Environmental Factors Responsible for Variability of Hepatic Vein Flow: A Doppler Assessment in Healthy Twins

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Abstract

Doppler interrogation studies of the liver blood flow indicate altered hepatic vein waveforms in association with impaired hepatocellular function. However, little is known about the mechanisms responsible for variations of these parameters in the absence of disease. We aimed to investigate the contribution of heritable and environmental factors to the physiological variability of hepatic vein flow in a twin cohort. Two hundred twenty-eight healthy adult Hungarian twins (69 monozygotic, 45 same-sex dizygotic pairs) underwent Doppler sonography of the hepatic vein. Age- and sex-adjusted heritability of the highest velocity (amplitude of S wave) of hepatic vein flow was negligible. Shared environment contributed to 33% (95% CI, 16%-51%), and unshared environment was responsible for the largest portion (67%; 95% CI, 49%-84%) of the variance. Duration of sports activities was significantly (P < 0.05) related to the magnitude of hepatic vein flow, while other risk factors and lifestyle characteristics had no significant influence. The data suggest that genetic factors have little impact on the parameters of hepatic venous blood flow. The variability observed in healthy twins by the Doppler interrogation can be explained by the effect of unshared environmental components primarily related to regular physical activity. These findings underscore the importance of unique environments in physiological variations of hepatic venous blood flow.

Key Words: blood flow, hepatocellular function, liver, physical activity, velocity

Introduction

In recent years, there has been increased emphasis on performing hepatic venous Doppler studies to evaluate parenchymal abnormalities of the liver in conditions such as cirrhosis, graft rejection, diffuse fatty infiltration or acute viral hepatitis (14, 24, 28, 29). It is believed that hepatic venous blood flow is regulated in the liver sinusoids by complex humoral and neural mechanisms (24). The Doppler spectral waveform of the hepatic vein reflects pulsatile changes in blood flow during the cardiac cycle through the tricuspid valve (29). The normal triphasic waveform of the hepatic vein consists of two hepatofugal phases related to atrial and ventricular diastole, and a short hepatopetal phase related to retrograde flow caused

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by the pressure increase in the right atrium at atrial systole (12, 29). While changes in hepatic waveforms may be the consequence of corresponding changes in liver parenchyma, significant physiological variability can be observed in individuals without hepatic or cardiovascular disease (22). It has been demonstrated that the pattern of hepatic vein flow is affected by age and sex, but less so by different body positions, exercise or food intake (8). Some environmental factors are known to be related to hepatic injury via various oxidative and inflammation mediators (4, 9). Whether the observed variability of hepatic vein flow is primarily inherited or acquired, and whether this variability contributes to changes associated with disease conditions remains unclear. We hypothesized no larger genetic influence because we found in our previous works that the role of inheritance affecting arterial velocities in cerebral vessels and carotid artery is modest only (11, 26).

In this study, we aimed to evaluate the role of hereditary and environmental factors in physiological variations of the hepatic blood flow in a cohort of healthy Hungarian twins. The twin study design involves the enrollment of monozygotic and dizygotic twins and provides valuable information on the relative contribution of factors that may influence study outcomes by dividing the variance into genetic (A), shared environmental (C), and unshared environmental (E) factors.

Materials and Methods

Subjects and Study Design

We recruited 228 adult twins (69 monozygotic, 45 same-sex dizygotic pairs; mean age 43.6 ± 13.6 years) from the Hungarian Twin Registry to participate in this cross-sectional study (10). Only same-sex dizygotic twin pairs were included in the study to avoid bias of the heritability estimates in the presence of gender-specific or X chromosome effects. A multiple-choice self-reported seven-part questionnaire was used for zygosity classification, which reportedly has 99% accuracy (6). Twins having acute infection, chronic liver disease, pregnancy and heart failure were excluded from the analysis as these conditions are known to cause significant changes in hepatic venous blood flow (5, 19, 21).

Twins underwent weight and height measurements and body mass indices were calculated according to the formula: weight (kg)/height (m)². Systolic blood pressure, diastolic blood pressure, and mean arterial pressure were assessed by oscillometry (TensioMed Arteriograph, TensioMed Ltd., Budapest, Hungary). Furthermore, all study subjects underwent phlebotomy after at least 6 h fasting, and serum levels of total

cholesterol, high-density lipoprotein cholesterol, lowdensity lipoprotein cholesterol and triglycerides were determined. Participants completed a questionnaire to assess past medical history and potential health risk factors, e.g., cigarette smoking, alcohol and coffee consumption, physical activities or lack thereof. These studies were performed at two large hospitals in Budapest (Department of Radiology and Oncotherapy, Semmelweis University, and Department of Cardiology, Military Hospital). Sonography studies were performed in the ultrasound laboratory of Department of Radiology and Oncotherapy of Semmelweis University. All participants gave informed consent. The study was approved by the Ethics Committee of Semmelweis University and was conducted in full compliance with regulations of the Declaration of Helsinki.

Liver Sonography

Limited abdominal sonography was performed by using B-mode and Doppler sonography on an Esaote MyLab 70X Vision device (Genoa, Italy) equipped with a curved array (1-8 MHz, CA431) and a linear array transducer (13 MHz, LA523). Standardized digital images of the liver and the hepatic veins were recorded and examined in the supine and lateral decubitus position. The extent of liver steatosis was determined by a standard technique based on increased echogenicity, loss of portal vein walls, decreased through-transmission and closely packed echoes (20). Doppler waveforms of the hepatic vein were recorded during suspended respiration for at least 5 s. A well identifiable (usually middle) hepatic vein was imaged and the Doppler gate was placed in the middle of the vessel to measure hepatic vein waveforms. Velocity measurements were conducted at 30-60°. The highest velocity of the hepatic vein (amplitude of the S wave) was marked by an automatic caliper. The S wave was chosen for reference because it can be easily measured and the largest amount of anterograde blood flow occurs during this phase (1). To minimize variations and errors, all parameters were measured by the same observer on the same machine.

Statistical Analysis

SPSS Statistics 17 (SPSS Inc., Chicago, IL, USA) was used to perform descriptive analysis (mean, standard deviation, and percentage for categorical variables) and the parametric difference *t*-test. A descriptive estimate of the genetic influence on a single trait was calculated using the within-pair co-twin correlations in monozygotic and dizygotic pairs corrected for age and gender. Heritability estimates were

	Tata1	Zygo	P-value	
	Total	Monozygotic	nozygotic Dizygotic	
Participants, n	228	138	90	N/A
Gender ratio (females:males)	164:64	106:32	58:32	N/A
Age, years (mean \pm standard deviation)	43.6 ± 13.6	42.6 ± 16.4	45.2 ± 16.3	NS
Highest velocity (S wave) of hepatic vein flow, cm/s	16.8 ± 8.2	17.2 ± 8.6	16.2 ± 7.6	NS
Body mass index, kg/m^2 (mean \pm SD)	25.7 ± 4.8	25.6 ± 4.9	25.7 ± 4.7	NS
Current smokers, n (%) Ex smokers, n (%)	36 (16.1) 31 (13.9)	21 (15.3) 17 (12.4)	15 (17.4) 14 (16.3)	NS
Hypertension, n $(\%)^{\dagger}$	70 (31.7)	44 (32.8)	26 (29.9)	NS
Systolic blood pressure, mmHg	128.0 ± 15.1	128.9 ± 15.8	126.5 ± 14.0	NS
Diastolic blood pressure, mmHg	75.2 ± 11.2	75.9 ± 12.2	74.0 ± 9.5	NS
Mean arterial pressure, mmHg	92.8 ± 11.8	93.5 ± 12.4	91.7 ± 10.8	NS
Hypercholesterolemia, n (%)	49 (22.2)	29 (21.6)	20 (23.0)	NS
Total cholesterol, mM	5.1 ± 0.9	5.1 ± 0.9	5.2 ± 1.0	NS
HDL cholesterol, mM	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	NS
LDL cholesterol, mM	3.2 ± 0.8	3.2 ± 0.9	3.3 ± 0.8	NS
Triglycerides, mM	1.5 ± 0.9	1.5 ± 0.8	1.5 ± 0.9	NS
Presence of NAFLD, n (%)	48 (23.5)	32 (25.6)	16 (20.3)	NS
Diabetes, n $(\%)^{\dagger}$	13 (5.9)	8 (6.0)	5 (5.7)	NS
Alcohol intake, units/week [†]	1.8 ± 2.8	1.8 ± 3.0	1.9 ± 2.7	NS
Coffee consumption, cups/day [†]	1.1 ± 1.1	1.1 ± 1.1	1.3 ± 1.2	NS
Regular physical activity, n $(\%)^{\dagger}$	154 (73.0)	91 (71.7)	63 (75.0)	NS
Duration of sport activity, min/week [†]	73.7 ± 34.2	72.0 ± 35.6	77.0 ± 31.5	NS
Sleeping, hours/day [†]	7.4 ± 1.1	7.4 ± 1.0	7.4 ± 1.2	NS
Sitting, hours/day [†]	8.7 ± 3.9	8.6 ± 3.9	8.9 ± 3.8	NS
Light physical activity, hours/day [†]	4.1 ± 2.5	4.1 ± 2.6	4.0 ± 2.4	NS
Mid-strength physical activity, hours/day [†]	2.1 ± 2.0	2.1 ± 2.1	2.0 ± 2.0	NS
Hard physical activity, hours/day [†]	1.3 ± 2.2	1.2 ± 1.9	1.6 ± 2.5	NS

Table 1. Clinical and sonographic characteristics of the study subjects

[†]Defined according to the clinical history and subject referral. NS, not significant.

determined based on the consideration that greater levels of monozygotic than dizygotic within-pair correlation indicate a genetic influence on a phenotype, while similarity of co-twin correlations suggests that the variance is due to shared environmental sources. In contrast, dizygotic co-twin correlations substantially exceeding monozygotic correlations indicate the role of unshared environmental components. Structural equation modeling (A-C-E model) was performed by using the Mplus Version 7.1 (15, 16). According to the A-C-E model, three latent variables drive the variance in the phenotype for each twin - these include additive genetic effects (A) the impact of common (or shared) environment (C), and unshared (or unique) environmental factors (E) (17). Empirical 95% confidence intervals were calculated with Bollen-Stine Bootstrap (3). All inferential statistics were estimated using full information maximum likelihood.

Results

The mean ages of monozygotic (MZ) and dizygotic (DZ) twins participating in the study were $42.6 \pm$ 16.4 years and 45.2 ± 16.3 years, respectively. There was no significant difference between monozygotic and dizygotic twins in their examined clinical parameters and sonographic characteristics (Table 1). However, we found significant age- and sex-adjusted partial correlation between the highest velocity (S wave) of hepatic vein flow and reported weekly duration of regular physical activity $(73.7 \pm 34.2 \text{ min per})$ week, P < 0.05). Borderline significance was demonstrated between the S wave and the duration of midstrength physical activity (P = 0.06). Presence of various disorders and environmental factors identified in the study showed no significant relationship with the amplitude of S wave (Table 2).

Co-twin correlations were somewhat higher in

	Correlation with highest velocity (S wave) of hepatic vein flow	<i>P</i> -value
Hypertension, yes vs. no	15.6 vs. 17.4	NS
Systolic blood pressure, mmHg	0.041	NS
Diastolic blood pressure, mmHg	0.129	NS
Mean arterial pressure, mmHg	0.097	NS
BMI, kg/m ²	0.106	NS
Hypercholesterolemia, yes vs. no	17.5 vs. 16.6	NS
Total cholesterol, mM	-0.131	NS
HDL cholesterol, mM	0.012	NS
LDL cholesterol, mM	-0.045	NS
Triglycerides, mM	-0.209	NS
No vs. presence of NAFLD	17.2 vs. 15.5	NS
Active vs. never smokers	18.7 vs. 16.6	NS
Former vs. never smokers	16.3 vs. 16.6	NS
Diabetes, yes vs. no	14.0 vs. 17.0	NS
Alcohol intake, units/week	-0.041	NS
Coffee consumption, cups/day	0.214	NS
Regular physical activity, yes or no	17.4 vs. 16.6	NS
Duration of sport activity, min/week	-0.237	0.05*
Sleeping, hours/day	0.154	NS
Sitting (work, driving, relaxing), hours/day	0.046	NS
Light physical activity (stroll, shopping), hours/day	0.124	NS
Mid-strength physical activity (light sport), hours/day	-0.229	0.06*
Hard physical activity (hard work, active sport), hours/day	-0.141	NS

 Table 2. Age- and sex-adjusted partial correlation coefficients and results of independent t-tests of the highest velocity (S wave) of hepatic vein flow and various disorders or environmental factors

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease (based on sonographic criteria); NS, not significant.

*Borderline significance.

dizygotic twins compared to monozygotic twins (Table 3). The impact of age- and sex-adjusted heritability on the highest velocity (amplitude of S wave) of hepatic vein flow was insignificant. Shared environment indicated a contribution of 33% and unshared environment was responsible for the remainder of the variance (67%). C-E model was the most parsimonious structural equation model.

Discussion

In this twin analysis, heritability factors had no discernible contribution to the highest velocity (S wave) as a key parameter of the hepatic vein flow, and most of the observed physiological variance was explained by unshared environmental components. Regulation of hepatic blood flow under duress or in disease may be affected by genetic factors that remained silent or unrecognized in the current study. Nevertheless, our findings underscore the importance of unique environments linked to differences detected by Doppler interrogation of hepatic waveforms among twins in the absence of major disease. Our analysis of various lifestyle and risk factors points to the role of regular physical activity as a major environmental factor in this respect.

A number of conditions may affect hepatic venous blood flow in health and disease. In the normal hepatic vein waveform, the magnitude of S wave is due to systolic movement of the tricuspid annulus toward the cardiac apex causes a large anterograde rush of blood toward the heart (21). There is evidence that increased stiffness in the liver parenchyma, especially in the form of fibrosis and fat infiltration around the hepatic veins, have impacts on the waveform of hepatic vessels that become less pulsatile with no retrograde flow (2, 17, 18, 29). It has also been reported that the incidence of abnormal hepatic vein waveforms increases with the severity of fatty infiltration (13). Indeed, patients with nonalcoholic

		8											
Dependent variable		AIC	BIC	-2LL	χ^2 <i>P</i> -value	rMZ	rDZ	А	95% CI	С	95% CI	Е	95% CI
						0.280	0.414						
Highest						(0.068,	(0.092,						
velocity						0.506)	0.703)						
of hepatic	А-С-Е	1565.875	1582.292	1553.87	0.012			0.00	0.00-0.36	0.33	0.05-0.52	0.67	0.48-0.85
vein	A-E	1566.522	1580.203	1556.52	0.008			0.34	0.14-0.52	0.00	0.00-0.00	0.66	0.48-0.86
	$C-E^{\dagger}$	1563.875	1577.556	1553.87	0.018			0.00	0.00-0.00	0.33	0.16-0.51	0.67	0.49-0.84

 Table 3. Age- and sex-adjusted parameter estimates for additive hereditary (A), common environment (C) and unique environmental influences (E) on highest velocity (S wave) of hepatic vein flow by structural equation modeling

Included in this study were 69 monozygotic and 45 dizygotic twin pairs. AIC, Akaike information criteria; BIC, Bayesian information criteria; LL, loglikelihood; χ^2 , *Chi* square test *P*-value, based on model loglikelihood comparative model fit test; rMZ, saturated correlation between monozygotic twins; rDZ, saturated correlation between dizygotic twins. [†]best fitting model.

fatty liver disease have been reported to have high rates of abnormal hepatic vein Doppler waveform patterns (23). This association is reflected by our analysis in which study subjects with sonographically detectable liver steatosis had a lower hepatic flow velocity ($15.5 \pm 8.3 vs. 17.2 \pm 8.5 cm/s$), although the difference did not reach statistical significance (Table 2). Importance of lifestyle on hepatic disease was highlighted in our previous work (25).

Physical activity has been reported as a key lifestyle component to influence systemic and hepatic circulation by accelerating cardiac output, which may contribute to individual variability in parameters assessed by Doppler sonography of the liver (7). Exercise has been reported to increase flow velocity within the hepatic veins of healthy volunteers, although waveform morphology was unaffected (27). Here we found that weekly duration of regular physical activity reported by study subjects showed significant association with the highest velocity (S wave) of hepatic vein flow in an age- and sex-adjusted fashion. To eliminate potential acute effects on individual variance, twins in our cohort refrained from physical activity at least 2 h before Doppler measurements.

Our study had several limitations. In our subjects, we imaged a single, well-identified tributary of the hepatic vein (usually the middle hepatic vein) since spectral waveform patterns in the three major hepatic veins of within the same individual are usually similar (21). However, heterogeneous flow parameters could result from focal or segmental fat infiltration, and respiratory maneuvers and intra-abdominal pressure may also lead to different spectra in the hepatic veins (21). Inter-observer variability is another factor that may increase the E variance, although we aimed to minimize this effect by having two sonographers in the study and both members of each twin pair were assessed by the same sonographer. Finally, the number of dizygotic twins was relatively small compared to usual twin studies, which may have also affected the E variance.

In conclusion, our findings indicate that environmental factors account for most physiological variations in the regulation of the hepatic venous blood flow as assessed by Doppler study characteristics in a twin cohort. Thus, physiological variability of the hepatic vein flow detected among individuals without apparent clinical disease can be primarily explained by unshared environmental components, specifically by the level of regular physical activity. Further studies are necessary to understand the impact of this variability on subsequent changes in hepatic circulation observed in the setting of cardiovascular and liver disease.

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