

Total and functional hepatic blood flow decrease in parallel with ageing

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Abstract

Objectives: to study changes in hepatic blood flow with age.

Design: functional hepatic flow (FHF) and total hepatic flow (THF) were determined by non-invasive methods in 40 normal subjects in four age groups (<45, 45–60, 61–75 and >75 years). All subjects had normal routine liver function tests and no history of liver disease.

Results: THF was measured by pulsed echo-Doppler, as the sum of portal and hepatic artery blood flow; FHF was measured by the hepatic clearance of D-sorbitol. THF significantly decreased with age, particularly in subjects over 75 (from 1445 ± 220 ml/min to 1020 ± 148 ; $P < 0.001$), and a similar reduction was observed in FHF (from 1514 ± 250 ml/min to 1015 ± 163 ; $P < 0.001$). THF and FHF were strictly correlated in the whole population ($r = 0.871$; $P < 0.001$) and both correlated with age ($r = -0.510$ and $r = -0.596$; $P < 0.005$).

Conclusion: with ageing there is a reduction of hepatic blood flow without any additional intrahepatic shunting.

Keywords: ageing, echo-Doppler, functional hepatic flow, D-sorbitol clearance, total hepatic flow

Introduction

Liver volume and portal blood flow decrease after the age of 50 [1, 2]. Liver function, measured by dynamic functional tests (such as galactose elimination capacity), decreases progressively with ageing [3, 4]. The potential roles of reduced blood flow and intrahepatic shunting, due to subclinical alterations in hepatic morphology, have never been determined.

Studies of the hepatic extraction of drugs show that total hepatic blood flow is reduced in elderly subjects. These data were obtained by invasive techniques (hepatic vein catheterization) [5, 6]. Non-invasive methods are now available, making it possible to measure the functional hepatic flow (FHF) by clearance techniques [7] and total hepatic flow (THF) by pulsed echo-Doppler [8, 9]. THF is the sum of the flow of the portal vein and of the hepatic artery. In normal subjects, all the blood perfusing the liver is theoretically in close contact with functioning hepatocytes, therefore FHF should be equivalent to THF.

In this study we aimed to measure THF and FHF non-invasively in a group of normal subjects of various ages, in order to study changes in hepatic haemodynamics in the course of ageing.

Patients and methods

Subjects

We studied 40 healthy subjects divided into four age groups: <45, 45–60, 61–75 and >75 years. Each group consisted of 10 subjects: five men and five women. Subjects were selected from a total of 48; eight had to be excluded because of inadequate echo-Doppler visualization of the hepatic vessels.

Eight subjects were members of the medical staff or their relatives and were examined as outpatients, while 32 were hospitalized for mild gastrointestinal diseases, osteoarthritis or chronic bronchitis; all were living independently at home. Their body weights were within 10% of the ideal body weight. All had normal routine liver function tests (serum albumin, cholesterol, bilirubin, alkaline phosphatase, aspartate and alanine transaminase concentrations and prothrombin activity) and had no history of previous or active liver disease or cardiovascular disease. At the time of the study no subject was taking drugs known to affect either liver function or the cardiovascular system.

All subjects gave their informed consent to take part

in the study, which was carried out according to the ethical guidelines of the Helsinki declaration. The protocol of the study was approved by the department's senior staff committee.

Methods

THF was measured by means of echo-Doppler, as the sum of portal blood flow and hepatic artery blood flow, while FHF was determined by the hepatic clearance of D-sorbitol. All measurements were performed in fasting subjects, at the same time each morning.

Echo-Doppler measurements of the portal vein and of the common hepatic artery [8–10] were obtained using equipment that combines a real-time electronic sector scanner and a pulsed Doppler unit (Esaote-Ansaldo AU4 Idea, Genova, Italy). The echo-Doppler examination was always performed by the same investigator, with over 10 years of experience in Doppler examination of deep abdominal vessels. Patients were examined in the supine position and were asked to hold their breath during normal respiration. The measurements were repeated until three consistent, consecutive values of blood velocity were obtained (maximum variability: portal velocity, 1 cm/s; hepatic artery velocity, 5 cm/s) [11] and the mean values considered for statistical purposes.

The portal vein was scanned longitudinally, and the sample volume was positioned in the middle of the portal trunk, in the tract just underneath the hepatic artery [8, 11]. The cross-sectional area of the portal vein was determined from the radius by assuming the vessel to be circular. Mean portal blood velocity was calculated automatically, while portal blood flow was calculated by multiplying blood velocity by the cross-sectional area of the portal vein.

The hepatic artery measurements were taken where a straight stretch runs parallel to the portal vein, some centimetres away from the coeliac axis [9]. The gastroduodenal and gastric arteries have usually already branched by this point, so that only hepatic artery blood flow is measured. Care was taken to keep the θ angle (the angle between the ultrasonic beam direction and the blood flow direction) below 55°. The

cross-sectional area of the hepatic artery was determined on the basis of the calibre, while mean blood velocity was calculated by multiplying the averaged maximum velocity by 0.62, as suggested by Nakamura [10]. Hepatic artery flow was determined by multiplying the mean blood velocity by the sectional area of the artery.

THF was calculated as the sum of portal flow and hepatic artery flow.

In a subgroup of 10 subjects day-to-day reproducibility of Doppler measurements was assessed by measuring each vessel, under the same conditions, on two consecutive days.

Functional hepatic plasma flow was determined from the hepatic clearance of D-sorbitol, [7], after a 2 g intravenous bolus of sorbitol followed by a 2-h infusion at a rate of 54 mg/min. FHF was calculated by multiplying plasma flow by the haematocrit.

The data in the text and in the tables are expressed as mean values \pm SD. Statistical analyses were performed using Student's *t*-test for unpaired data. Differences between the mean values of the different parameters, in the various age groups, were tested for significance by means of one-way analysis of variance (ANOVA). The *r* coefficients of linear correlation analysis were also determined.

Results

Results of hepatic blood flow in the various age groups are reported in Table 1.

Day-to-day variation of echo-Doppler measurements were within 8% for portal blood flow and within 15% for hepatic artery flow, Doppler-assessed THF showing a maximum variation from -7.2 to $+7.5\%$.

Portal vein calibre did not change with age, varying from 1.16 to 1.03 cm, while echo-Doppler measured portal blood velocity and flow decreased from age 45 onwards.

Hepatic artery velocity and flow did not change significantly in the various age groups (ANOVA, $P=0.275$ and $P=0.363$), although a mild increase was observed between 45 and 75 years.

Table 1. Relation between age and Doppler-assessed portal flow, hepatic artery flow, and total and functional hepatic flow

Age (years)	Portal vein		Hepatic artery		Hepatic flow (ml/min)	
	Blood velocity (cm/s)	Flow (ml/min)	Blood velocity (cm/s)	Flow (ml/min)	Total	Functional
<45	19.4 \pm 3.5	1209 \pm 205	35 \pm 6	235 \pm 76	1445 \pm 220	1514 \pm 250
45–60	16.7 \pm 1.6	980 \pm 337	43 \pm 12	313 \pm 117	1293 \pm 340	1326 \pm 348
61–75	15.8 \pm 2.5	978 \pm 194	43 \pm 13	318 \pm 144	1297 \pm 253	1258 \pm 226
>75	15.0 \pm 1.8	749 \pm 117	40 \pm 8	271 \pm 94	1020 \pm 148	1015 \pm 163
ANOVA (<i>P</i>)	0.0046	0.0018	0.275	0.3632	0.0088	0.0023

Data are mean values \pm SD.

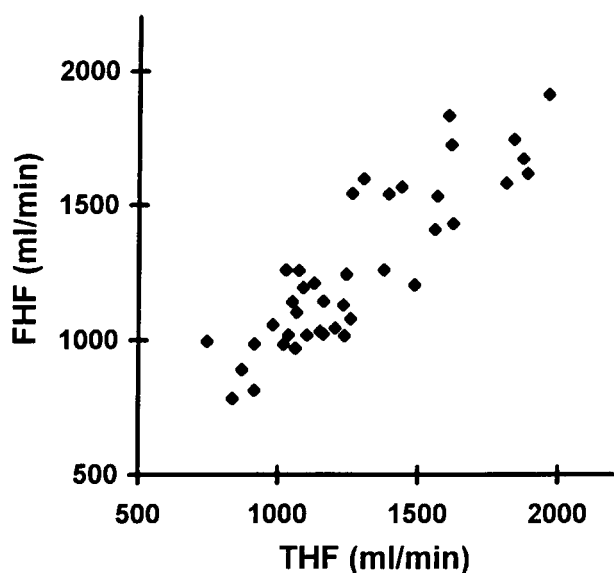


Figure 1. Correlation between total hepatic flow (THF) and functional hepatic flow (FHF) in ageing subjects ($r=0.871$; $P<0.001$).

THF significantly decreased with age, particularly in subjects over 75 (1445 ± 220 versus 1020 ± 148 ml/min; $t=3.597$, $P<0.001$). When corrected for body surface, THF significantly decreased in the oldest subjects (from 838 ± 107 to 629 ± 84 ml/min per m^2 ; ANOVA: $P=0.019$).

FHF, evaluated by sorbitol clearance, was significantly reduced with age, particularly in the oldest subjects (1514 ± 250 versus 1015 ± 163 ml/min; $t=4.14$; $P<0.001$), and similar data were observed when FHF was corrected for body surface (from 884 ± 150 to 627 ± 104 ml/min per m^2 ; ANOVA: $P=0.006$). FHF ranged from 1128 to 1870 ml/min (median 1523) in subjects under 45, and from 744 to 1258 ml/min (median 1037) in subjects over 75.

The difference between THF and FHF did not reveal any systematic deviation from random distribution, being on average only 14 ± 154 ml/min. FHF and THF were strictly correlated in the whole population ($r=0.871$; $P<0.001$; Figure 1).

A negative correlation was observed between age and THF ($r=-0.510$; $P<0.005$) or FHF ($r=-0.596$; $P<0.001$; Figure 2).

Discussion

We found that total and functional hepatic flow decrease with age in parallel, the reduction being particularly evident after 75 years. This might explain the well-known age-related reduction in liver function and capacity to metabolize drugs.

THF i.e. the amount of blood circulating in the liver, independent of any metabolic activity, has been studied by indocyanine green clearance [12]. The

Hepatic flow in ageing

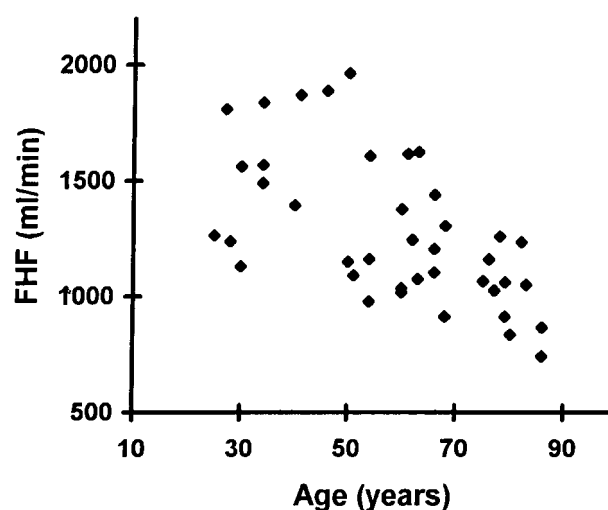


Figure 2. Correlation between functional hepatic flow (FHF) and age ($r=0.596$; $P<0.001$).

relatively high hepatic intrinsic clearance of indocyanine green and absence of extrahepatic elimination makes the substance suitable for the measurement of total hepatic blood flow in control subjects. Unfortunately, the correct measurement of indocyanine green clearance requires hepatic vein catheterization [12, 13], and such invasiveness is not counterbalanced by precision, since great variability occurs on repeated measurements [14].

To determine THF we used pulsed echo-Doppler, a non-invasive technique that is increasingly being used in clinical practice and which enables us to measure portal and hepatic artery flow [8–10, 15]. By measuring the portal flow past the origin of the left gastric vein, and the arterial flow at the common trunk of the hepatic artery, we theoretically measured all the blood flowing through the liver.

The limits of the technique and the sources of error in the measurement of blood velocity and flow have been discussed previously [8, 9, 16]. They stem from uncertainty about the measurement of blood velocity and vessel calibre, and the possible non-circular cross-section of the vessel. To minimize these errors, we examined only patients in whom the vessels could easily be visualized. In addition, in agreement with a recent study [11], Doppler data were obtained by the same well-trained operator, using the same equipment and following strict guidelines in the measurement of blood velocity. In experienced hands, valid measurements are feasible in about 80% of cases and are reproducible [11, 17, 18]. We accepted a variability in blood velocity in the order of 10% during three repeated measures, which gives a variability of $<5\%$ in blood flow. Variability may be amplified by uncertainty about vessel calibre, particularly in the small hepatic artery, but well-trained operators may limit the error to $<15\%$. Finally, the error inherent in

the assumption of circular cross-sectional area is probably lower than that which would ensue from the actual measurement of vessel area. Adherence to a strict protocol in echo-Doppler examination is possibly the reason for the good day-to-day reproducibility we observed, particularly for portal blood flow determination.

FHF is the amount of blood perfusing the liver and making close contact with functioning hepatocytes so as to exert metabolic activities. The hepatic clearance of D-sorbitol gives a reliable estimate of FHF, i.e. the flow through functioning sinusoids, and studies have validated a non-invasive technique by comparison against invasive procedures based on the hepatic extraction of sorbitol and indocyanine green according to Fick's principle [7, 19, 20].

The close correlation we observed between FHF and THF confirms the utility of non-invasive techniques for the measurement of hepatic flow in control subjects. The differences between values obtained by the two methods are not systematic, and are most likely due to technical imprecision. However, two studies reported that the hepatic clearance of sorbitol is greater than indocyanine green clearance, assumed to equal THF [7, 19]. In any case, improvements in echo-Doppler equipment could also contribute to level out the differences observed, especially in the few control cases where differences were as large as ± 284 ml/min.

Between the ages of 45 and 75 we observed a decrease in portal flow which was partly counterbalanced by an increase in hepatic artery flow. This could be explained by the well-known reciprocal relationship between portal and hepatic artery blood flow, which tends to maintain constant the volume of blood flowing through the liver [21, 22]. In younger subjects the hepatic artery flow constitutes 17% of total flow; after age 45 it rose to about 25%, the proportion then remaining stable. In the oldest group (>75) hepatic artery flow did not change, while portal flow decreased, so that THF decreased by 30%.

Several factors could explain the reduction in THF in elderly subjects. A reduced resting cardiac output seems unlikely, since cardiac output is in the normal range in fit elderly people [23]. Our observation of a normal hepatic artery flow and a reduced portal flow can be explained by several conditions: selective involvement of atherosclerotic lesions in the mesenteric area, or neural or humoral autoregulation.

Our study also shows that in elderly subjects the whole blood perfusing the liver is available for metabolic exchanges without any intrahepatic shunting. Age-related reductions in liver weight and volume have been previously shown, as well as a decrease in the number and size of hepatocytes [4, 24, 25]. Serum concentrations of liver enzymes, such as alkaline phosphatase, alanine and aspartate aminotransferase, appeared not to be affected by age, and serum albumin concentrations in the elderly subjects were just at the

lower limit of the normal range, and rarely statistically reduced. Changes in liver volume and in liver flow seem therefore not to affect the synthesis or metabolism of endogenous products or substrates. However, when the reserve capacity of the liver is challenged by means of exogenous substrates, a decreased capacity of the liver is clearly found [3, 4]. Our finding of a 30% reduction in THF, which is paralleled by an equivalent reduction in FHF, raises the question of whether changes in liver function and capacity to metabolize drugs may be flow-related.

Galactose elimination capacity, which proved to be reduced in elderly subjects in two independent studies [3, 4], is not influenced by hepatic blood flow. In contrast, FHF appeared to be significantly reduced and strictly related to the reduction in THF. These two tests (galactose and sorbitol) explore two different aspects of the ageing process, which interact but have no cause-and-effect relationship.

Reduced hepatic blood flow could also explain the delayed hepatic regeneration after injury [26] and the age-related decrease in the clearance of drugs metabolized primarily by the liver. The decline observed with age in first-pass hepatic metabolism is clearly flow-related [25, 26], and also the reduction in phase I reactions may be partly due to reduced hepatic flow.

In conclusion, the simultaneous determination of FHF and THF gives a comprehensive picture of the haemodynamic and functional changes which occur in the liver in the course of ageing.

Key points

- There is an age-related reduction of blood perfusing the liver without any additional intrahepatic shunting.
- The reduction in hepatic blood flow is particularly evident after the age of 75.
- The reduction in total and functional hepatic blood flow might explain age-related reduction in liver function and capacity to metabolize drugs.

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