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● *Original Contribution*

TIME-HARMONIC ELASTOGRAPHY OF THE LIVER IS SENSITIVE TO INTRAHEPATIC PRESSURE GRADIENT AND LIVER DECOMPRESSION AFTER TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS) IMPLANTATION

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Abstract—We investigated the correlation between hepatic venous pressure gradient (HVPG) and liver shear wave speed (SWS) measured by multi-frequency time-harmonic ultrasound elastography (THE) before and after transjugular intrahepatic portosystemic shunt (TIPS) implantation. Ten patients with ascites, cirrhotic liver disease and portal hypertension were prospectively examined with invasive HVPG measurement and THE before and after TIPS implantation. HVPG and SWS decreased after TIPS placement from 20.4 ± 2.2 mmHg to 9.8 ± 4.1 mmHg (mean ± standard deviation) and from 3.87 ± 0.54 m/s to 3.27 ± 0.44 m/s. Mean reduction HVPG was −10.6 ± 3.7 mmHg, $p < 0.001$; mean reduction SWS was −0.60 ± 0.29 m/s, $p < 0.001$. A linear correlation was observed between HVPG and SWS ($R = 0.59$, $p = 0.0061$). THE-measured SWS is a first potential direct ultrasound marker for liver decompression following TIPS in ascites-associated cirrhotic liver disease and therefore might be suitable to non-invasively detect portal hypertension. (E-mail: christian.althoff@charite.de) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Time harmonic elastography, Multi-frequency vibration, Blood volume, Portal hypertension, Hepatic blood flow, Transjugular intrahepatic portosystemic shunt.**

INTRODUCTION

Portal hypertension is caused by an increase in blood flow, an increase in hepatic resistance or a combination of both (Martell et al. 2010). Chronic portal hypertension causes ascites, variceal hemorrhage and splenomegaly. Notably, esophageal varices are associated with high mortality of up to 20% due to bleeding in case of rupture (D'Amico et al. 2003). Transjugular intrahepatic portosystemic shunt (TIPS) placement is an effective method to decrease portal hypertension (Eesa and Clark 2011). Currently, the diagnosis and follow-up of portal hypertension require invasive catheter-based examinations.

Different ultrasound elastography techniques have been described for non-invasive diagnosis and follow-up of liver disease (Cosgrove et al. 2013; Sarvazyan et al. 2011; Zaleska-Dorobisz et al. 2014). Some common dynamic methods are transient elastography (TE), point shear wave elastography (pSWE) and supersonic shear wave imaging (SSI) (Bercoff et al. 2004; Palmeri et al. 2008; Sandrin et al. 2003).

Several studies reported a correlation between hepatic venous pressure gradient (HVPG) in portal hypertension and liver stiffness determined using TE (Sirli et al. 2015), SSI and pSWE (Kim et al. 2015; Procopet et al. 2015; Salzl et al. 2014). Ultrasound-based elastography methods and magnetic resonance elastography (MRE) demonstrated a high sensitivity of splenic stiffness to decompression of the hepatosplenic vascular system but were less sensitive to TIPS when focusing on the liver alone (Gao et al. 2012; Guo et al. 2015; Novelli et al. 2015). We here hypothesize that liver stiffness can be used as a sensitive marker of HVPG reduction by TIPS when measured using multi-frequency harmonic tissue stimulation in larger portions of the liver (Ipek-Ugay et al. 2016; Tzschatzsch et al. 2014). Classical approaches in

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ultrasound-based elastography have limited access to the liver due to their maximum penetration depth of 8 cm and small sampling windows, which is a challenge especially when examining obese patients (Cosgrove et al. 2013) and in the presence of ascites—a common finding in patients with portal hypertension (Thiele et al. 2015). In contrast, time-harmonic ultrasound elastography (THE) covers large tissue windows of up to 14-cm depth (Tzschätzsch et al. 2014) with high sensitivity to vascular effects such as increased hepatic fluid blood volume due to water ingestion (Ipek-Ugay et al. 2016).

We therefore used THE to examine the livers of patients with cirrhosis and ascites once before and a second time after TIPS intervention to test if determination of liver stiffness can be used in future studies for assessing the efficacy of a TIPS intervention as part of an ultrasound examination.

MATERIALS AND METHODS

Patients

This prospective study was approved by the local Institutional Review Board of the Humboldt University of Berlin–Charité (ethics committee). Written informed consent was obtained from all patients. Ten patients (age range, 47–71 y; 4 females) with the diagnosis of liver cirrhosis, a body mass index (BMI) ranging from 18.4 to 35.6 (mean, 26.7) and portal hypertension were enrolled. The clinical indication for TIPS placement was due to therapy refractory ascites in all patients. Detailed patient information is compiled in the Table.

THE

THE was performed after overnight fasting before and 24–72 h after TIPS intervention. The setup and post-processing have been previously described (Ipek-Ugay et al. 2016; Tzschätzsch et al. 2015). For shear wave generation, an actuator-integrated vibration bed (see Fig. 1) generates a multi-frequency waveform consisting of 7 superimposed frequencies (from 30 Hz to 60 Hz). For positioning of the elastography profile and acquisition of shear waves in the liver, a conventional ultrasound device (SonixMDP, Ultrasonix, Scottsdale, AZ) with a 1.7-MHz transducer (SA2-2/24 phased array) was used. After B-mode-guided positioning, the M-mode was acquired over 1 s during expiration. For online post-processing and real-time elastography feedback, a THE system (GAMPT m.b.H., Merseburg, Germany) was used (Fig. 1). As detailed in Tzschätzsch et al. (2015), projection bias was minimized by repeated measurement at 40 different probe positions and cosine-fit-based averaging. Finally, the shear wave speed (SWS) (in m/s) indicating liver stiffness was displayed. Total examination duration per patient was approximately 5 min.

TIPS

TIPS placement was performed by a board-certified interventional radiologist (C.E.A.) under local anesthesia and mild sedation. Four patients received a nitinol bare metal stent (Luminexx; Angiomed GmbH & Co Medizintechnik KG, Karlsruhe, Germany) and 6 patients received polytetrafluoroethylene-covered stent grafts (Gore, Flagstaff, AZ), each with a diameter of 10 mm. Stents and stent grafts were selected based on anatomic information such as liver size, shunt position, distance among the main portal vein and right hepatic vein and right-sided heart function. HVPG was measured during the intervention before and after TIPS placement as the pressure difference between portal venous pressure and systemic venous pressure at the

Table. Clinical and elastography data for all patients before and after TIPS intervention

No.	Age y	Sex m/f	Diagnosis	BMI	Stent	CHILD A/B/C	Ascites y/n	Varicosis grade	$HPVG_{pre}$ mmHg	$HPVG_{post}$ mmHg	ΔHVPG mmHg	c_{pre} m/s	c_{post} m/s	Δc m/s
1	63	m	C2	27.7	Luminexx	B	y	I	24	12	−12	4.91	4.12	−0.80
2	59	m	C2	35.6	Luminexx	C	y	0	18	4	−14	3.38	2.61	−0.76
3	47	f	C2	18.4	Viatorr	B	y	I	21	10	−11	4.15	3.77	−0.38
4	71	m	C2	28.0	Viatorr	B	y	I	19	13	−6	3.89	3.22	−0.67
5	54	m	C2	21.8	Viatorr	B	y	II	19	5	−14	4.01	3.46	−0.56
6	47	f	C2	21.5	Viatorr	C	y	II	19	13	−6	4.51	3.42	−1.08
7	54	f	C2	22.1	Viatorr	B	y	0	23	9	−14	3.67	2.92	−0.75
8	62	m	Cryptogenic Cirrhosis	30.5	Luminexx	A	y	0	19	13	−6	3.54	2.97	−0.57
9	63	f	Autoimmune Hepatitis	26.8	Viatorr	B	y	I	19	4	−15	3.45	3.01	−0.44
10	49	m	Hepatitis C	34.1	Luminexx	A	y	II	23	15	−8	3.21	3.19	−0.03
Mean	56.9			26.7					20.4	9.8	−10.6	3.87	3.27	−0.60
SD	8.0			5.7					2.2	4.1	3.7	0.54	0.44	0.29

TIPS = transjugular intrahepatic portosystemic shunt; No. = number; BMI = body mass index; CHILD = Child-Pugh stage; HPVG = hepatic venous pressure gradient; C2 = alcohol-induced cirrhosis; c = shear wave speed; SD = standard deviation.