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PROSPECTIVE ASSESSMENT OF DECREASED AZYGOS BLOOD FLOW AFTER ORAL ADMINISTRATION OF NON-SELECTIVE BETA-BLOCKER, QUANTIFIED BY 2D CINE PHASE-CONTRAST MAGNETIC RESONANCE IMAGING : PRELIMINARY RESULTS

ÉVALUATION PROSPECTIVE DE LA VARIATION DU DEBIT AZYGOS APRES INTRODUCTION D'UN TRAITEMENT PAR BETA BLOQUANT, QUANTIFIEE PAR IRM DE FLUX EN CONTRASTE DE PHASE : RÉSULTATS PRÉLIMINAIRES

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List of abreviation

ABF	Azygos blood flow
ARFI	Acoustic radiation force imaging
EV	Esophageal varice
GRAPPA	Generalized autocalibrating partially parallel acquisition algorithm
HCC	Hepatocellular carcinoma
HPVG	Hepatic venous pressure gradient
MELD	Model for end-stage liver disease
MRI	Magnetic resonance imaging
NSBB	Non selective beta blocker
PC	Phase-contrast
ROI	Region of interest
US	Ultrasound
UGE	Upper gastrointestinal endoscopy

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PROSPECTIVE ASSESSMENT OF DECREASED AZYGOS BLOOD FLOW AFTER ORAL ADMINISTRATION OF NON-SELECTIVE BETA-BLOCKER, QUANTIFIED BY 2D CINE PHASE-CONTRAST MAGNETIC RESONANCE IMAGING : PRELIMINARY RESULTS

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ABSTRACT

Objective The main objective of this study was to assess the azygos blood flow (ABF) changes quantified by 2D cine phase-contrast Magnetic Resonance Imaging, in cirrhotic patients starting non-selective beta-blocker (NSBB) therapy in primary prophylaxis against variceal bleeding. Secondary objectives were to evaluate the evolution under treatment of liver and spleen stiffness, splenomegaly and portal venous blood flow measured by Doppler ultrasound. **Patients and methods** Inclusion criteria were the endoscopic discovery of grade 2 or grade 3 esophageal varices (EVs) requiring introduction of primary prophylaxis treatment by NSBB. A total of 26 were involved in the final analysis. A baseline examinations set was performed before introducing NSBB including clinical and laboratory data, liver and spleen Doppler Ultrasonography with Acoustic Radiation Force Imaging™ (ARFI) stiffness assessment, liver stiffness measurements by Fibroscan™, and azygos blood flow quantified by 2D cine phase-contrast Magnetic Resonance Imaging. Examinations were repeated at 1-month follow-up. **Results** The variation of ABF after 1-month NSBB therapy was significantly correlated with both the variation of the spleen stiffness (ρ = 0.5229 ; p = 0.006) and right hepatic lobe stiffness quantified by ARFI™ (ρ = 0.4254 ; p = 0.03). The baseline ABF was significantly correlated to the baseline Child-Pugh score (r = 0.505 ; p = 0.008) and to the baseline MELD score (ρ = 0.4773 ; p = 0.014). The median baseline ABF was 8.9 mL/s (IQR [5.8 · 13.3]), and 6.0 mL/s (IQR [4.6 · 8.8]) after 1-month under NSBB therapy. In all patients, the median decrease of ABF at 1-month was −31.1% (IQR [−46.2 · −5.7]). No correlation was found between post-NSBB decrease in ABF and HVPG (ρ = -0.0962 ; p = 0.821). **Conclusion** Our study suggests that, 2D cine PC-MRI is able to measure, in a non-invasive way, the variation of ABF after NSBB administration. Moreover correlation to liver and spleen stiffness suggests future simple non-invasive tools for evaluation of the efficiency of NSBB as primary prophylaxis of esophageal rupture in cirrhotic patients.

INTRODUCTION

At the time of diagnosis, more than 50% of patients with liver cirrhosis present a clinically significant portal hypertension, defined as hepatic venous pressure gradient (HPVG) higher than 10mmHg (1,2). This condition is known to be sufficient for the development of esophageal varices (EVs), which represent a major cause of morbidity and mortality in cirrhotic patients. The first episode of upper-gastrointestinal (GI) haemorrhage related to variceal rupture occurs with an annual incidence estimated at 4% for all cirrhotic patients and reaches 15% in case of grade 2 or 3 EVs (3), mostly within the first year following the diagnosis (4). Therefore, primary prophylaxis has emerged as an essential practice to prevent variceal bleeding. Since the first proof of concept more than 30 years ago (5,6), non-selective beta-blockers (NSBB), especially propranolol, are considered as the standard of care in this indication. This preventative treatment has to be initiated as soon as medium/large EVs are diagnosed (7).

To date, the only validated technique to assess NSBB efficiency remains the quantification of hemodynamic response, obtained by twice pre- and post-treatment HVPG measurements. According to this modality, patients are defined as responder when HVPG is decreased by ≥20% from the baseline value or for an absolute gradient value lower than 12mmHg. For these responders, a significant decrease of the bleeding risk by EVs rupture and improving survival is reached (8,9). Such an hemodynamic response is achieved in only a minority of the cases, estimated at approximately 30% of patients (10–12). However, it has been proved that HVPG is not directly correlated to intra-variceal pressure and might therefore underestimate the beneficial effects of propranolol (13). This suggests that HVPG is not suitable to accurately assess response to treatment, and probably fails to identify all patients effectively protected against variceal bleeding. More, this invasive and costly procedure has several limitations in clinical practice and requires local expertise, particularly in these patients with frequent coagulopathy. As a result, HVPG measurement is no longer routinely performed and NSBB therapy is continued over a lifetime as long as there are no contraindications to use (14–16), despite potential long-time deleterious effects (7,17–19). A more precise identification of non-responder patients would allow treatment modifications such as α-adrenergic blockade (as by carvedilol) or endoscopic band ligation (EBL) (20).

Measurement of flow in the azygos vein that drains most esophageal varices has been

proposed as a practical means of assessment to reflect changes in the gastroesophageal collateral circulation in patients with cirrhosis. The results of several studies using an invasive method, the continuous thermodilution, have validated the importance and clinical applications of azygos blood flow measurement (21–24). Azygos blood flow (ABF) is markedly increased in patients with portal hypertension and significantly correlated to the intra-variceal pressure (22,25). More recently, Magnetic Resonance (MR) angiography using the non breath-hold 2D cine phase-contrast (PC) imaging has been reported as a technique capable of evaluating the ABF non-invasively, and in an accurate and reproducible manner in patients with cirrhosis (26–30). This also proved to be a promising method for identifying high-risk hemorrhagic oesophageal varices and severe portal hypertension (28,31).

The main objective of this study was to assess the azygos blood flow changes quantified by 2D cine phase-contrast Magnetic Resonance Imaging, in cirrhotic patients starting non-selective beta-blocker therapy in primary prophylaxis against variceal bleeding. Secondary objectives were to evaluate the evolution under treatment of non-invasive measurements of liver and spleen stiffness, splenomegaly and portal venous blood flow measured by Doppler ultrasound (US).

PATIENTS AND MÉTHODS

Study population

This is an intermediate descriptive analysis of the ongoing prospective multicentric, non-controlled AZYMR trial. This study was approved by our local ethics committee and each participating patients gave written informed consent. Between August 2014 and June 2016, all cirrhotic patients referred to the Hepatology department for assessment of portal hypertension were screened for inclusion. Inclusion criteria were the endoscopic discovery of grade 2 or grade 3 esophageal varices (EVs) requiring introduction of primary prophylaxis treatment by NSBB. Non inclusion criteria were: patient with concurrent vasoactive treatment, a history of upper gastrointestinal bleeding, previous endoscopic or surgical EVs treatment, contra-indications to NSBB, contra-indications to MR imaging, portal vein thrombosis, presence of hepatocellular carcinoma (HCC), life expectancy under one month, psychological state not allowing signature of informed consent, age under 18. For this

intermediate analysis, patients who were not reviewed at the 1-month follow-up visit have been excluded.

Thirty-seven cirrhotic patients with portal hypertension and EVs grade ≥2 diagnosed by upper gastrointestinal endoscopy (UGE) were prospectively evaluated for inclusion. Five patients were excluded: refusal to consent (n=1), insufficient lifetime expectancy related to advanced chronic liver disease (n=1) and related to metastatic recurrence of testicular seminoma (n=1), contra-indication to NSBB (n=1), NSBB treatment started before baseline MRI (n=1). Thirty-two patients were thus selected to undergo baseline explorations, whose 6 have been secondarily excluded before the control visit: HCC finding on baseline MRI (n=1), decease related to refractory ascites and malnutrition (n=3), refusal to continue the study (n=1), patient lost to follow-up (n=1). Consequently, a total of 26 patients (19 men and 7 women) were included in this preliminary analysis, whose age ranged from 44 to 83 years (median 65.8). Liver cirrhosis was attributed to excessive alcohol consumption (n=14), nonalcoholic steatohepatitis (n=4), mixed excessive alcohol consumption and nonalcoholic steatohepatitis (n=3), chronic hepatitis B viral infection (n=1), chronic hepatitis C viral infection (n=1), secondary biliary cirrhosis (n=1), hereditary hemochromatosis (n=1) and Wilson's disease (n=1) (figure 1).

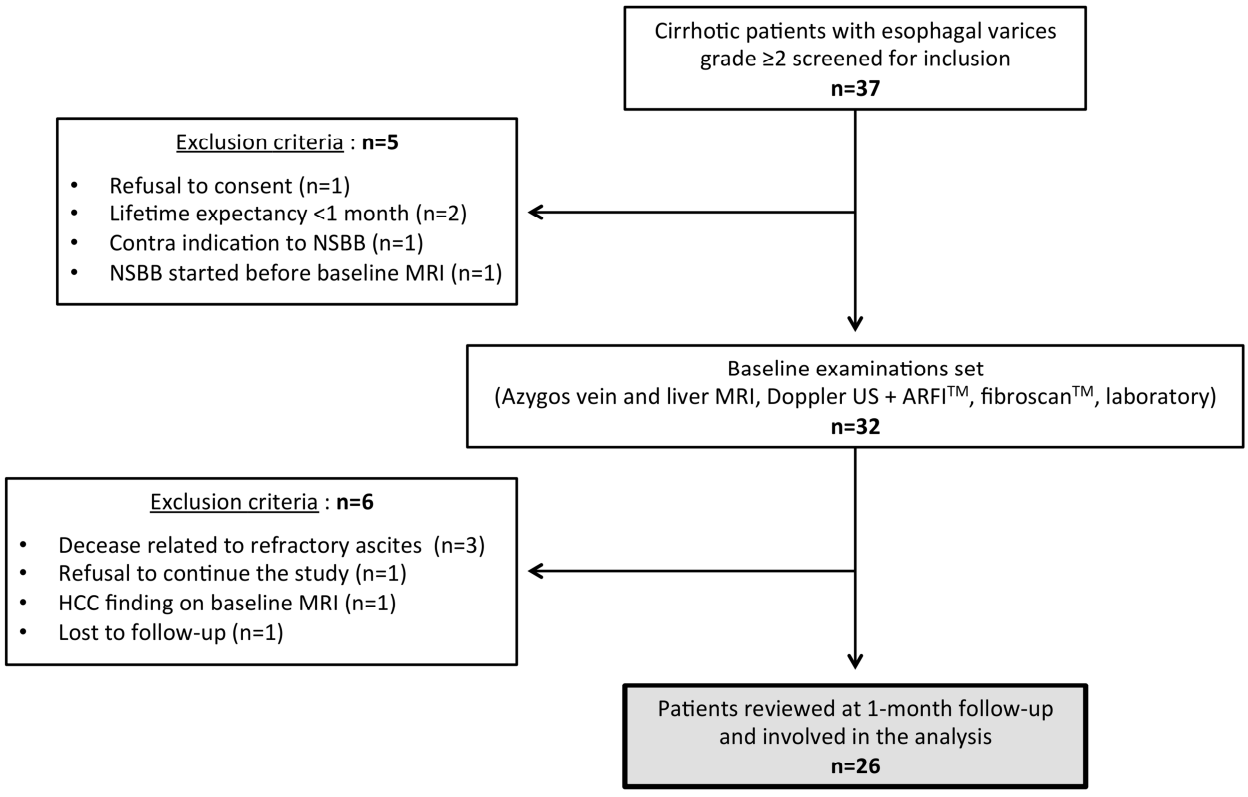

Figure 1 Cohort selection profile: the gray area marks the patients involved in the analysis

MRI magnetic resonnance imaging, HCC hepatocelular carcinoma, NSBB nonselective beta-blocker, ARFI acoustic radiation force imaging

Study endpoints

The primary endpoint was defined as the median decrease of azygos blood flow between baseline and after one-month under NSBB therapy, measured by 2D cine PC-MR imaging (mL/s).

The secondary endpoints were the variations after treatment of liver stiffness measured by Fibroscan™ (kPa) and Acoustic Radiation Force Imaging (ARFI™) elastography (m/s), spleen stiffness measured by ARFI™ elastography (m/s) and both bipolar spleen length (cm) and portal venous flow velocity measured by Doppler US (cm/s).

The relative difference between baseline and 1-month follow-up measurements were determined using the formulation 100x[(1month measurement – baseline measurement)/baseline measurement].

Study design & baseline examinations set

Recruitment started from the day of EVs diagnosis. Endoscopic procedures were performed by a skilled endoscopist (MP) with Olympus GIF endoscopes (Olympus, Lake Success, NY, USA). EVs were classified according to the North Italian Endoscopic Club criteria (graded 0–3) (32). Patients were then addressed to study-referents hepatologist and radiologist to achieve all clinical and para-clinical baseline examinations, within the shortest period as possible, not to delay introduction of NSBB therapy.

Clinical and laboratory data necessary to determine the origins of cirrhosis, its degree of compensation, assess the liver function, and establish Child-Pugh classification and MELD scores were recorded. MELD was determined using the formulation 3.78×Ln (bilirubin mg/dl)+11.2×Ln (INR)+9.57×Ln (creatinine mg/dl)+6.43 (33).

Patients underwent non-invasive liver parenchyma stiffness assessment using transient elastography (FibroScan® Echosens, Paris, France) performed by certified operators with experience in FibroScan™ technology (34). We recorded the median value of the 10 successful measurements (kPa).

Liver ultrasound (US) imaging with Doppler examination was performed the same day as MR Imaging, in dedicated visceral and hepato-biliary imaging department. Patients had fasted for at least 6 hours. Following data were collected: craniocaudal spleen length (cm), maximum portal blood flow velocity (cm/s) in absence of paraumbilical drainage or

hepatofugal blood flow orientation. The maximum portal blood flow velocity corresponded to the mean maximum velocity calculated via the software integrated to the ultrasound scanner, over at least 5 seconds recording, with a beam/vessel angle <60°.

During the same US examination, liver and spleen stiffness were quantified using Acoustic Radiation Force Impulse Imaging™ (ARFI) (Siemens Acuson S2000®, Erlangen, Germany). Patients were positioned in the supine position with the right arm in maximum abduction and with a soft breath-hold. Elastography was performed using Virtual Touch™ quantification with a convex abdominal probe (4C1). The size of the region of interest (ROI) was fixed at 10 × 5 mm. The ROI was positioned within the parenchyma under visual control in two-dimensional B-mode, with a depth of approximately 2-5 cm from the capsule, while avoiding surrounding blood vessels and biliary structures. Attempts were repeated to obtain successful measurements 10 times in the right liver lobe, 5 times in the left liver lobe and 5 times in the spleen. We recorded the median of these values (m/s).

Hepatic venous pressure gradient measurement was not initially planned in the research protocol, but has been secondarily added to the baseline exam set, and systematically performed in all patients included since November 2015. This involves 8 patients (30.7%) of the present analysis. The HVPG value, expressed in mmHg and computed as a mean of three valid measurements, was calculated as the difference between the wedged hepatic venous pressure and the free hepatic venous pressure. Pressure measurements were performed using a catheter with a pressure transducer at the tip, which was passed under fluoroscopic guidance into either the middle or right hepatic vein, accessed by transjugular approach in all patients.

MR imaging was performed within a maximum of 7 days following endoscopy. The complete MR Imaging flow measurement protocol is detailed below. We recorded the median azygos blood flow value (mL/s). In addition, the baseline MRI included a standard liver exploration including multi-b-value diffusion weighted imaging (b=50 ; b=800 s/mm^2) and dynamic gadolinium chelate-enhanced imaging, in order to screen exclusion criteria such as portal thrombosis or HCC. Non-invasive HCC diagnosis was based on European Association for the Study of the Liver (EASL) guidelines hallmarks (35). Gadolinium-chelate contrast-enhanced 3D T1WI with fat suppression was used to determine the presence of esophageal varices and, when detected, to classify it as medium (<5mm) or large (>5mm) (36,37). Endoscopy was considered as the standard reference in EVs classification.

The NSBB treatment was immediately started the day after baseline MRI. In all

patients, the first-line prescribed treatment was oral administration of propranolol at the maximum recommanded dose (160mg/day) (38–40).

MR Imaging azygos blood flow measurement protocol

MR examinations were performed at fixed MR imaging room temperature with 1.5-Tesla whole-body MR scanner (MAGNETOM Aera; Siemens Medical Solutions, Erlangen, Germany). All of the MR images were obtained with a reception coil combination consisting of a spine matrix coil and a body matrix coil, which resulted in an 18-channel coil system. All subjects were examined with retrospective electrocardiographic gating after they had fasted for at least 6 hours. First, true fast imaging with steady-state free precession (TRUE-FISP) MR sequences were performed in the axial, coronal, and sagittal planes to localize the azygos vein, the azygos arch and appreciate eventual anatomical variations such as dominant hemi-azygos drainage. Then, T2-weighted imaging HASTE sequence was performed in an inclined axial plane for optimal flow quantification. Azygos flow was thus measured along a plane orthogonal to the vessel axis, at the most cephalic level of the paravertebral vertical segment and below the azygos arch to take into account the maximum of esophageal afferences. Field of view (FOV) was inclined clockwise, in an axis parallel to that passing through both ascending and descending thoracic aortas, and phase-encoding direction was set from right-to-left to avoid projection of motion-related artifacts due to aortas and pulmonary arteries pulsations (figure 2).

Azygos flow encoding sequences were performed during free breathing and respiratory gating, to respect the physiological blood flow variations related to respiratory cycle (41). Velocity-encoding (Venc) optimization was achieved by running test measurements thanks to a dedicated Venc–scout 2D cine phase-contrast sequence (table 2). A discrete set of four Venc values for the azygos flow were encoded (30, 40, 50 and 60 cm/sec) at the predefined slice level. The final choice of encoding velocity was determined in real-time at the acquisition console, by a radiologist experimented in MR flow imaging. A particular attention was paid to the absence of aliasing artifact in azygos vein lumen on the phase image. Blood flow was then encoded using the most adequate Venc, at a time resolution of 50 frames in one cardiac cycle, using a 2D cine phase-encoding sequence combined with a parallel imaging in the generalized autocalibrating partially parallel acquisition algorithm (GRAPPA).

Flow data were processed at an independent workstation by using flow analysis software (SyngoVIA® Flow quantification; Siemens Medical Solutions). Each data set was reconstructed to yield a magnitude image, an amplitude image and a phase image. Circular ROIs outlining the vessel external wall were manually drawn and positioned on the magnitude image. Care was taken to include a thin peripheral circumferential area of pixels with decreased blurred signal intensity around the vessel so that all of the pixels inside the vessel would be included. For all 50 reconstructed phases, each ROI was then copied onto the phase image from the corresponding magnitude image, taking into account variations of the vein calibre due to respiratory and cardiac cycles (41).

Table 1 2D cine phase-contrast sequence imaging parameters

Parameter	V_{enc}-scout	Azygos flow quantification
TR (msec)/TE (msec)	25.28/3.59	25.28/3.59
Flip angle (degrees)	20	20
Number of acquisition	1	3
Matrix size	192 x 173	192 x 173
Field of view (mm)	196 x 196	196 x 196
In-plane spatialrResolution (mm)	113 x 102	113 x 102
Temporal resolution (phase/cardiac cycle)	30	50
Bandwith (Hz/pixel)	457	457
GRAPPA Acceleration factor	2	2
Section thickness (mm)	6	6
Intersection gap (mm)	1.2	1.2
Acquisition time	30sec	3min52sec

GRAPPA Generalized autocalibrating partially parallel acquisition, V_{enc} Velocity encoding, TR/TE Repetion time/echo time

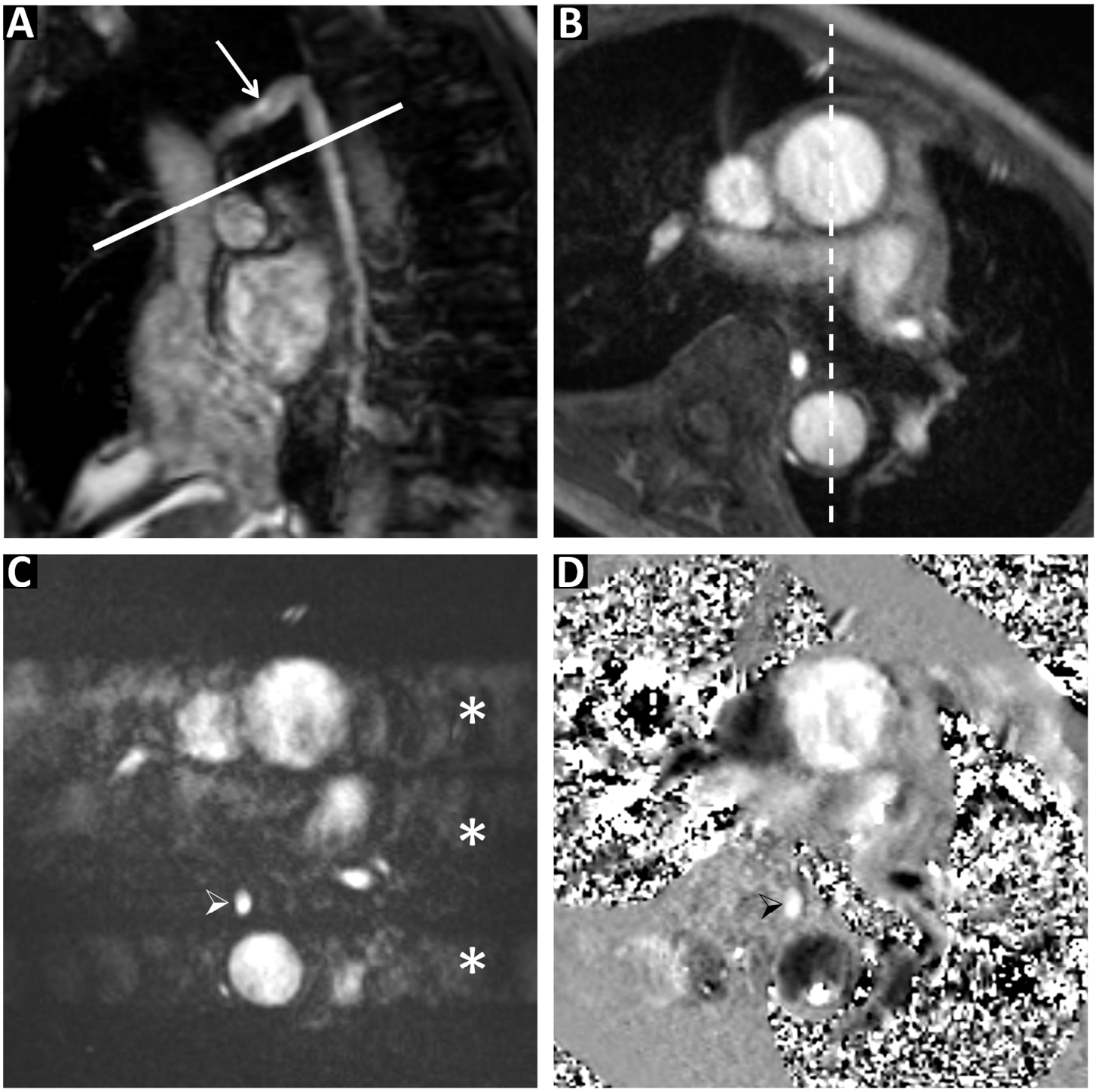

Figure 2 MR Imaging azygos blood flow encoding process in 52-year-old men with grade 2 esophageal varices

(A) True fast imaging with steady-state free precession (TRUE-FISP) MR sequence in the sagittal plane used to localize the azygos vein and the azygos arch (white arrow) and to determine the optimal plane for flow quantification, orthogonal to the vessel axis, at the most cephalic level of the paravertebral vertical segment below the arch (white line). (B) T2-weighted imaging HASTE sequence performed in the plane previously dermined, with a field of view inclined clockwise, in an axis parallel to that passing through both ascending and descending thoracic aortas (dotted white line). (C-D) 2D cine phase-contrast sequence encoded at 40cm/s and reconstructed in amplitude image (C) and phase image (D). Phase encoding direction set from right-to-left avoids projection of motion-related artifacts due to aorta and pulmonary arteries pulsations (white stars) on the azygos blood flow signal (white arrowhead). A visual control of the optimal encoding velocity is finally performed to ensure of the absence of aliasing artifact in the azygos vein lumen (black arrowhead).

Follow-up

Patients were prospectively followed-up by both referent hepatologist and radiologist. Control visit was scheduled one month after the first dose of beta-blocker. Physical and laboratory analysis, liver and spleen stiffness assessment, as well as liver US Doppler were repeated on the same basis as baseline examinations set.

The compliance with treatment was evaluated by asking the patient how many times he/she had not complied with the prescription, and by controlling heart rate. In case of alcohol-related cirrhosis, evolution of intoxication over time was notified and all patients were invited to maintain abstinence.

MR-based azygos blood flow measurements were repeated in all patients by the same radiologist, using an identical measurement technique. Considering the doubling time of HCC, it was not deemed necessary to repeat MRI exploration of the liver parenchyma during this 1-month review.

In the 8 patients included after Novembre 2015, response to treatment was assessed by transjugular HVPG. Patients were considered as non-responder to NSBB in case of HVPG higher than 12mmHg or if the decrease was lower than 20% of the initial value (8,9). In this situation, as well as in patients suffering inconvenient side effects, a dose adjustment or a beta-blocker switching was performed following recommendations, for the further study (7). No further upper GI endoscopy was scheduled in patients on beta-blockers treatment (32).

Statistical analysis

Baseline characteristics of the study population were described by median and inter-quartile range (IQR) for continuous variables and by percentages for categorical variables.

The correlation between baseline azygos blood flow and Child-Pugh score were assessed using the Spearman's rank test. The Kruskal-Wallis test was used to compare azygos blood flow among patients with a Child-Pugh class of A, B, or C. When a significant difference among the three groups was indicated, multiple two-by-two comparisons were performed using the Mann-Whitney-U test. Pearson coefficients were used to assess correlations between baseline azygos blood flow and MELD score. Staging of EVs based on MR visual analysis results and such grade based on endoscopic results were compared by using k statistics. k Values of up to 0.20 were considered to indicate slight agreement;

values of 0.21–0.40, fair agreement; values of 0.41–0.60, moderate agreement; values of 0.61–0.80, substantial agreement; and values of 0.81–1.00, very good agreement (42). The Mann-Whitney-U test was used to compare the decrease of ABF between observant patients and patients who missed at least one dose of NSBB and between abstinent and nonabstinent patients. Statistical difference between baseline and 1-month follow-up measurements for study endpoints were assed using the Wilcoxon signed-rank test. Pearson coefficients were used to assess correlation between the variation of azygos blood flow after treatment and the variations of maximum portal venous blood flow, craniocaudal spleen length, spleen and liver stiffness and HVPG.

All tests were two sided. A p-value <0.05 was considered to indicate significance.
The statistical analyses were performed using the statistical software SPSS® v.24 for Macintosh (IBM Corp., USA).

RÉSULTS

The baseline clinical and endoscopic features of the study patients are reported in table 2.

The time elapsed between endoscopic diagnosis of EVs and the baseline MRI ranged from 0 to 14 days with a median delay of 3.5days (IQR [2 · 5.75]). The time elapsed between the first dose of NSBB and the 1-month MR-based ABF measurement ranged from 26 to 41 days with a median delay of 29 days (IQR [27 · 32]). The feasibility of the 2D cine-PC MR measurement was 100%, and no technical failure was encountered regardless of the patient's conditions.

Baseline MRI detected presence of EVs in 100% of patients and classified it as medium in 22 cases and large in 4 cases. A fair correlation was found between MR-based EVs staging and the endoscopic reference (k=0.361 ; 95% CI: 0.115 · 0.558).

The baseline ABF was significantly correlated to the baseline Child-Pugh score (r = 0.505 ; p = 0.008) and to the baseline MELD score (ρ = 0.4773 ; 95% CI: 0.11 · 0.73 ; p = 0.014).

Table 2 Baseline clinical and endoscopic characteristics of patients (n=26)

Men; n (%)	19 (73%)
Age (median [IQR])	65.8 [51.7-69.6]
BMI, kg/m^2 (median [IQR])	25.8 [22.3-31.1]
Esophageal varices; n (%)	
Grade 2	25 (96.1%)
Grade 3	1 (3.9%)
Child-Pugh score (median [IQR])	7.5 [5.25-10]
Child-Pugh classification; n (%)	
A	12 (46.2%)
B	5 (19.2%)
C	9 (34.6%)
MELD score (median [IQR])	12.5 [8-17.5]

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×ln(total bilirubin))+(11.2×ln(INR))+(9.6×ln(creatinine))+(6.43)
Esophageal varices were classified according to the North Italian Endoscopic Club criteria (graded 0–3)

The baseline ABF was significantly different in patients with Child-Pugh class C cirrhosis than in patients with Child-Pugh class A cirrhosis (p = 0.019) and than in patients with Child-Pugh class B cirrhosis (p = 0.02). No significant difference was observed between the patients with Child-Pugh class B cirrhosis and the patients with Child-Pugh class A cirrhosis (p = 0.673) (figure 3).

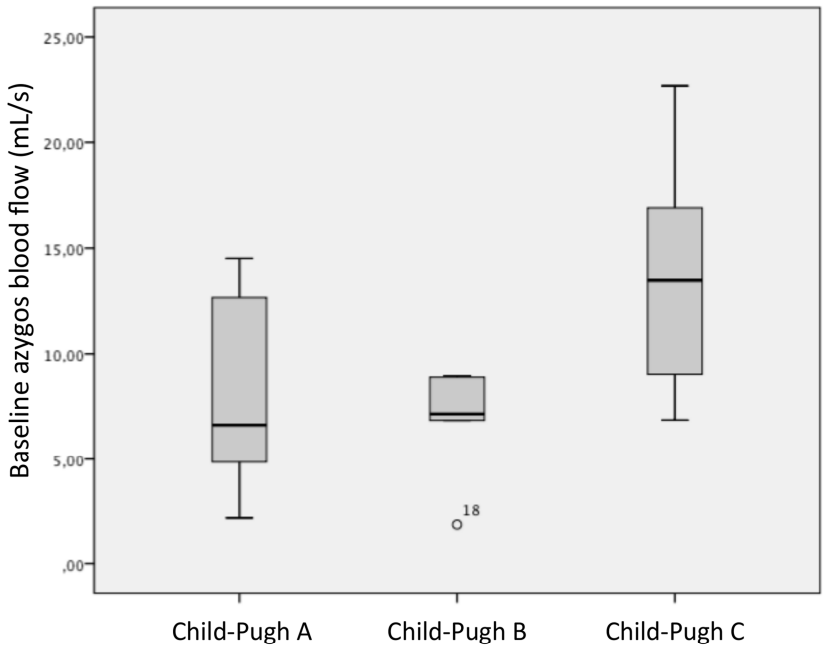

Figure 3 Box plots of baseline azygos blood flow according to Child-Pugh classification (n=26)

Boundary of boxes closest to zero indicates 25th percentile, horizontal line spanning boxes indicates mean, and boundary of boxes farthest from zero indicates 75th percentile. Error bars indicate smallest and largest values within 1.5 box lengths of 25th and 75th percentiles.

The baseline ABF ranged from 1.9 to 22.6 mL/s (median 8.9 mL/s IQR [5.8 · 13.3]), and from 1.8 to 15.8 mL/s after 1-month under NSBB therapy (median 6.0 mL/s IQR [4.6 · 8.8]), with a significant difference between these measurements ($p < 10^{-3}$). In all patients, the variation of ABF at 1-month ranged from −68.9% to +22% (median −31.1% IQR [−46.2 · −5.7]). We noticed an increased ABF in 5 out of the 26 patients (19.2%). Among these 5 patients, one declared an imperfect compliance with treatment, one declared an active alcohol consumption and one declared both imperfect compliance and alcohol consumption. In the two last cases, compliance with treatment was declared as perfect and no alcohol consumption was reported.

There was a significant difference between baseline and 1-month measurements concerning both liver stiffness calculated by Fibroscan™ ($p = 0.01$) and craniocaudal spleen length ($p = 0.018$). The variation after treatment in these two parameters ranged respectively from −63 to +43.4% (median −15.6 % IQR [−24.4 · 1.1]) and from −17.9 to +15.6% (median −3.9 % IQR [−10.5 · 1.7]). No significant difference was found between the baseline and 1-month measurements regarding the portal venous blood flow, neither for both spleen and liver stiffness measured by ARFI™ (p-values ranging from 0.06 to 0.819).

The overall results for study endpoints are reported in table 3.

Table 3 Variation under treatment at 1-month follow-up for study endpoints measurements (n=26)

PRIMARY ENDPOINT				
	Baseline	1-month follow-up	p-value	Relative difference
Azygos blood flow (mL/s)				
Median [IQR]	8.9 [5.8 · 13.3]	6.0 [4.6 · 8.8]	**$<10^{-3}$**	−31.1 % [−46.2 · −5.7]
SECONDARY ENDPOINTS				
	Baseline	1-month follow-up	p-value	Relative difference
Maximum portal blood flow velocity (cm/s)				
Median [IQR]	20.3 [17 · 23.3]	17.7 [14 · 20.8]	0.06	−15.9 % [−28.8 · 0.3]
Median right hepatic lobe stiffness ARFI™ (m/s)				
Median [IQR]	3.3 [2.6 · 3.6]	3.4 [2.8 · 3.8]	0.258	+7.6 % [−7.9 · 16.9]
Median left heaptic lobe stiffness ARFI™ (m/s)				
Median [IQR]	2.9 [2.3 · 3.6]	2.9 [2.4 · 3.6]	0.354	+4.8 % [−7.1 · 14.4]
Median spleen stiffness ARFI™ (m/s)				
Median [IQR]	3.2 [3 · 3.6]	3.4 [2.7 · 3.7]	0.819	−0.4% [−12.8 · 16.7]
Median liver stiffness Fibroscan™ (kPa)				
Median [IQR]	72 [34.4 · 75]	56.7 [32.9 · 63]	**0.01**	−15.6 % [−24.4 · 1.1]
Craniocaudal spleen length (cm)				
Median [IQR]	13 [11.9 · 14.4]	12.8 [11 · 13.7]	**0.018**	−3.9 % [−10.5 · 1.7]

ARFI™ Acoustic Radiation Force Imaging, NSBB Non-selective beta-blocker
Statistical differences between baseline and measurements after 1 month under NSBB were assessed with Wilcoxon signed-rank test
Relative differences between baseline and measurements after 1 month under NSBB were calculated using the formulation :
100x[(1-month measurement - baseline measurement)/baseline measurement]

The variation of ABF after 1-month NSBB therapy was significantly correlated with both the variation of the spleen stiffness quantified by ARFI^{TM} (ρ = 0.5229 ; 95% CI: 0.17 · 0.757 ; p = 0.006) and right hepatic lobe stiffness quantified by ARFI^{TM} (ρ = 0.4254 ; 95% CI: 0.04 · 0.698 ; p = 0.03) (figure 4). No correlation was found between the variation of ABF and the variation of left hepatic lobe stiffness quantified by ARFI^{TM} (ρ = −0.1212 ; 95% CI: −0.486 · 0.279 ; p = 0.555), neither liver stiffness quantified by Firboscan^{TM} (ρ = 0.0781 ; 95% CI: −0.39 · 0.514 ; p = 0.751), nor maximum portal venous flow (ρ = 0.3721 ; 95% CI: -0.037 – 0.674 ; p = 0.07) or the craniocaudal spleen length (ρ = 0.3129 ; 95% CI: −0.085 · 0.624 ; p = 0.119).

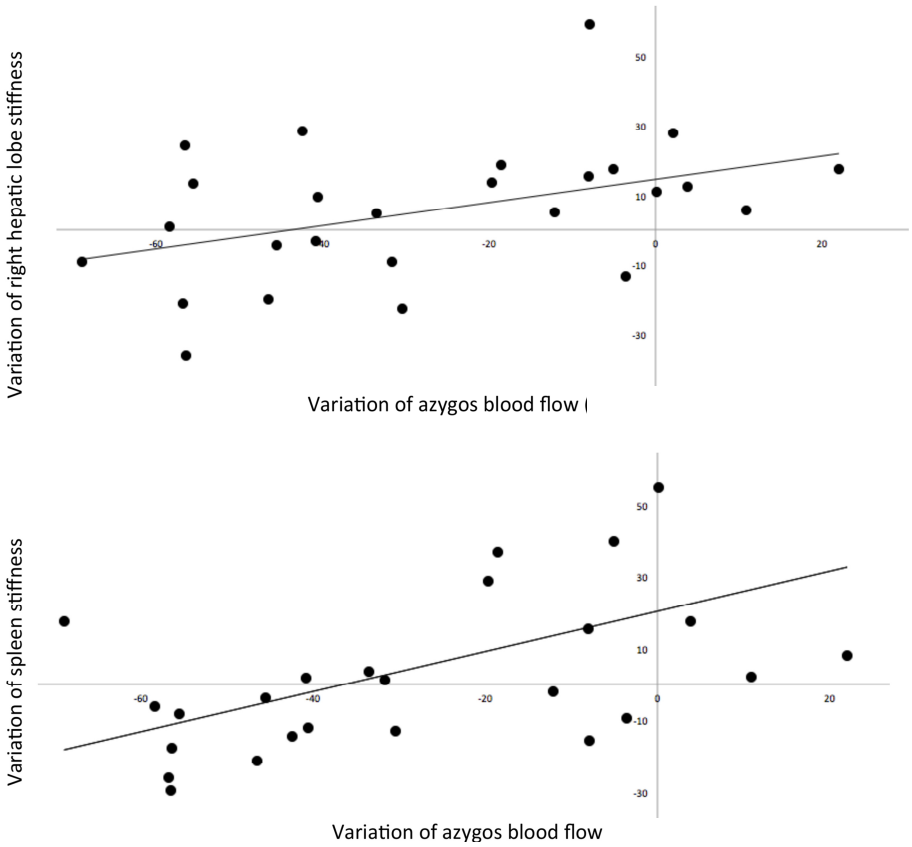

Figure 4 Scatter plot of variation of azygos blood flow (ABF) against variation of stiffness meassured by ARFI^{TM}

a Right hepatic lobe (Right hepatic lobe stiffness=0.336 ABF +14.549 ; R^2=0.18); **b** Spleen (Spleen stiffness=0.558 ABF +20.29 ; R^2=0.27)

At the inclusion time, 17 patients had alcohol-related cirrhosis, whose 5 were abstinent and 12 presented an active excessive consumption (46.1% of the whole study cohort). At the 1-month follow-up visit, none of these 12 patients has stopped alcohol consumption and 3 of them have been hospitalized for acute alcoholic hepatitis during this period. The variation of ABF in abstinent patients ranged from −58.4 to +10.9% (median −56.4% IQR [−56.8 · −40.5]) and the variation of ABF in nonabstinent patients ranged from −68.9 to +22% (median −24.5% IQR [−36.7 · −4.6]), without significant difference between these to groups (p = 0.234).

At the 1-month follow-up visit, twenty patients (76.9%) declared a perfect compliance with treatment and 6 patients (23.1%) declared having missed one dose or more of NSBB during the past month. The variation of ABF in these patients ranged respectively from −68.9 to +3.8% (median −40.6% IQR [−58.8 · −16.7]) and from −12.1 to +22% (median −4.3% IQR [−10.4 · 0.7]), with a significant difference between this two groups (p = 0.011).

Concerning the 8 patients who suffered a transjugular HVPG monitoring, the baseline HVPG measurement ranged from 9 to 29mmHg (median 18 mmHg IQR [17 · 19.2]), the 1-month HVPG measurement ranged from 10 to 21mmHg (median 15.5 mmHg IQR [14.7 · 17.5]) i.e. a variation after treatment ranging from −27.6 to +11.1% (median −11.8% IQR [−18.4 · −3.7]). Hemodynamic response criteria were achieved in 4 out of these 8 patients (50%). No correlation was found between post-NSBB decrease in ABF and HVPG (ρ = -0.0962 ; 95% CI : −0.75 · 0.6527 ; p = 0.821).

We did not register any episode of variceal bleeding during the 1-month follow-up period.

DISCUSSION AND CONCLUSION

More than 20 years after abandonment of the thermodilution practice, our study shows that 2D cine PC-MRI is able to quantify non-invasively and accurately the hemodynamic changes in azygos blood flow induced by vasoactive treatment in portal hypertensive patients.

Measurements of ABF have found their major applications in the evaluation of pharmacological therapy for portal hypertension (25,43–47). It is now accepted that the beneficial effect of a vasoactive agent is evidenced by its ability to decrease portal pressure, but also by a significant reduction of ABF (46,48). This concept has emerged from the findings that drugs used to stop variceal haemorrhage by lowering portal pressure, such as vasopressin or somatostatin, also cause a marked reduction of ABF (25,49,50). Similarly, it has been demonstrated that decreased ABF is one of the major hemodynamic effects of propranolol (43,47,51). After oral administration of propranolol, we registered a median decrease in azygos blood flow of −31.1% from the baseline measurement. These results are quite similar to those previously reported using thermodilution method, considered as the gold standard. Indeed, according to this technique, the mean reduction of azygos flow ranged from −34% to −38% after introduction of propranolol, regardless the way of administration (oral: 40 to 160mg or intra-venous: 15mg) (11,43,52). Considering that the accuracy of the MR-based measurement technique has been previously validated both in vitro and in vivo conditions (28,53,54), we hypothesise numerous reasons which could explain this slight difference. First, 23% of patients declared an imperfect compliance with prescribed treatment with a decreased ABF significantly lower compared to observant patients. Second, our study population was different than previous studies and included 46% of patients with active alcohol consumption, which may have induced some hazardous modifications on their hemodynamic state, making difficult to discriminate between the loss of pharmacological activity and the progression of the underlying disease. And third, this difference could be related to an insufficient size of sample, at this preliminary stage of the trial. Sugano et al. reported a reduction in ABF, quantified by MRI, of −40.7% 5 hours after oral administration of propranolol (30mg) in cirrhotic patients (55). But these measurements have been performed in only 7 patients at 24:00 h, during the azygos flow peak, and may thus have been influenced by changes in cardiovascular regulatory mechanisms during the

night from humoral agents and/or neurogenic factors.

We found a significant difference between baseline and 1-month measurement in portal blood flow, with a median decrease about −16%. However, there was no correlation between changes in azygos flow and portal flow velocity. Although mechanisms of portal hypertension are not totally understood and there are still conflicting reports about reduced or increased portal flow among patients with cirrhosis (56–58); it has been proved that there is no correlation between portal vein Doppler US and portal pressure (59). The balance between intrahepatic resistance and altered collaterals opposing blood flow may be a factor to explain this result. Reflecting the complexity of portal haemodynamics, Debatin et al. showed a lack of correlation between azygos and portal blood flow changes quantified by MRI, in patients with portal hypertension pre- and post- intrahepatic shunt placement (30). Quantitative measurements of portal vein flow can also been questioned because of operator and patient variability.

As attended, we found an absence of correlation between the variations of ABF and HVPG. It is well established that vasoactive drugs cause different hemodynamic changes in ABF and HVPG (43,45,49,50). This is especially true with propranolol, which reduces similarly the azygos flow in HVPG-responders and HVPG-nonresponders patients (13,47). Non-selective beta-blockers decrease portal pressure by reducing the portal venous inflow as a result of decreased cardiac output (β1-adrenergic blockade), and by reducing the splanchnic blood flow as a result of increased vascular resistance (β2-adrenergic blockade) (5,6,60,61). One of the propranolol particularities, is to specifically increase vasoconstriction and vascular resistance in the portosystemic collaterals, hence the benefits against variceal rupture (47,51,61,62). However, the HVPG indirectly reflects the portal pressure but is not directly correlated to intravariceal pressure, contrary to the ABF which provide this major advantage. This explains why only measuring HVPG might underestimate the beneficial effects of the drug (13) and measurements of azygos blood flow is potentially a more sensitive method to assess flow changes in the gastroesophageal collateral system (21,22). As our results agree with this actual state of knowledge, we thus consider it as an additional proof of the MRI's ability to accurately assess ABF changes induced by a vasoactive treatment.

We did not take into account the heart rate as a parameter to explain changes in azygos flow, even in patients who increased in azygos flow. The titration of propranolol dose against heart rate, aims empirically 25% reduction (5,6). But heart rate decrease only reflects β1-adrenergic blockade whereas the beneficial effects of NSBB in portal hypertension

are due to blockade of both β1 and β2-adrenoceptors, and the degree of β1 blockade does not correlate with the fall in portal pressure (39,63). More, heart rate has a huge intrasubject variability related to various factors. That is why such a marker is only used to monitor the compliance with treatment but not its efficiency.

The correlations between the azygos flow and both the Child-Pugh and MELD scores, are consistent with the results of previous studies (28,31). This finding is of utmost importance since the Child-Pugh score is a risk factor for EVs rupture and is also related to short-term prognosis in patients with acute variceal bleeding. More, MELD score is currently used to define prognosis by modelling hepatic dysfunction, and to prioritize liver transplantation. Child-Pugh and MELD scores are valuable clinical tools, but contrary to MRI blood flow, do not provide direct evidence of the hemodynamic state of cirrhosis. This finding may thus have an additional impact on hypertensive management.

Vizzutti et al reported a strong correlation between HVPG and liver stiffness (64). But in comparison, the diagnostic performance of spleen stiffness seems significantly better because it indirectly reflects dynamic component of portal hypertension (65). We found a tendency to decreased spleen length. Portal hypertension results in splenic congestion, congestion of the red pulp and tissue hyperplasia (66). In addition, portal hypertension also induces architectural changes in the splenic arteries and veins and induces splenic fibrosis which increases spleen stiffness (67). Studies have shown excellent correlation between spleen stiffness and portal hypertension as measured by HVPG (68–70), lending support to the biologic plausibility of measuring spleen stiffness for detecting the presence and size of EVs (68,71). On the other hand, liver elastography measures hepatic fibrosis, which only correlates with the fixed component of portal hypertension related to intrahepatic resistance, but is unable to account for the dynamic component related to hyperdynamic splanchnic circulation and portal venous blood flow (72). To our knowledge this study is the first to demonstrate that both spleen and liver stiffness are correlated to the hemodynamic changes in postosystemic collaterals, represented by azygos flow. It seems that spleen length has tendency to decrease with propranolol but it without correlation with changes in azygos flow. However, regarding the small size of sample, no definitive conclusions can be established for now. Relation between azygos flow and spleen and liver stiffness will be more accurately assessed in this final analysis, including in addition liver and spleen Share Wave Elastrography™ measurements as well as fibrosis blood test (Fibrometer™, Cirrhometer™).

The sensibility of post contrast imaging to detect esophageal varices was excellent

(100%), which is relevant to previous observations, but in our study the radiologist was not blind to endoscopic findings (36). However, as reported by Gouya et al., we found a poor correlation between MR visual analysis and endoscopic evaluation of EVs (28). We recorded a tendency to overestimate the varices size, which may be due to an inadequate section thickness (5 mm) inducing partial volume effects. Varix grading could thus be improved by using higher spatial resolution, but it was not the main goal of our study.

In addition to previous experiences, we brought some methodological improvements. We increased the number of acquisitions to improve the signal/noise ratio. We also paid a particular attention in the selection of the optimal plane for flow registration, using FOV rotation to minimise artifacts due to arterial pulsation. Increasing temporal resolution to 50 frames in one cardiac cycle, we increased in parallel the duration of images acquisition and post-treatment, but we guess that it will help to improve the reproducibility in measurements.

The key role of azygos blood flow in hypertension managements underlined the need for noninvasive alternatives. To date, every studies including our, reported a 100% feasibility of the 2D cine PC-MRI technique for ABF assessment regardless of the patient's BMI, ascites volume or the severity of the underlying liver desease (28,31,41,53,54,73). Considering that the availability of MRI increases over time and that a 2D cine PC sequence only adds a few minutes to a standard exam, it is reasonable to suggest that MR-based ABF measurement could be routinely practiced in the future.

Our study has limitations. First, the sample size lacked sufficient power which main explain some results for secondary endpoints. Nevertheless, prospective recruitment is still active and the inclusion period runs until September 2017, aiming 100 patients for the final analysis. Second, the preliminary analysis was limited to the results of a single observer, which did not allow assessing the reproductibility of our measurments.

In conclusion, ABF measurement could play a key role in the monitoring of portosystemic collaterals pressure, particularly esophageal varices. Our study suggests that 2D cine PC-MRI is able to measure in a non-invasive way variation of ABF after NSBB administration. Moreover correlation to liver and spleen stiffness suggests future simple non-invasive tools for evaluation of the efficiency of NSBB as a prophylaxis of bleeding risk in cirrhotic patients.

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BAZERIES Paul

ÉVALUATION PROSPECTIVE DE LA VARIATION DU DEBIT AZYGOS APRES INTRODUCTION D'UN TRAITEMENT PAR BETA BLOQUANT, QUANTIFIEE PAR IRM DE FLUX EN CONTRASTE DE PHASE : RÉSULTATS PRÉLIMINAIRES

RÉSUMÉ

Objectif L'objectif principal de cette étude était d'évaluer les variations de débit sanguin azygos quantifiées en IRM en séquences de flux en contraste de phase, chez les patients cirrhotiques démarrant un traitement par béta-bloquants (BB) non cardio sélectifs en prophylaxie primaire contre la rupture de varices oesophagiennes. Les objectifs secondaires étaient d'évaluer l'évolution sous traitement de la dureté du foie et de la rate, de la splénomégalie et des vitesses portales en Doopler. **Patients et méthodes** Le critère d'inclusion était la découverte endoscopique des varices oesophagiennes de grade 2 ou grade 3 nécessitant l'introduction d'un traitement prophylactique par BB. Un total de 26 ont été inclus dans cette analyse. Les examens réalisés avant l'introduction des BB comprenaient un receuil des données cliniques et biologiques, la mesure non invasive de la dureté hépatique et splénique par Acoustic force Imaging RadiationTM (ARFI), les mesures de la dureté hépatique par FibroscanTM et une quantification du flux sanguin azygos par IRM avec séquence de flux en contraste de phase. Les examens ont été répétés à 1 mois de suivi. **Résultats** Le débit azygos initial médian était de 8,9 / ml s (IQR [5.8 · 13.3]), et de 6,0 mL / s (IQR [4.6 · 8.8]) après 1 mois de traitement. Le débit sanguin azygos initial était significativement corrélée au score de Child-Pugh (r = 0,505; p = 0,008) et au score MELD (ρ = 0,4773, p = 0,014). La baisse médiane de débit azygos à 1 mois était -31,1% (IQR [-46,2 · -5,7]). La variation du débit azygos après 1 mois de traitement était significativement corrélée à la fois avec la variation de la dureté de la rate (ρ = 0,5229, p = 0,006) et celle du lobe hépatique droit en ARFITM (ρ = 0,4254, p = 0,03). Aucune corrélation n'a été trouvée entre la baisse de débit azygos et la baisse de gradient de pression (ρ = -0,0962; p = 0,821). **Conclusion** Notre étude suggère que, les séquences IRM de flux en contraste de phase sont capables de mesurer, d'une manière non-invasive, la variation de débit sanguin azygos après administration de béta-bloquants. La corrélation avec l'évolution sous traitement de la dureté splénique et hépatique suggère de nouvelles possibilités non invasives pour l'évaluation de l'efficacité de ce traitement en prophylaxie primaire chez les patients cirrhotiques.

Mots-clés : Varices oesophagiennes, hypertension portale, débit sanguin azygos, contraste de phase

PROSPECTIVE ASSESSMENT OF DECREASED AZYGOS BLOOD FLOW AFTER ORAL ADMINISTRATION OF NON-SELECTIVE BETA-BLOCKER, QUANTIFIED BY 2D CINE PHASE-CONTRAST MAGNETIC RESONANCE IMAGING : PRELIMINARY RESULTS

ABSTRACT

Objective The main objective of this study was to assess the azygos blood flow (ABF) changes quantified by 2D cine phase-contrast Magnetic Resonance Imaging, in cirrhotic patients starting non-selective beta-blocker (NSBB) therapy in primary prophylaxis against variceal bleeding. Secondary objectives were to evaluate the evolution under treatment of liver and spleen stiffness, splenomegaly and portal venous blood flow measured by Doppler ultrasound. **Patients and methods** Inclusion criteria were the endoscopic discovery of grade 2 or grade 3 esophageal varices (EVs) requiring introduction of primary prophylaxis treatment by NSBB. A total of 26 were involved in the final analysis. A baseline examinations set was performed before introducing NSBB including clinical and laboratory data, liver and spleen Doppler Ultrasonography with Acoustic Radiation Force Imaging™ (ARFI) stiffness assessment, liver stiffness measurements by Fibroscan™, and azygos blood flow quantified by 2D cine phase-contrast Magnetic Resonance Imaging. Examinations were repeated at 1-month follow-up. **Results** The variation of ABF after 1-month NSBB therapy was significantly correlated with both the variation of the spleen stiffness (ρ = 0.5229 ; p = 0.006) and right hepatic lobe stiffness quantified by ARFI™ (ρ = 0.4254 ; p = 0.03). The baseline ABF was significantly correlated to the baseline Child-Pugh score (r = 0.505 ; p = 0.008) and to the baseline MELD score (ρ = 0.4773 ; p = 0.014). The median baseline ABF was 8.9 mL/s (IQR [5.8 · 13.3]), and 6.0 mL/s (IQR [4.6 · 8.8]) after 1-month under NSBB therapy. In all patients, the median decrease of ABF at 1-month was −31.1% (IQR [−46.2 · −5.7]). No correlation was found between post-NSBB decrease in ABF and HVPG (ρ = -0.0962 ; p = 0.821). **Conclusion** Our study suggests that, 2D cine PC-MRI is able to measure, in a non-invasive way, the variation of ABF after NSBB administration. Moreover correlation to liver and spleen stiffness suggests future simple non-invasive tools for evaluation of the efficiency of NSBB as primary prophylaxis of variceal rupture in cirrhotic patients.

Keywords : Esophageal varice, portal hypertension, azygos blood flow, phase-contrast MR

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