
Etiology, n (HCV/HBV/alcohol/other)	25/2/15/8
Child-Pugh class (A/B/C)	26/13/11
Child-Pugh score	7.0 ± 2.2
Esophageal varices (no/small/large)	12/15/23
MELD score	11 ± 4
Treatment with beta-blockers, n (%)	13 (26)
Ascites, n (%)	18 (36)
Previous decompensation, n (%)	22 (44)
Bilirubin (mg/dl)	1.8 ± 1.4
INR	1.29 ± 0.25
Albumin (g/dl)	3.6 ± 0.7
Creatinine (mg/dl)	0.98 ± 0.23
Platelets (n^3/mm^3)	115 ± 63
Spleen diameter (cm)	14.9 ± 2.8
HVPG (mmHg)	16.6 ± 6.0
ICG hepatic clearance (ml/min)	208 ± 127
ICG extraction index (%)	38 ± 23
Mean arterial pressure (mmHg)	90 ± 14
Heart rate (beats per minute)	74 ± 15

The percentage of US-HBF provided by PBF and HABF was calculated as: PBF/US-HBF * 100 and HABF/US-HBF * 100.

Congestion index of the portal vein was calculated as previously reported by Moriyasu *et al.* [15] as follows:

$$\text{Congestion index} = \text{cross-sectional area of the portal vein (cm}^2\text{)/portal vein mean flow velocity (cm/s)}.$$

Statistical analysis

Means of ICG-HBF and US-HBF were compared by paired T-test or Kruskall-Wallis test, while medians were compared by Wilcoxon's test. Correlations between ICG-HBF and US-HBF and its components were made by Pearson's test. Agreement between the two techniques was assessed by intraclass correlation coefficients (ICC) for consistency and absolute concordance. According to Landis *et al.*, ICC were interpreted as follows: 0–0.2 indicates poor agreement; 0.3–0.4 indicates fair agreement; 0.5–0.6 indicates moderate agreement; 0.7–0.8 indicates strong agreement; and >0.8 indicates almost perfect agreement [16].

We arbitrarily defined as "clinically important difference", a difference between US-HBF and ICG-HBF ⩾20%. Receiver operating characteristics curve (ROC) analysis was used to identify the most specific cut-off of the tested parameters able to detect this clinically important difference in HBF as compared with ICG-HBF.

The α value was set at 0.05. All *p*-values are two-sided. Statistical analysis was performed with SPSS 16.0 package (SPSS, Chicago, IL, USA).

Results

Table 2 shows the results of DUS examination, US-HBF, and ICG-HBF in the 50 patients included, and Table 3 shows the correlation of Doppler-US examination with HVPG, Child-Pugh score, and grade of esophageal varices. As shown, among the Doppler-US variables studied, the congestion index of the portal vein