

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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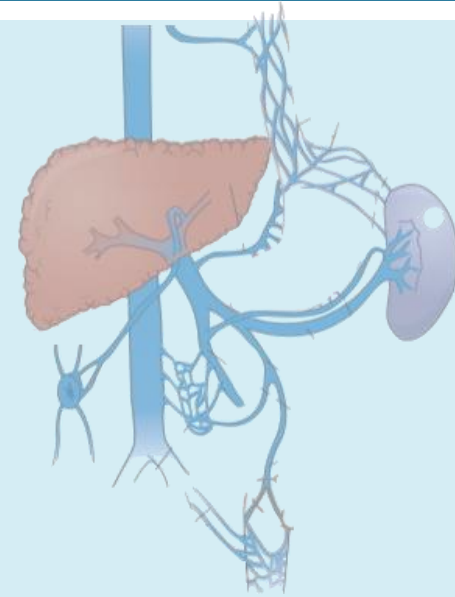
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PURPOSE

□ Esophageal varices (EV) :

- ▣ Major complication of portal hypertension
- ▣ May develop when pressure gradient $\geq 10\text{mmHg}$
- ▣ Risk of bleeding when pressure gradient $\geq 12\text{ mmHg}$
- ▣ Annual bleeding risk of 15% for stage 2 and 3 EV



PRIMARY PROPHYLAXY OF VARICEAL BLEEDING :

- **Non selective Beta-blocker** as first-line treatment
 - As soon as EV stage ≥ 2 diagnosis
 - Over a lifetime

□ Hemodynamic response to NSBB :

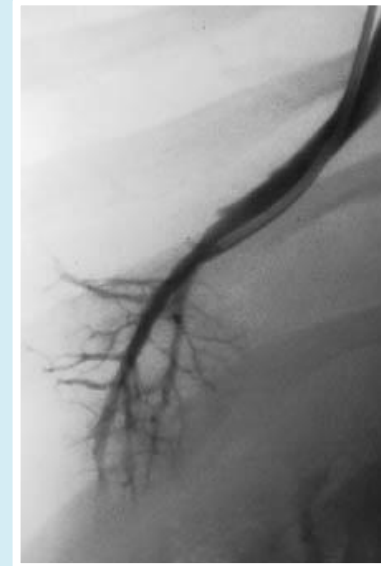
- ▣ Assessed by 2 transjugular HVPG measurements
- ▣ Defined by a decrease $\geq 20\%$ or HVPG < 12 mmHg
- ▣ 30% de répondeurs selon ces critères

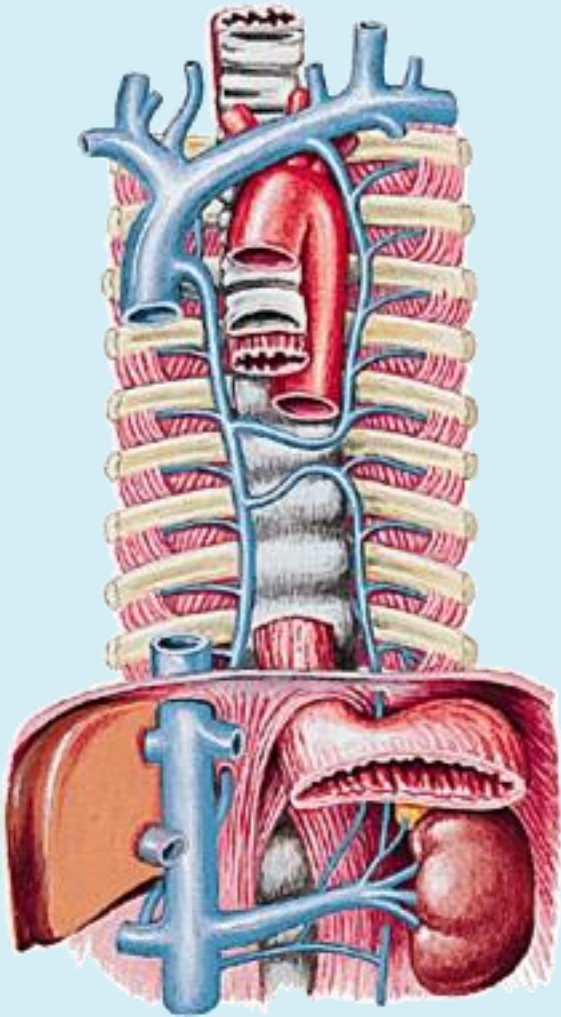
▣ But :

- ▣ Invasive procedure in high bleeding risk patients
- ▣ Unsuitable : 30% of patients are protected but classified as non-responder

▣ In clinical practice :

- ▣ No evaluation of response to NSBB : no HVPG measurement
- ▣ Treatment continued over a lifetime
- ▣ Despite 1/3 patients non-responder & serious long-term adverse effects





- The azygos vein drains most of the esophageal blood flow
- The azygos blood flow (thermodilution) :
 - ▣ Significantly increased in case of portal hypertension
 - ▣ Corrélé à la pression intra-variqueuse
 - ▣ Indirectly reflects the hemodynamic in portosystemic collaterals
- Can be measured non-invasively :

2D cine phase-contrast MR Imaging

Main objective :

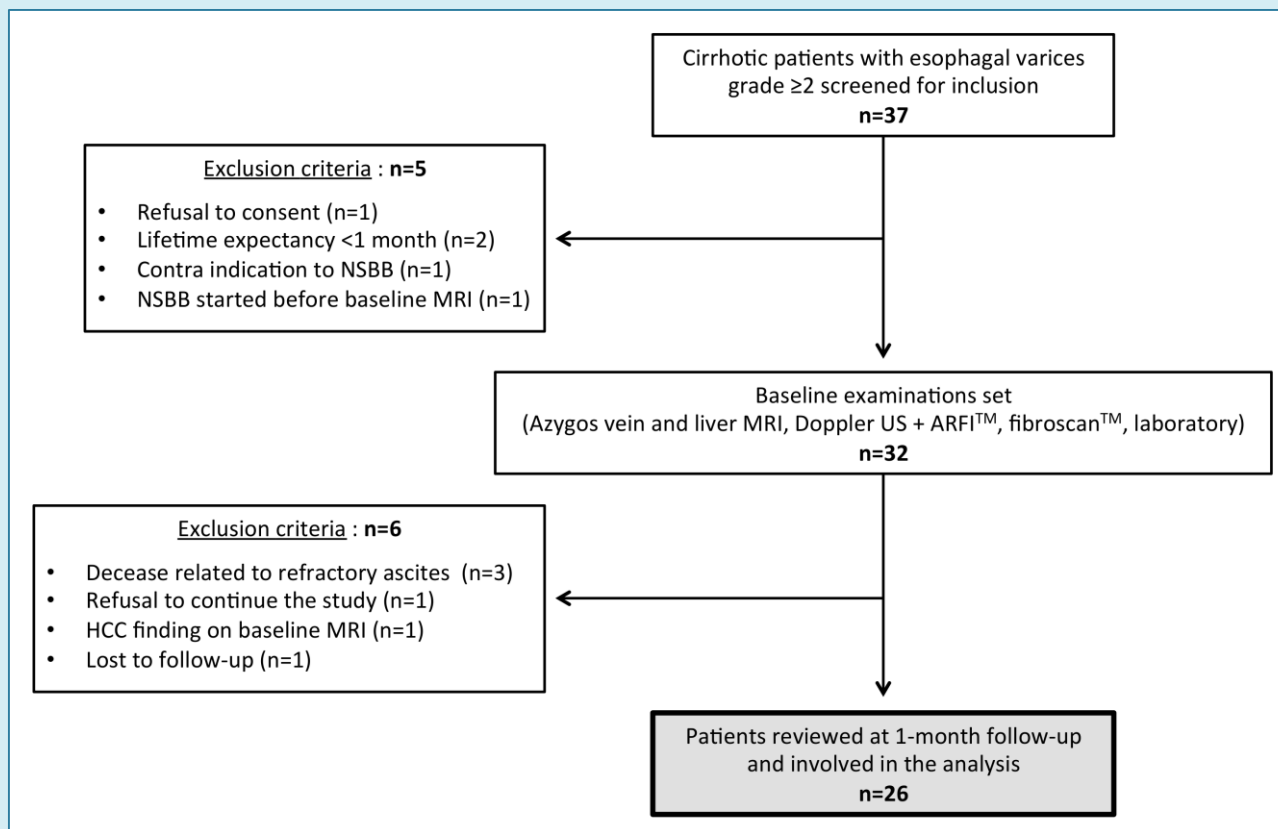
- To use 2D cine PC MRI to quantify the variations of the azygos blood flow in cirrhotic patients starting NSBB therapy as primary prophylaxis against variceal bleeding

Secondary objectives :

- To assess the variations after treatment of liver and spleen stiffness, splenomegaly and portal venous blood flow

MATERIALS & METHODS :

- Multicentric prospective non-controlled study
- Inclusion criteria : endoscopic diagnosis of EV **stade ≥ 2**
- Preliminary results on 26 patients



BASELINE :

- ❑ Clinical and laboratory data : Child-Pugh - MELD score
- ❑ Liver Doppler Ultrasonography
- ❑ Liver stiffness : Fibroscan™ & ARFI™ (10right/5left)
- ❑ Spleen stiffness : ARFI™
- ❑ Complete liver MRI & azygos blood flow <7 days after EV diagnosis
- ❑ HVP (> November 2015) : n=8

- NSBB therapy started the day after MRI
- All measurements were repeated 1 month after
- Evaluation of the observance

- Endpoints = variation at 1 month under NSBB
 - ▣ Median azygos blood flow (mL/s)
 - ▣ Median liver stiffness with FibroscanTM (kPa)
 - ▣ Median liver stiffness with ARFITM (m/s)
 - ▣ Median spleen stiffness with ARFITM (m/s)
 - ▣ Mean of maximum portal venous blood flow (cm/s)
 - ▣ Spleen length (cm)

- Azygos blood flow measurement protocol (1.5T) :
 - ▣ Fasting > 6h - non breath-hold
 - ▣ Retrospective cardiac gating
 - ▣ 2D cine PC with Venc scout ranging from 30-60cm/s

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 spatial Resolution (mm)	113 x 102	113 x 102
Temporal resolution (phase/cardiac cycle)	30	50
Bandwidth (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 Repetition time/echo time		

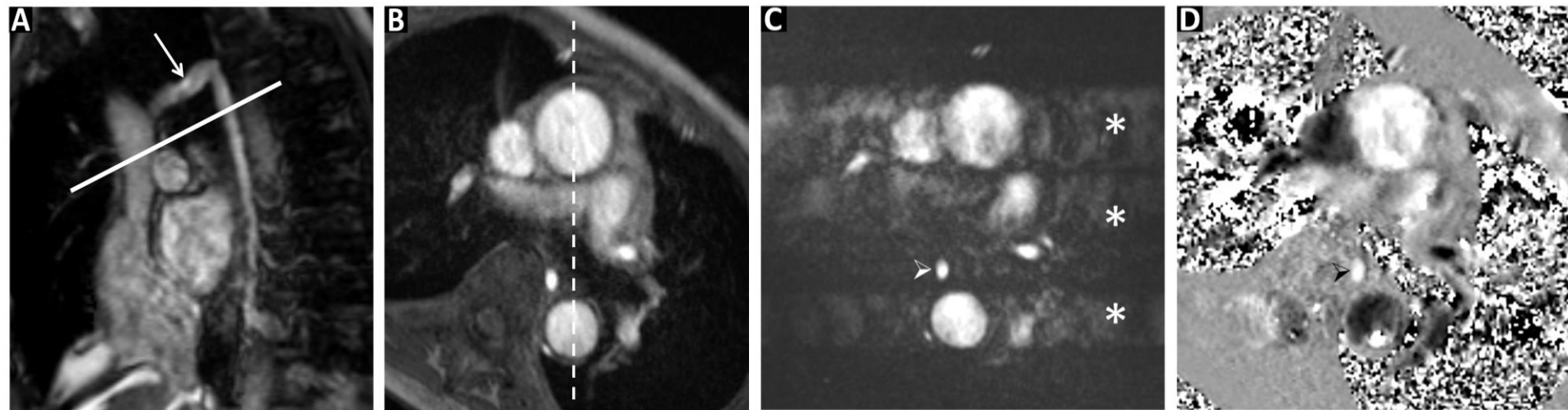


Figure 2 MR Imaging azygos blood flow encoding process in 52-year-old men with grade 2 esophageal varices

(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 determined, 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).



RÉSULTATS :

□ Clinical and endoscopic characteristics :

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]

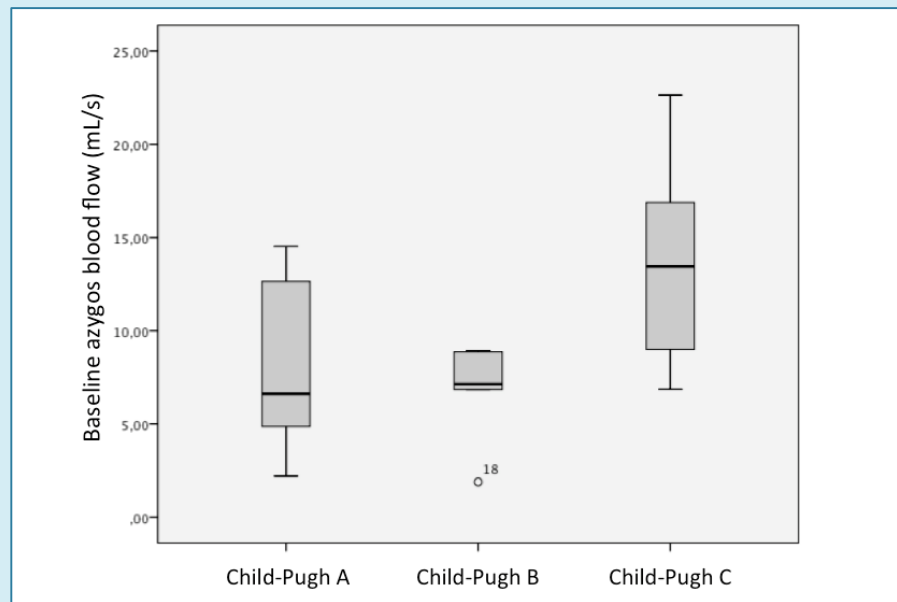
MELD Model for end stage of liver disease, BMI Body mass index, IQR Interquartile range

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: $(3.8 \times \ln(\text{total bilirubin})) + (11.2 \times \ln(\text{INR})) + (9.6 \times \ln(\text{creatinine})) + (6.43)$

Esophageal varices were classified according to the North Italian Endoscopic Club criteria (graded 0–3)

- Azygos blood flow was significantly correlated to Child-Pugh score ($r=0.505$; $p=0.008$) and MELD score ($p = 0.4773$; 95% CI: $0.11 \cdot 0.73$; $p=0.014$)
- Significant difference of azygos blood flow between Child C and Child A patients ($p=0.019$) and between Child C and Child B patients ($p=0.02$)
- No significant difference between Child A and B patients ($p = 0.673$)



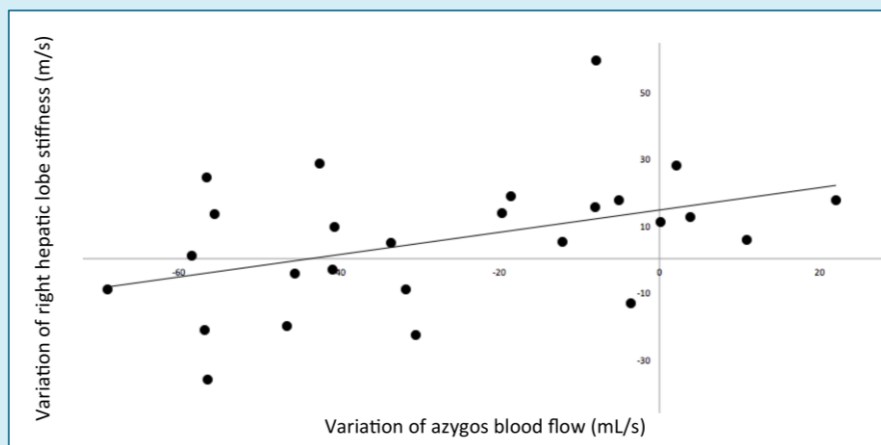
□ Endpoints :

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]
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]
Left hepatic 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]
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]
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]
<p>ARFI™ Acoustic Radiation Force Imaging, NSBB Non-selective beta-blocker</p> <p>Statistical differences between baseline and measurements after 1 month under NSBB were assessed with Wilcoxon signed-rank test</p> <p>Relative differences between baseline and measurements after 1 month under NSBB were calculated using the formulation : $100 \times [(1\text{-month measurement} - \text{baseline measurement}) / \text{baseline measurement}]$</p>				

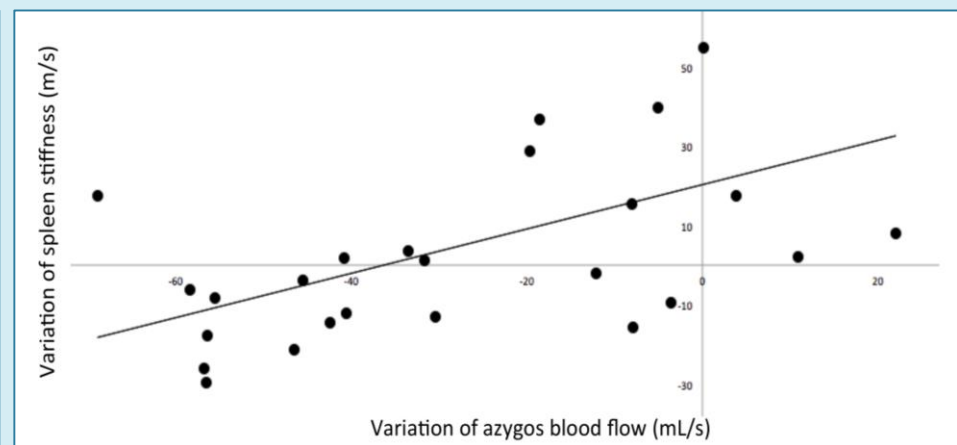
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ARFI™ Acoustic Radiation Force Imaging, NSBB Non-selective beta-blocker Statistical differences between baseline and measurements after 1 month under NSBB were assessed with Wilcoxon signed-rank test Relative differences between baseline and measurements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

- Variation of azygos blood flow after 1 month of NSBB therapy was **significantly correlated** to :
 - ▣ Spleen stiffness using ARFITM ($\rho = 0.523$; 95% CI ; $p = 0.006$)
 - ▣ Right hepatic lobe stiffness using ARFITM ($\rho = 0.425$; 95% CI ; $p = 0.03$)
- No correlation with variation of left hepatic lobe stiffness using ARFITM, liver stiffness using FibroscanTM, portal venous blood flow or spleen length



(Dureté du lobe droit = $0.336 \text{ ABF} + 14.549$; $R^2 = 0.18$)



(Dureté splénique = $0.558 \text{ ABF} + 20.29$; $R^2 = 0.27$)

- Decrease of azygos blood flow was significantly higher in observant patients (77%) : -40.6% vs -4.3% ($p = 0.011$)
- 4/8 patients were proved as responders (HVPG)
- No corrélation between variations of azygos blood flow and HVPG ($\rho = -0.0962$; 95% CI ; $p = 0.821$)

DISCUSSION

- 2D cine PC MRI allows to quantify precisely and in a non-invasive way the variations of azygos blood flow under treatment
- Our results are similar to those previously published using invasive thermodilution (gold standard) : -31.1% vs -34 to -38%
- But :
 - ▣ 23% patients non perfectly observant
 - ▣ 46% patients active alcohol consumption
 - ▣ Small sample
- Sugano et al. also studied the propranolol effects on azygos blood flow using MRI (-40.7% à midnight) but with nycthemeral variations

- Our study is the first to report a correlation between azygos blood flow variation and variation of both liver and spleen stiffness
- Spleen stiffness is correlated to HVPg and can predict the presence and the size of EV
- Spleen stiffness : dynamic
- Liver stiffness : fixed liver fibrosis

- No correlation between azygos and portal blood flow :
 - ▣ No correlation between portal blood pressure and blood flow
 - ▣ No correlation after TIPS placement

- No correlation between variation of azygos blood flow and HVPG :
 - ▣ HVPG correlated to portal pressure but no to EV pressure
 - ▣ Same decrease of azygos blood flow in HVPG-responders and HVPG-nonresponders
 - ▣ Azygos blood flow is more relevant to assess response to treatment

- Correlation between azygos blood flow and both Child and MELD score : additionnal information about the hemodynamic of cirrhotic patients

- Limits :
 - ▣ Preliminary results : small sample
 - ▣ Single observer : reproductibility

CONCLUSION:

CONCLUSION :

- Azygos blood flow plays a key role in the monitoring of the hemodynamic changes in portosystemic collaterals
- MRI can quantify precisely and in a non-invasive way the variation of azygos blood flow
- The correlation with both spleen and liver stiffness suggests a simple non-invasive tools to assess efficiency of NSBB as a prophylaxis against bleeding risk in cirrhotic patients

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