THE MODIFICATION OF SPLENIC STIFFNESS ON ACOUSTIC RADIATION FORCE IMPULSE PARALLELS THE VARIATION OF PORTAL PRESSURE INDUCED BY TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT.

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Short title: Spleen stiffness modification before and after TIPS

Abbreviations: ARFI: Acoustic radiation force impulse. TIPS: Transjugular intrahepatic portosystemic shunt.

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Key points:

- Acoustic radiation force impulse (ARFI) imaging is an ultrasound-based technique in which shear wave velocity is evaluated to assess the elastic properties of target tissues.
- The aim of this study is to establish if the modification of portal pressure induced by a TIPS parallels the modification of spleen or liver stiffness
- In our study we demonstrated that spleen stiffness is superior to liver stiffness in detecting the modification of portal pressure induced by TIPS.
- Spleen stiffness could be a potential non invasive method to monitor the modification of portal hypertension.

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Abstract

Background: Spleen and liver stiffness measured by Acoustic radiation force impulse (ARFI) imaging has been showed to be useful in identifying patients with portal hypertension.

Aim: to establish if the modification of portal pressure induced by a TIPS parallels the modification of spleen or liver stiffness measured by ARFI in order to understand if ARFI may be used to monitor the modification of portal pressure in patients with cirrhosis.

Patients and Methods: 38 patients with severe portal hypertension underwent liver stiffness (LS) and spleen stiffness (SS) before TIPS and one week after TIPS. Portal atrial gradient (PAG) was measured before and after the shunt opening.

Results: PAG decreased significantly from 19.5 mmHg to 6 mmHg ($p<0.001$). SS decreased significantly after TIPS (pre-TIPS 3.7 m/s VS 3. 1 post-TIPS m/s; $p<0.001$), while LS was also significantly modified by TIPS (pre-TIPS 2.8 m/s VS post-TIPS 2.4 m/s; $p=0.003$). PAG and spleen stiffness variation were not significantly correlated ($r=0.19$; $p=0.27$). Two patients developed a persistent hepatic encephalopathy refractory to medical treatment and were submitted to the reduction of the stent diameter. The modification of spleen stiffness was parallel to the modification of PAG.

Conclusion: Spleen stiffness is superior to liver stiffness in detecting the modification of portal pressure induced by TIPS. This make spleen stiffness a potential non invasive method to monitor the modification of portal hypertension. Further investigations are needed to establish applicability and clinical utility of this promising tool in the treatment of portal hypertension.

Word count of the abstract: 250

Key words: ARFI imaging, spleen stiffness, liver stiffness, TIPS, portal hypertension.

Introduction

Acoustic radiation force impulse (ARFI) imaging (1) is an ultrasound-based technique in which shear wave velocity is evaluated to assess the elastic properties of target tissues. ARFI has been proposed as an alternative method to assess tissue elasticity (2,3). ARFI can be performed under clear observation of the actual measuring site by B-mode imaging (4) and thus, may be more feasible than tissue elastometry, which may be difficult in patients with ascites, obesity or narrow intercostal space. Promising results on the accuracy of ARFI technology for non-invasive assessment of liver fibrosis have been reported (2,3).

Splenomegaly in liver cirrhosis is believed to be a consequence of portal congestion and tissue hyperplasia and to be strongly related to the degree of portal hypertension (5-7). Spleen diameter and platelets count have been related to the severity of portal hypertension and included in several models to predict the presence of clinically significant portal hypertension or oesophageal varices (8,9). Spleen stiffness (SS) measured by tissue elastometry has been showed to be significantly correlated to the hepatic venous pressure gradient (10). Moreover, the capacity of spleen stiffness measured either by tissue elastometry (10-12) or by ARFI (13) in identifying patients with portal hypertension (i.e. HVPG>10 mmHg), clinically significant portal hypertension (HVPG>12 mmHg) or varices at endoscopy has been shown to be superior to liver stiffness (LS) although not in all studies (14-16). Thus spleen stiffness can be considered a promising method for the non-invasive diagnosis of portal hypertension (17-19). However, little is known on the relationship between the modification of the portal pressure and the modification of splenic stiffness. The demonstration of the possibility that changes in portal pressure could be estimated accurately by changes in spleen stiffness would have relevant clinical consequence, especially for the treatment of portal hypertension.

Transjugular intrahepatic porto-systemic shunt is a radiological technique used for the treatment of the complications of portal hypertension, especially in patients with recurrent variceal bleeding or

refractory ascites (20). TIPS construction leads to an immediate and large modification of portal pressure, which in most cases reaches normal values immediately after the shunt opening.

Aim of the present study was to establish if the modification of portal pressure induced by a TIPS parallels the modification of spleen or liver stiffness measured by ARFI; in order to understand whether or no ARFI may contribute to indirect monitoring the modification of portal pressure in patients with portal hypertension.

Patients and Methods

Between September 2013 and December 2015, all 48 consecutive patients with portal hypertension submitted to TIPS were considered for this prospective study. Ten patients submitted to rescue TIPS were not included because of the impossibility in performing the ARFI examinations before the procedure for practical problems during the emergency procedure. The characteristics of these 10 patients were similar to those eventually included in the study (Table 1).

The 38 patients included in the study had a clinically significant portal hypertension complicated by variceal bleeding or ascites refractory to conventional non-derivative treatment. All patients were affected by liver cirrhosis. However, one patient was affected by concomitant schistosomiasis and HCV infection while two patients were affected by a Budd Chiari syndrome. In all these three patients the cirrhosis was biopsy proven. The characteristics of the patients are reported in Table 1.

All TIPS procedures were carried out by the same radiologist. PTFE-covered stent-grafts (Gore Viatorr® TIPS endoprosthesis, W.L. Gore & Associates, Inc., Flagstaff, AZ, USA) were used. The anesthesiological procedure (21-23) and the technical details of TIPS implantation with PTFE-covered stent-grafts were previously described (24, 25). All subjects were evaluated and followed up by the same medical team by a prospective protocolized diagnostic work-up and a surveillance strategy as previously described (24, 25). Before TIPS, the patients' histories were collected;

physical examinations, calculations of Child-Pugh's (26) and MELD (27) scores, Doppler ultrasonography and upper gastrointestinal endoscopy were carried out.

An informed, written consent was obtained. The "Sapienza" University of Rome Ethical Committee approved the study (Rif.1720/01.10.09).

Portal atrial gradient determination

The portal atrial gradient (PAG) was calculated as the difference between the portal and the atrial pressure (28). Portal atrial pressure was measured in the deeply sedated (not intubated) patient by means of a pressure transducer before and immediately after TIPS construction. The first PAG measurement was obtained after the portal puncture, once the catheter is advanced into a patent portion of the main portal vein. The second PAG measurement was obtained after the deployment of the covered stent between the portal and hepatic vein, balloon dilatation of the stent with a balloon catheter of size equivalent to the nominal diameter of the graft and after a portography showing the shunt patency.

A recent Spanish study (29) has proved that the porto-systemic gradient measured a few days after TIPS opening is more accurate than the one measured immediately after TIPS. Although the difference between the two measurements was in the order of 1.5 mmHg.

US and Doppler examination

A complete ultrasound and Doppler examination was performed in each patients before TIPS by three expert operators (A.D.S. with more than 30 years of experience, and C.B. and C.I. with almost 10 years of experience). Each exam was conducted to record the spleen bipolar and the liver right lobe diameters, portal, splenic and mesenteric vein diameter and the portal flow velocity and direction. One week after TIPS, ultrasonography assessment of the shunt patency with colour-Doppler measurement of the mean flow velocity and direction within the shunt at three sites

(proximal, medial, and distal portion), in the portal vein and in the intrahepatic portal branches was obtained. The diameters of the stent, the portal vein and the spleen were also measured.

Spleen and liver stiffness determination

All ARFI measurements were obtained using a Siemens Acuson S2000 ultrasound system by the same experienced sonographer (ADS). After an overnight fast, each patient was placed in the supine position and underwent ARFI on B-mode imaging during deep inspiration (30). A region of interest (fixed-dimension 1 x 0.5–cm box; maximum evaluable depth, 8.5 cm) in the liver or spleen parenchyma, free of large blood vessels, was selected using the intercostal approach. Liver stiffness was measured in the right lobe of the liver, almost 1 cm below the liver capsule, using the intercostal approach. Ten consecutive successful measurements were performed in each patient and mean value in meters per second was considered as results.

In the first three patients spleen and liver stiffness were measured the day before TIPS and 24 hours and 7 days after TIPS. Values of SS measured 24 hours after TIPS were only partially decreased in comparison with those obtained one week after TIPS (from 3.64 $\pm$ 0.43 to 3.05 $\pm$ 0.17 and to 2.66 $\pm$ 0.22 m/s; $p<0.001$). Therefore in the remaining patients perform ARFI was performed only a week after the stent placement.

Statistical analysis

Results were expressed as median (first quartile, third quartile). Comparisons between groups were performed for quantitative data by Wilcoxon's paired rank-sum test paired data and Chi-square test when appropriate. The relationship between variables was analyzed by Spearman's correlations and related test. The software R (R Development Core Team, Vienna, Austria) was used for the computations.

Results

TIPS was successfully implanted in all patients. The portal atrial gradient measured immediately before and after TIPS as well as the ultrasound/doppler parameters and the spleen and liver stiffness values measured before and one week after TIPS are reported in Table 2. At the time of the second measurement the shunt were patent in all patients.

Immediately after stent-graft placement the portal pressure gradient decreased significantly from a median of 19.5 mmHg to 6 mmHg ($p<0.001$). SS decreased significantly after TIPS (pre-TIPS 3.7 m/s VS 3. 1 post-TIPS m/s; $p<0.001$), while LS was also significantly modified by TIPS (pre-TIPS 2.8 m/s VS post-TIPS 2.4 m/s; $p=0.003$).

One week after TIPS, all ultrasound parameters remained stable compared to basal values whereas portal flow velocity was significantly increased from a median of 12.7 to 21 cm/sec ($p<0.001$ at Wilcoxon test). Splenic and liver stiffness decreased significantly (Table 2).

Figure 1 reports the individual values of portal pressure, spleen and liver stiffness recorded before and after TIPS in each patient. One week after TIPS, splenic stiffness was reduced in 35 out of 38 patients. In the remaining 3 patients, spleen stiffness remained stable in two and was slightly increased of about 10% in one patient. In this patient the measurements were repeated one month after the procedure and the value resulted lower than those recorded before and one week after TIPS (3.23 before TIPS, 3.37 one week after TIPS and 2.58 m/s one month after TIPS). It was not possible to repeat the ARFI measurements in the remaining two patients because one patient died one week after discharge for liver failure due to acute alcoholic hepatitis and the other patients was detained. At variance with splenic stiffness, the modification of liver stiffness after TIPS was highly variable (Figure 1). The larger reduction was observed in the two patients with Budd Chiari syndrome.

The PAG and spleen stiffness values measured before and after TIPS were significantly correlated (Figure 2).

Two patients developed a persistent hepatic encephalopathy refractory to medical treatment 1 and 8 months after TIPS placement respectively and were submitted to the reduction of the stent diameter, as previously described (21, 22). In these patients PAG gradient was determined before and after the reduction of the stent diameter, while liver and spleen stiffness were performed the day before and one week after the radiological procedure. In one of these two patients ascites and large oesophageal varices were again evident one month after the stent diameter reduction and the patient was submitted to a re-dilatation of the stent. Figure 3 reports the modifications of PAG and spleen stiffness observed in these two patients before, after TIPS and after the stent diameter modifications. A parallel modification of spleen stiffness and PAG was observed. No significant variation of liver stiffness were observed in these patients.

Discussion

In this study we showed that the reduction of portal pressure gradient induced by a TIPS led to a significant reduction of the spleen stiffness but not of liver stiffness measured by ARFI imaging. Our data confirm the observation of Ran HT and of Gao J (31, 32) and of Novelli PM et al. (33). Interestingly, in the two patients with persistent post-TIPS hepatic encephalopathy in whom the stent diameter was modified, the spleen stiffness paralleled the portal pressure gradient modifications induced by the reduction or re-dilatation of the stent. With the exception of the two patients with Budd Chiari syndrome in whom liver stiffness was largely reduced after TIPS, this parallelism was not observed when liver stiffness was measured, suggesting that this parameter is influenced less intensely by portal pressure modifications. Spleen stiffness, although related also to hepatic fibrosis (34), seems to be more sensitive to the variation of portal pressure probably because the splenic pressure is more directly dependent on the splenic vein outflow obstruction and on the hyperdynamic circulation due to the exclusive arterial supply of the spleen. In fact, in our series, PAG and spleen stiffness values measured before and after TIPS were significantly correlated. It

should be noted that PAG and SS were measured in different times: immediately after the shunt opening and after one week, respectively. Preliminary measurements performed in few patients showed that SS may continue to decrease one week after a TIPS compared to the values observed 24 hours later. This may also occur for PAG measurements due to adaptation of the hearth to the opening of the shunt. Thus the correlation between PAG and SS observed in our experimental condition could be much better if the two measurements could be made at the same time.

The increase in spleen stiffness after the reduction of the stent diameter observed in the two patients with persistent hepatic encephalopathy suggests that in patients submitted to TIPS this parameter may be used to monitor the shunt function, confirming the observation of Gao J et al. (35). However, the efficacy and the sensitivity of splenic stiffness in detecting the occurrence of a shunt dysfunction after a TIPS needs further investigations.

The use of splenic stiffness measurement as a non invasive method to detect the presence of clinically significant portal hypertension (10) or of oesophageal varices (13) was already suggested, although the models based on spleen stiffness for the identification of the patients with large varices need to be fully validated (36, 37). Spleen stiffness has been showed to be useful also in patients with portal hypertension due to portal vein obstruction (18). In addition to the above applications, our findings support the possibility that the modification of portal pressure could be monitored by spleen stiffness measurement by ARFI imaging. This possibility has clinical implications. Portal pressure has been showed to have a prognostic impact on survival and development of the complications in patients with liver cirrhosis (38, 39). Moreover, at variance with arterial hypertension, the pharmacological treatment of portal hypertension is usually carried on without monitoring the portal pressure. Recent data suggest that less than half of the patients treated with beta-blockers respond in terms of portal pressure reduction (40). As alternative drugs or procedures such as carvedilol (41, 42) or endoscopic band ligation (43) are available, a reliable method to

monitor non invasively the portal pressure modifications during treatment would be very welcome. Until now HVPG is the only reliable method to estimate the degree of portal hypertension and its reduction during treatment. However, the diffusion and the applicability of HVPG measurements is limited by its invasiveness. Our findings, although promising, are far to let consider spleen stiffness measurement as a reliable method to monitor the modification of portal pressure, and in particular that induced by a pharmacological therapy. In fact, after a TIPS a very large reduction in portal pressure gradient occurs and values lower than 12 mmHg, generally believed not associated to the complications of portal hypertension, are quite usual. This values are rarely observable in patients submitted to pharmacological therapy (42) in whom the treatment is considered efficacious when a 20% reduction in HVPG respect to pre-treatment values is reached (43). Thus, studies with measurement of HVPG and spleen stiffness before and after a pharmacological treatment are needed to understand if spleen stiffness modifications are sufficiently sensitive to detect the drug induced modification of portal pressure.

In conclusion, spleen stiffness but not liver stiffness is useful to detect the modification of portal pressure gradient induced by a TIPS. This make spleen stiffness a potential non invasive method to monitor the modification of portal hypertension. Further investigations are needed to establish applicability and clinical utility of this promising tool.

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Figure1: Individual values of portal pressure (Panel A) measured immediately before and after TIPS and of spleen stiffness (Panel B) and liver stiffness (Panel C) measured before and one week after TIPS. Wilcoxon's rank-sum test was used for statistical analysis.

Figure 2: Spearman's correlation between variation of PPG and spleen stiffness values measured before and after TIPS (Spearman's correlation: r=0.19 p=0.27)

Figure 3: Modification of PPG (black line) and spleen stiffness (grey line) in the two patients who needed to be submitted to modification of the shunt diameter because of refractory hepatic encephalopathy.