

# Portal hypertension in patients with cirrhosis: indirect assessment of hepatic venous pressure gradient by measuring azygos flow with 2D-cine phase-contrast magnetic resonance imaging

Hervé Gouya<sup>1</sup> · Sophie Grabar<sup>2</sup> · Olivier Vignaux<sup>1</sup> · Anastasia Saade<sup>1</sup> · Stanislas Pol<sup>3</sup> · Paul Legmann<sup>1</sup> · Philippe Sogni<sup>3</sup>

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## Abstract

**Objectives** To measure azygos, portal and aortic flow by two-dimensional cine phase-contrast magnetic resonance imaging (2D-cine PC MRI), and to compare the MRI values to hepatic venous pressure gradient (HVPG) measurements, in patients with cirrhosis.

**Methods** Sixty-nine patients with cirrhosis were prospectively included. All patients underwent HVPG measurements, upper gastrointestinal endoscopy and 2D-cine PC MRI measurements of azygos, portal and aortic blood flow. Univariate and multivariate regression analyses were used to evaluate the correlation between the blood flow and HVPG. The performance of 2D-cine PC MRI to diagnose severe portal hypertension (HVPG $\geq$ 16 mmHg) was determined by receiver operating characteristic curve (ROC) analysis, and area under the curves (AUC) were compared.

**Results** Azygos and aortic flow values were associated with HVPG in univariate linear regression model. Azygos flow ( $p < 10^{-3}$ ), aortic flow ( $p = 0.001$ ), age ( $p = 0.001$ ) and presence

of varices ( $p < 10^{-3}$ ) were independently associated with HVPG. Azygos flow (AUC=0.96 (95 % CI [0.91–1.00])) had significantly higher AUC than aortic (AUC=0.64 (95 % CI [0.51–0.77])) or portal blood flow (AUC=0.40 (95 % CI [0.25–0.54])).

**Conclusions** 2D-cine PC MRI is a promising technique to evaluate significant portal hypertension in patients with cirrhosis.

## Key Points

- Noninvasive HVPG assessment can be performed with MRI azygos flow.
- Azygos MRI flow is an easy-to-measure marker to detect significant portal hypertension.
- MRI flow is more specific than varice grade to detect portal hypertension.

**Keywords** Magnetic resonance imaging · Azygos vein · Flow · Portal hypertension · Liver

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✉ Hervé Gouya  
princetgouya@yahoo.fr

<sup>1</sup> Department of Radiology, Hôpital Cochin and Paris-Descartes University, Assistance Publique-Hôpitaux de Paris, 27 rue du faubourg St Jacques, 75014 Paris, France

<sup>2</sup> Biostatistics and Epidemiology Unit, Hotel-Dieu and Paris-Descartes University, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, 27 rue du faubourg St Jacques, 75014 Paris, France

<sup>3</sup> Liver Unit, Hôpital Cochin and Inserm U-1016, Paris-Descartes University, Assistance Publique-Hôpitaux de Paris, 27 rue du faubourg St Jacques, 75014 Paris, France

## Abbreviations

MRI	Magnetic resonance imaging
HVPG	Hepatic venous pressure gradient
UGE	Upper gastrointestinal endoscopy
IQR	Interquartile range
ROC	Receiver operating characteristic
AUC	Area under the curve

## Introduction

Portal hypertension is a major complication of cirrhosis. The direct measurement of portal pressure is highly invasive and is no longer performed in clinical practice. The current reference assessment method is measurement of the hepatic venous

pressure gradient (HVPG) which, albeit indirect, has been shown to be the best predictor for the development of varices and to provide predictive prognostic values of the liver disease itself [1, 2]. In addition to its diagnostic and prognostic role of both compensated and decompensated cirrhosis, HVPG is an important tool for monitoring the pharmacological treatment of portal hypertension [3]. However, the HVPG technique has several limitations in clinical practice, two of which are the need for local expertise and its invasive nature. This underlines the need for noninvasive alternatives to measure portal pressure. Two-dimensional cine contrast-phase magnetic resonance imaging (2D-cine PC MRI) could be a promising safe, non-invasive, and reproducible technique for this purpose [4–6]. This technique can directly evaluate azygos and portal blood flow dynamics in patients with cirrhosis [6, 7]. The accuracy of the MRI-based azygos flow measurement for identifying high-risk hemorrhagic oesophageal varices in patients with chronic liver disease and portal hypertension has been recently reported [5]. However, the accuracy of this method for the noninvasive assessment of portal hypertension has not yet been evaluated in comparison with HVPG. The aims of the present study were to prospectively measure azygos, portal and aortic flow by 2D-cine PC MRI, and to compare the MRI values to HVPG measurements, the reference method, in patients with cirrhosis with or without oesophageal varices.

## Materials and methods

### Study population

This was a prospective single-centre study. All participating patients gave their written informed consent and the study was approved by the local Ethics Committee. Consecutive patients ( $n=105$ ) with suspected liver cirrhosis who were referred to our liver department were screened for inclusion between December 2012 and April 2014. Patients were eligible for the study if they had biopsy-proven liver cirrhosis (F4 according to the METAVIR classification) performed by the transjugular route with concomitant HVPG measurement [8]. Clinical (ascites, encephalopathy) and laboratory data (including liver function tests) were recorded. Child-Pugh and Model for End-Stage Liver Disease (MELD) scores classifying the severity of cirrhosis were also calculated.

Thirty-four patients had exclusion criteria including: encephalopathy ( $n=2$ ); concurrent  $\beta$ -blocker treatment ( $n=8$ ); a history of variceal haemorrhage ( $n=14$ ); contra-indications to MRI ( $n=4$ ), and no HVPG measurement ( $n=2$ ) or percutaneous liver-biopsy ( $n=4$ ). Of the 71 patients who were eligible for inclusion, two declined to participate. Consequently, 69 patients (45 men and 24 women; median age: 58 years) were included.

All patients underwent independently upper gastrointestinal endoscopy (UGE) and 2D-cine PC MRI within the first week after inclusion. All operators were blinded to the results of the other examinations.

### HVPG measurement

All patients underwent transjugular liver biopsy and HVPG measurement by the same physician with over 20 years of experience (PS), as previously described [1, 9]. (see Supplementary material 1).

### Upper gastrointestinal endoscopy

All examinations were performed by one of our experienced experts. Oesophageal varices were categorized into three groups (Table 1) based on the following classification criteria: grade 0=absence of varice; 1=varices that collapse on inflation of the oesophagus with air; 2=varices between grade 1 and 3; 3=varices which are large enough to occlude the lumen.

**Table 1** Clinical and endoscopic characteristics of patients ( $n=69$ )

Men; $n$ (%)	45 (65.2)
Age (median [IQR])	58 [50–67]
Age range	34–81
BMI, $\text{kg/m}^2$ (median [IQR])	25.4 [22.6–28.8]
Esophageal varices; $n$ (%)	
Group 1	20 (29)
Group 2	17 (25)
Group 3	32 (46)
Child-Pugh classification; $n$ (%)	
A	13 (18)
B	28 (41)
C	28 (41)
MELD score (median [IQR])	15 [12–18]

*MELD* Model for end stage of liver disease, *BMI* Body mass index, *IQR* Interquartile range

The Child-Pugh was classified based on the following scores: A=5 or 6; B=7 to 9; C=10 to 15

The MELD score was calculated as follows:  $(3.8 \times \ln(\text{total bilirubin})) + (11.2 \times \ln(\text{INR})) + (9.6 \times \ln(\text{creatinine})) + (6.4 \times F)$

Total bilirubin in  $\text{mg/dL}$ , creatinine in  $\text{mg/dL}$ , *INR*=International Normalized Ratio, *F* depends on the etiology of the liver disease (0 if alcoholic or cholestatic, 1 in the other cases)

Esophageal varices were divided into three groups based on the following classification: grade 0=absence of varice; 1=varices that collapse to inflation of the esophagus with air; 2=varices between grade 1 and 3; 3=varices which are large enough to occlude the lumen

Group 1 corresponds to grade 0 and 1 which do not require prophylaxis; group 2 and group 3 correspond to grade 2 and 3, respectively

Group 1 corresponds to grade 0 and 1, which do not require prophylaxis for the prevention of variceal haemorrhage; group 2 and group 3 correspond to grade 2 and 3, respectively.

## 2D-cine PC MRI blood flow examination

MR examinations were performed with 1.5-T imaging software (Avanto, VB 15; Siemens Medical Solutions, Erlangen, Germany) equipped with gradients with a peak strength of 45 mT/m and a maximal slope of 200 T/m. All of the patients were examined with electrocardiographic gating using a 32-channel coil system after they had fasted for at least 6 hours, as recommended in the literature [10].

True fast imaging with steady-state precession (FISP) MRI sequences was performed in the axial, coronal, and sagittal planes to determine the optimal plane for flow quantification. In the second step, velocity encoding (Venc) optimization was achieved by running test measurements with a discrete set of Venc values with a Venc-scout sequence.

Blood flow was then quantified using the cine phase-encoding sequence combined with parallel imaging in the generalized autocalibrating partially parallel acquisition (GRAPPA) algorithm for breath-hold acquisitions. The quantification was then performed along the orthogonal plane of the vessel. The aortic flow and portal venous flow encoding sequences were performed using a breath-hold technique, with the patient in full inspiration, whereas the azygos flow encoding sequence was performed during free breathing and respiratory gating.

Aortic flow was imaged in the axial plane above the celiac trunk localized in the sagittal plane. Portal venous flow was measured in an orthogonal double-oblique plane to the sagittal plane and in the coronal oblique planes 20 mm proximal to the portal bifurcation. The azygos flow was measured in the axial plane at the most cephalic level of the parallel segment localized in the coronal and sagittal planes, below the azygos arch [5] (Fig. 1).

Imaging sequence parameters are reported in Table 2.

## Imaging interpretation

The flow data were processed at an independent workstation using flow analysis software (Syngo Argus Flow; Siemens Medical Solutions). Each data set was reconstructed to yield a magnitude image and a phase image (see Supplementary material 2).

## Statistical analyses

Baseline characteristics of the study population were described by median and interquartile range (IQR) for continuous variables and by percentages for categorical variables. Values of the blood flows according to liver scores and varice

grade were compared with the Kruskal Wallis test. Univariate and multivariate regression analysis were used to study the association between the HVPG and the different flows after common logarithm transformation to achieve a normal distribution. Multivariate analyses were adjusted for the variables that were determined to have a  $p$  value < 0.10 in univariate analysis. The MELD and Child-Pugh scores were entered in separate models, as these two scores are highly correlated.

Separate areas under the receiver operating characteristic curve (AUC-ROC) analysis were used to evaluate the diagnostic accuracy of the MR azygos, portal and aortic flow measurements for the diagnosis of a severe portal hypertension (HVPG  $\geq 16$  mmHg). AUCs and their 95 % confidence intervals (CI) were estimated for each flow and compared by a non-parametric method [11]. The best cutoff value of the azygos flow was chosen by maximizing the Youden index. The sensitivity, specificity, positive and negative predictive values, and likelihood ratios, with their corresponding exact 95 % CIs, are provided for azygos flow as well for varice grade  $\geq 2$  for the diagnosis of a severe portal hypertension (HVPG  $\geq 16$  mmHg) [12]. Univariate and multivariate logistic regressions were used to identify independent factors associated with severe portal hypertension (HVPG  $\geq 16$  mmHg). Multivariate models were adjusted for age, aortic and portal flows that had a  $p$  value < 0.10 in univariate analysis and additionally for the MELD (model 1) or Child-Pugh score (model 2) or varice grade (model 3).

The statistical analyses were performed using SAS 9.3 (SAS Institute Inc., North Carolina). The tests were two sided, and  $p$  values  $\leq 0.05$  were considered to be the threshold for statistical significance.

## Results

### Study population

The clinical and endoscopic features of the patients are summarized in Table 1. The two main causes of cirrhosis were hepatitis C virus ( $n=28$ , 40.6 %) and alcohol ( $n=20$ , 29 %). HVPG ranged from 3 to 25 mmHg, with a median of 16 mmHg (IQR [13–18]). A total of 32 patients (46 %) had grade 3 varices.

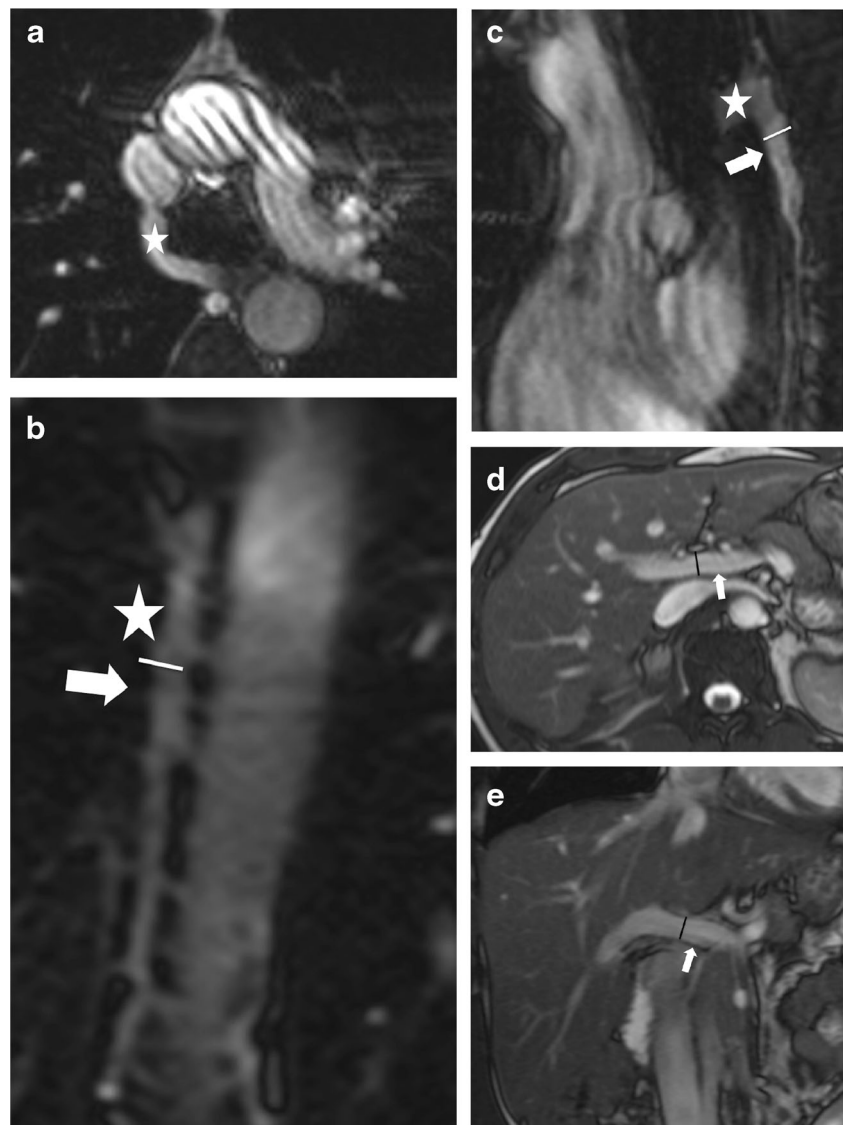
MRI mean blood flow values in all patients and in relation to the Child-Pugh score and varice grade are reported in Table 3.

### HVPG and blood flow

The scatter plot of HVPG against log blood flows is presented in Fig. 2.

The azygos flow and HVPG were significantly correlated ( $R^2=0.77$ ;  $p<10^{-3}$ ). On the contrary, no significant association

**Fig. 1** MR azygos and portal flow measurement in a 45-year-old man. True FISP MR sequences in **a** axial, **b** coronal and **c** sagittal planes were used to identify the most cephalic level of the parallel segment (*arrow*) located below the azygos arch (*star*). Azygos flow was measured in along a plane perpendicular to the course of the vessel localized with true FISP MR sequences (*white line*). True FISP MR sequences in **d** axial and **e** coronal planes were used to localize the main extra-hepatic portal vein (*arrow*). A plane was selected perpendicular (*black line*) to the main extra-hepatic portal vein to measure portal vein flow



**Table 2** Sequence imaging parameters

Parameter	$V_{enc}$ -scout	Aortic flow quantification	Portal flow quantification	Azygos flow quantification
TR (msec)/TE (msec)	66.1/4.89	47.3/2.5	44.1/4	25.45/3.62
Flip Angle (degrees)	30	30	30	30
Number of Signals acquired	1	1	1	3
Matrix size	256 x 128	256 x 128	256 x 128	256 x 128
Field of View (mm)	320 x 220	320 x 224	320 x 224	200 x 200
In-plane Spatial Resolution (mm)	1.25 x 1.72	1.25 x 1.75	1.25 x 1.75	0.78 x 1.56
Temporal resolution (msec)	66.10	47.3	44.4	25.45
Bandwidth (Hz/pixel)	391	391	391	723
GRAPPA Acceleration Factor	2	2	2	2
Section thickness (mm)	6	6	6	4
Intersection gap (mm)	1.2	1.2	1.2	0
Acquisition time	20s	16 s	21 s	3mn 32 s (max 4mn 58 s)

GRAPPA Generalized autocalibrating partially parallel acquisition, NA Not applicable,  $V_{enc}$  Velocity encoding, TR/TE Repetition time/echo time

**Table 3** MRI mean blood flow (mL/s) values in all patients and in relation with the Child-Pugh score and varices grade

	Study Population (n=69)	Child-Pugh score			Varices grade		
		A	B	C	1	2	3
Azygos flow (median [IQR])	4.5 [2.7–6.8]	1.6 [1.2–1.9]	4.4 [2.8–5.3]	6.5 [4.8–12.1]	1.8 [1.5–2.6]	4.1 [3.7–4.5]	6.6 [4.8–9.0]
Portal flow (median [IQR])	9.4 [3.9–17]	15.9 [3.6–16.9]	8.9 [3.3–10.4]	9.7 [7.6–27.3]	10.0 [3.5–15.9]	16.9 [10.4–19.5]	7.8 [2.6–9.4]
Aortic flow (median [IQR])	52.3 [45.2–69.4]	48.7 [35.3–55.8]	51.1 [45.2–56.5]	68.7 [46.3–99.3]	53.3 [47.0–66.6]	57.1 [47.1–90.5]	49.2 [44.0–68.5]

was found between HVPG and the portal flow ( $R^2=0.02$ ,  $p=0.07$ ) or between HVPG and aortic flow ( $R^2=0.14$ ,  $p=0.08$ ).

In univariate analysis, HVPG was significantly associated with age, the severity of liver disease expressed by the MELD or the Child-Pugh score, varice group, and azygos and aortic blood flow. Conversely, no significant association was found between HVPG and the portal blood flow. When analyzed by multivariate linear regression, azygos and aortic blood flow, age and varice group remained independently associated with HVPG whatever the multivariate model. Neither the MELD nor the Child-Pugh score retained statistical significance (Table 4).

**Distribution of each blood flow by varice grade and Child-Pugh score**

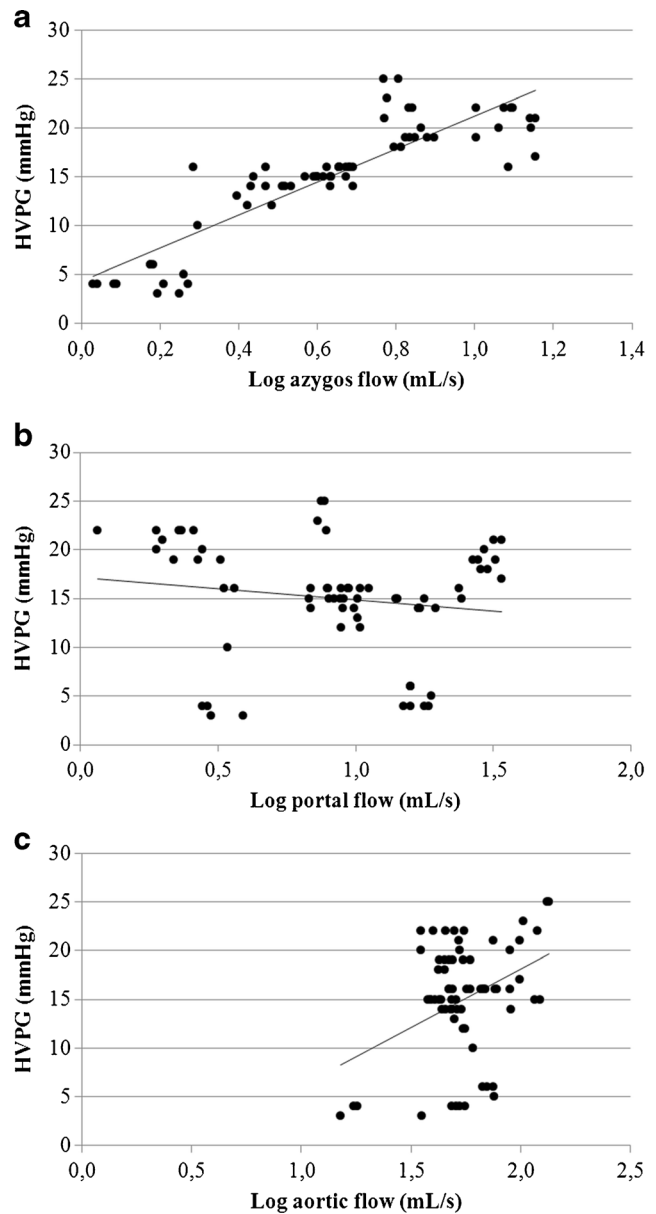
Azygos blood flow measures were significantly different according to the varice group ( $p<10^{-3}$ ) (Fig. 3a) and the Child-Pugh score ( $p<10^{-3}$ ) (Fig. 3b).

In contrast, aortic blood flow measures were significantly different according to the Child-Pugh score ( $p=0.01$ ) but not to the varice group ( $p=0.43$ ). Portal blood flow measures were significantly different according to the varice group ( $p=0.03$ ) but not the Child-Pugh score.

**Diagnostic accuracy of the flow measurements and varice grade  $\geq 2$  for HVPG  $\geq 16$  mmHg**

ROC analysis (Fig. 4) for the diagnosis of severe portal hypertension (HVPG  $\geq 16$  mmHg), demonstrated that the azygos blood flow had a significantly higher area under the ROC curve (AUC=0.96 (95 % CI [0.91–1.00]) than the aortic (AUC=0.64 (95 % CI [0.51–0.77]) or portal blood flows (AUC=0.40 (95 % CI [0.25–0.54]) ( $p<10^{-3}$  for each comparison).

The best cutoff value maximizing the Youden index for the diagnosis of an HVPG  $\geq 16$  mmHg was 4.4 mL/s. Table 5 summarizes the diagnostic performance of azygos blood flow with this cutoff value and of a varice grade  $\geq 2$  for the diagnosis of an HVPG  $\geq 16$  mmHg. Azygos blood flow measurement was as sensitive as varice grading but markedly more specific.



**Fig. 2** Scatter plot of hepatic venous pressure gradient (HVPG) against mean blood flows. **a** azygos blood flow (HVPG=16.86 azygos flow+4.35;  $R^2=0.77$ ); **b** portal blood flow (HVPG=-2.32 portal flow+17.19;  $R^2=0.02$ ); aortic blood flow (HVPG=12.02 aortic flow - 5.93;  $R^2=0.14$ )



**Table 4** Factors associated with HVPG. Univariate and multivariate linear regression analyses

	Univariate analysis			Multivariate model 1 ( $R^2=0.85$ )			Multivariate model 2 ( $R^2=0.84$ )		
	Parameter estimate	Standard error	<i>p</i>	Parameter estimate	Standard error	<i>p</i>	Parameter estimate	Standard error	<i>p</i>
Azygos flow (log)	7.32	0.49	<10 <sup>-3</sup>	5.72	0.78	<10 <sup>-3</sup>	5.38	0.75	<10 <sup>-3</sup>
Aortic flow (log)	5.22	1.55	0.001	3.12	0.85	<10 <sup>-3</sup>	2.61	0.77	0.001
Portal flow (log)	-1.01	0.80	0.22						
Age	-0.19	0.06	0.001	-0.09	0.03	0.004	-0.07	0.03	0.01
MELD score	0.86	0.12	<10 <sup>-3</sup>	-0.16	0.11	0.16			
Child-Pugh score	6.07	1.22	<10 <sup>-3</sup>				-0.41	0.76	0.59
Varices group	5.37	0.50	<10 <sup>-3</sup>	1.47	0.60	0.02	1.46	0.61	0.002

Multivariate models were adjusted for age, varices grade, aortic and portal flows and either for Meld score (model 1) or Child-Pugh score (model 2) MELD Model for end stage of liver disease; HVPG Hepatic venous pressure gradient;  $R^2$  Coefficient of determination

Results of the logistic regression analyzes indicated that azygos flow was associated with severe portal hypertension, whatever the model (Table 6).

## Discussion

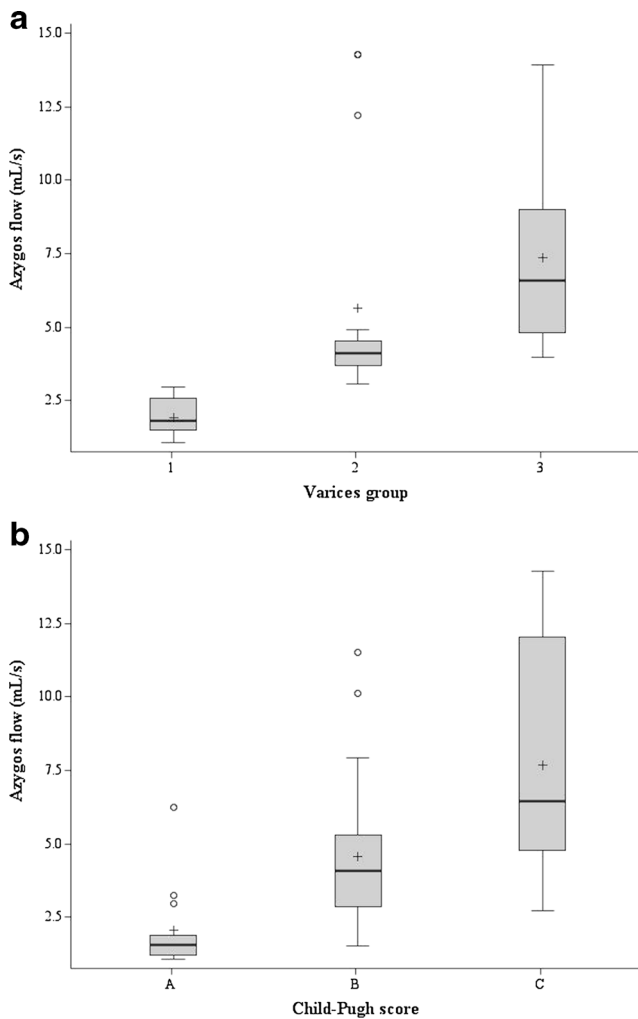
This study shows that 2D-cine PC MRI of azygos flow is a promising noninvasive method for assessing severe portal hypertension. We have established an easy-to-measure noninvasive marker to detect an HVPG  $\geq 16$  mmHg—azygos blood flow with an optimized cutoff value of 4.4 mL/s—which has a very high sensitivity and specificity. These results are clinically relevant as HVPG accurately estimates portal pressure in diseases in which the resistance to portal flow is located at the sinusoids, as is the case for the most common etiology of portal hypertension, namely liver cirrhosis [19]. Portal pressure measurement via HVPG stratifies cirrhosis into stages with defined outcomes, prognosis, and management strategies [13]. An HVPG of 10 mmHg defines the presence of clinically significant portal hypertension and is the best predictor of the development of varices, clinical decompensation and hepatocellular carcinoma [14, 15]. Additionally, in cases of decompensated cirrhosis, an HVPG  $\geq 16$  mmHg is an important predictor of poor outcome and identifies patients at risk of developing refractory ascites, bacterial infections, hepatorenal syndrome or recurrent variceal haemorrhage [16, 17]. Another key finding is that azygos flow measurement is as sensitive as, and markedly more specific than, varice grading for diagnosing significant portal hypertension (i.e., HVPG  $\geq 16$  mmHg). This is also clinically relevant, as it could result in primary pharmacological or endoscopic prophylaxis of variceal bleeding. We were not able to analyze the performance of MRI to stratify portal hypertension in patients based on an HVPG threshold of 10 mmHg because of the few patients in our population below this level. Moreover, our results

highlight a significant association between azygos flow measured by 2D-cine PC MRI and HVPG with simple and multivariate linear regression analysis.

Interestingly, the analysis showed that azygos and aortic flow were independently associated with HVPG. Cirrhosis causes considerable changes in the haemodynamics of blood flow, including splanchnic inflow, hepatic resistance and increased portal venous pressure [18]. In portal hypertension, the higher variceal pressure increases tension in the variceal wall. This has been associated with increased azygos flow, a known indicator of oesophageal collateral vessel flow [20, 21]. Because gastro-oesophageal collaterals drain into the azygos system, the measurement of the flow therein indirectly reflects the degree of gastro-oesophageal collateralization [22]. Portal hypertension leads to the formation of portosystemic collaterals with numerous pathways. Gastrooesophageal varices are the most relevant portosystemic collaterals because their rupture leads to variceal haemorrhage, the most lethal complication of cirrhosis. Thus, it is important to develop a sensitive noninvasive test correlated with HVPG in patients with gastrooesophageal varices.

Our results show high sensitivity and high specificity for mean azygos flow to detect severe portal hypertension. This high specificity may reflect the fact that the patients in our study had large gastro-oesophageal varices.

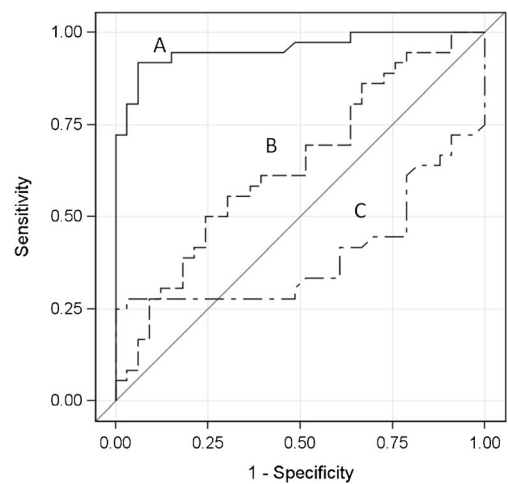
Other methods, such as endoscopic ultrasound (EUS) and thermodilution, may also be used to study the azygos flow [23, 24]. However, these techniques are not only invasive, but also require specific expertise. Another problem with EUS is the inter-observer variability [25]. In contrast, optimal results for inter-observer and intra-observer variability, as well as reproducibility, with 2D-cine PC MRI flow measurement have previously been demonstrated [5]. The significant independent association between HVPG and aortic blood flow may be related to the development of a hyper-dynamic



**Fig. 3** Box plots of azygos flow (mL/s) according to each group of varices (Fig. 2a) and to Child-Pugh score (Fig. 2b). The boundary of boxes closest to zero indicates the 25th percentile, the line within boxes indicates the mean, and the boundary of boxes farthest from zero indicates the 75th percentile. The error bars indicate the smallest and largest values within 1.5 box lengths of the 25th and 75th percentiles. The outliers are represented as individual points. Varices groups were categorized as follows: Group 1: varices grade 0 or 1; Group 2: varices grade 2; Group 3: varices grade 3

circulatory syndrome, which is coupled with the severity of portal hypertension [26]. Aortic flow is thus a well-known indirect marker of cardiac output.

In contrast, there was no significant association between the portal flow and HVPG. There are conflicting reports about reduced or increased portal flow among patients with cirrhosis [27–29]. These discrepancies may be due to the stage of cirrhosis or to the physiologic features of portal hypertension and extrahepatic hemodynamic abnormalities [20, 30]. Portal hypertension results from both increased resistance to portal flow and increased portal blood inflow. Portal flow depends on both the portal venous inflow and the resistance of the portosystemic collaterals opposing blood flow. We hypothesize that the balance between intrahepatic resistance and



**Fig. 4** Receiver operating characteristic (ROC) curves for mean azygos blood flow (mL/s), mean aortic blood flow (mL/s) and mean portal blood flow (mL/s) performances for the diagnosis of an HVPG  $\geq 16$ . AUC (azygos flow)=0.96 (95 % CI [0.91–1.00]); AUC (portal flow)=0.40 (95 % CI [0.25–0.54]); AUC (aortic flow)=0.64 (95 % CI [0.51–0.77])

altered splanchnic flow may be a key factor to explain our results. Reflecting the complexity of portal haemodynamics, Debatin et al. showed a lack of correlation between portal and azygos venous flow changes in patients with hypertension portal pre- and post- intrahepatic shunt placement [7].

Our results are in agreement with previous reports that have already highlighted the potential value of MRI in detecting high-risk oesophageal varices in patients with chronic liver disease and portal hypertension [4–6, 31]. Prior reports revealed an association between the risk of variceal haemorrhage and high azygos flow in patients with cirrhosis [5, 6]. In agreement with these data, we found a correlation between the azygos flow and the varice group.

In addition, our results showed a correlation between the MRI measured azygos flow and both the Child-Pugh and MELD scores, which is consistent with the results of previous studies [5]. As the Child-Pugh and MELD scores are valuable clinical tools in patients with cirrhosis, these results may have a major clinical impact. The Child-Pugh score is related to short-term prognosis in patients with acute variceal bleeding and is also a risk factor for oesophageal variceal haemorrhage. The Child-Pugh and MELD scores are currently used to define prognosis by modelling hepatic dysfunction. However, in contrast to MRI blood flow, these scores do not provide direct evidence of the stage or hemodynamic state of cirrhosis.

The robustness of the 2D-cine PC MRI blood flow sequence of this study has been validated in a previous study, both in vitro and in vivo in patients with or without portal hypertension [5]. Additionally, the sequence was combined with a retrospective ECG gating divided over 20 phases, resulting in high temporal resolution. We used the non breath-hold procedure for azygos flow evaluation. Breath-hold phase-contrast MRI flow has been reported to give

**Table 5** Comparative performances of mean azygos flow (cutoff=4.4 mL/s) and esophageal varices grade $\geq$ 2 for HVPG $\geq$ 16 mmHg

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
Azygos flow	92 % (83–100)	94 % (86–100)	94 % (87–100)	91 % (82–100)	15 (4–45)	9 (3–26)
Varices grade $\geq$ 2	94 % (87–100)	55 % (38–68)	69 % (56–82)	90 % (77–100)	2 (1–3)	0.1 (0.03–0.41)

Numbers in parentheses are the 95 % CIs

HVPG Hepatic venous pressure gradient

different estimates of azygos flow in patients with portal hypertension compared with the non-breath-hold technique [32]. The breath-hold method is more susceptible to variations in respiratory phase and the consequent alterations in intrathoracic pressure. The measurement in different phases of respiration is thus more representative of the blood flow through the azygos vein than flow in either full inspiration or end expiration. Thus, breath-hold phase-contrast MRI flow was not a valid alternative to the non-breath-hold flow method.

Another noninvasive imaging technique recently developed to detect liver fibrosis and portal hypertension is MR elastography, which has proved to be promising for assessing severe portal hypertension and high-risk oesophageal varices [33].

Nevertheless, further prospective studies with more patients should be conducted to evaluate the role of noninvasive functional MR elastography in the clinical setting of cirrhosis and to compare liver/spleen MR and 2C MR flow in the same population.

Our study is limited by several technical and clinical points. First, 2D-cine PC MRI requires the use of double-oblique imaging planes, which are challenging and time consuming

to position and coordinate with patient breath-holding or non-breath-holding. Second, the technique only allows visualization of two-dimensional anatomic collateral pathways of the portal venous system or azygos venous system. Such 2D anatomic information may be insufficient for a comprehensive flow evaluation, as the portosystemic collaterals associated with portal hypertension are highly variable and extend throughout the abdomen and the thorax. To overcome some of these limitations, 4D MRI flow mapping has recently emerged. 4D MR velocity mapping using temporally resolved 3D spatial encoding offers a combination of co-registered anatomic and hemodynamic information in the same examination. The feasibility of using radial 4D flow MRI to quantify blood flow in the hepatic and splanchnic vasculature of healthy volunteers and patients with portal hypertension has recently been reported [34]. Radial 4D flow MRI has large volumetric coverage including not only the portal circulation, hepatic arterial flow but also the azygos and portosystemic collaterals in a single breath hold with similar performance for flow parameter estimation when compared with standard Cartesian 4D flow and cine 2D phase-contrast measurements in vivo [35]. Nevertheless, the routine use of this technique is

**Table 6** Factors associated with HVPG  $\geq$ 16 mmHg. Univariate and multivariate logistic regression.

	UNIVARIATE analysis		MULTIVARIATE analysis (Model 1, AIC=46.438)		MULTIVARIATE analysis (Model 2, AIC=41.082)		MULTIVARIATE analysis (Model 3, AIC=42.390)	
	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>
Azygos flow	4.86 (2.05–11.52)	0.0003	5.81 (1.87–18.01)	0.002	11.58 (2.66–50.50)	0.001	29.58 (2.27–284.1)	0.010
Aortic flow	1.02 (1.00–1.04)	0.05	1.00 (0.96–1.04)	0.94	1.07 (1.00–1.14)	0.06	1.00 (0.96–1.05)	0.90
Portal flow	1.00 (0.95–1.06)	0.91						
Age	1.00 (0.96–1.04)	0.96						
MELD score	1.31 (1.13–1.52)	0.0003			0.65 (0.43–0.99)	0.04		
Child–Pugh score		0.0004		0.41				
A	1 (reference)		1 (reference)					
B	3.56 (0.66–19.27)		0.13 (0.006–3.18)					
C	25.3 (4.22–151.50)		0.26 (0.007–9.60)					
Varices grade		<10 <sup>-4</sup>						0.11
1	1 (reference)						1 (reference)	
2	6.3 (1.93–36.30)						0.009 (0.00–0.78)	
3	48.6 (8.49–278.25)						0.006 (0.00–1.23)	



limited by the time-consuming reconstruction algorithm, which should be improved so as to provide images at the time of imaging.

Third, the predictive values of MRI could be affected by the high proportion of patients in our population with major portal hypertension, as demonstrated by the high median HVPG. Nevertheless, this limitation is counterbalanced by the relatively large population size.

Fourth, as our study included patients with advanced portal hypertension (71 % of patients with varices that require preventive treatment for variceal rupture), we did not correlate MRI flow measurements with history of complications of portal hypertension, such as variceal haemorrhage.

In conclusion, our results demonstrate that 2D-cine PC MRI is a good technique for the indirect evaluation of significant portal hypertension in patients with cirrhosis.

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**Methodology:** prospective, diagnostic or prognostic study, performed at one institution.

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