Liver Fibrosis staging using Supersonic Shear Imaging: a clinical study on 142 patients.

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Abstract—**Supersonic Shear Imaging (SSI) has recently been demonstrated to be a fast, repeatable and reproducible technique allowing 2D viscoelasticity mapping of human liver. We present in this study a clinical evaluation of the performances of SSI for liver fibrosis staging in patients with chronic liver disease, and a comparison with the performances of 1D transient elastography (Fibroscan, Echosens, Paris). We studied 142 patients with chronic liver disease that underwent SSI using a dedicated curved ultrasonic probe (2.5 MHz, 128 elements), Fibroscan (FS), aspartate to platelets ratio index (APRI), Forns' index, Fib-4 and liver biopsy (LB) for reference. We assessed a comparison between the performances of SSI and FS. One-way Anova analysis shows a better agreement between METAVIR Fibrosis staging and elasticity assessement using SSI ($p = 4.44 \times 10^{-16}$) than using FS ($p = 7.21 \times 10^{-12}$). The areas under the ROC curves (AUROC) for elasticity values assessed from SSI method were respectively 0.95 for patients with $F \geq 2$, 0.96 for patients with $F \geq 3$, and 0.97 for patients with $F = 4$. The same analysis performed on the FS assessed on the same patients gives 0.90, 0.93, and 0.94.**
SSI appears to be a fast, simple, and reliable method for non-invasive liver fibrosis staging and shows better diagnostic accuracy than FS for each fibrosis stages. These results suggest that SSI elastography could be an efficient complementary routine examination for chronic liver diseases, and avoid a LB that can lead to patient discomfort and serious complications.

I. Introduction

Liver cirrhosis is responsible for over 700000 deaths annually [1] and is among the top 20 disease related causes of death. If left unmanaged, liver fibrosis has serious long-term consequences for patient morbidity and mortality. As a consequence, the assessment of liver fibrosis is of crucial clinical importance for the diagnosis and monitoring of chronic liver diseases at early stages [2] and for treatment monitoring [3]. Liver biopsy (LB) is still considered as the "gold standard" examination to assess liver fibrosis level, despite limitations [4], such as high proportion of patients refusal, patient discomfort, morbidity and mortality [5]–[7]. The specificity and sensitivity of LB remains moderate and its accuracy for fibrosis staging has also been questioned [2], [8], [9] because of sampling errors during punctions, fibrosis heterogeneities, and small length of liver samples [10]–[12]. These limitations led to the development of surrogate serum markers, nonivasive biochemical and hematologic tests [13]. Those blood indexes are reported to be not specific enough [14] and could be influenced by extrahepatic diseases or conditions such as hemolysis. Furthermore, the most important limitation of these direct and indirect fibrosis tests is the lack of discrimination at intermediate stages of fibrosis [14], [15]. As a consequence, there is a critical need for alternative fibrosis methods for liver fibrosis staging allowing high specificity and sensibility [6], [14] for early, intermediate, and advanced stages of liver fibrosis in order to initiate treatments and monitor their efficiency.

Mechanical properties assessment of biological tissues is of critical importance for diagnostic information. Elasticity imaging is now widely considered as a usefull technique for biological tissues characterization [16], [17]. Recently, several elasticity imaging techniques have been developped for the assessment of the mechanical properties of liver tissues and fibrosis level staging, using different imaging modalities, such as magnetic resonance elastography (MRE) [18]–[20], 2D static ultrasound elastography [21], 1D transient ultrasound elastography (FS) [22], 2D transient ultrasound elastography using acoustic radiation force impulse (ARFI) [23] and Supersonic Shear Imaging (SSI) [24]. Some of the proposed techniques involve a static compression of the liver and do not allow quantitative estimation of the liver stiffness [21]. The MRE procedure allows 2D quantitative mapping of the elastic properties of the liver with satisfying liver fibrosis staging [20]. However, as does 2D elastography based on ARFI, the expensive 2D MRE method is time consuming and needs corrections for breathing movements [25], [26]. FS is a quick estimator of the liver elastity in a mean volume of 4 cm^3 and is insensitive to respiratory motion artefacts. However, the fact that FS evaluates the liver elasticity along a single A-line can lead to biases in the elasticity measurement for heterogeneous livers [24]. Furthermore, the FS technique is not considered to be accurate enough for intermediate stages of liver fibrosis [14] and has the same performances as serum markers for early and intermediate stages of liver fibrosis [27].

In a recent paper [24], Muller *et al.* presented a feasability study of the SSI and Supersonic Shear Spectroscopy (SSS) for the quantitative mapping of human liver using a linear ultrasonic probe. This preliminary *in vivo* feasability study showed that the SSI technique is very promising and that the liver stiffness estimation on a large area (10 cm^2) using the SSI mode is fast (less than 1 s.), repeatable, and reproducible. The purpose of our clinical study is to determine the efficiency of this method for liver fibrosis level staging and prospectively compare the sensitivity and specificity of SSI with FS for staging hepatic fibrosis levels in patients with chronic liver disease. All patients have undergone LB, serum makers tests and FS, the histopathologic analysis and blood samples serving as reference.

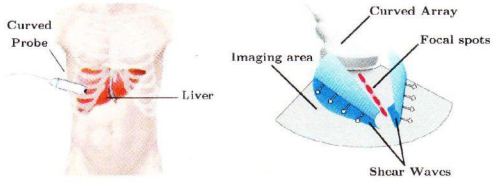
II. Material and Methods

A. Patients

A cohort of 142 consecutive patients whith chronic liver disease participated in the study after giving their informed consent. Each patient have undergone LB, FS, SSI elasticity mapping and blood tests in the gastroenterology department of Cochin Hospital (Paris, France) between 06/2008 and 06/2009. This study has been approved by the French National Committee for the Protection of Patients Participating in Biomedical Research Programs (Comité de Protection des Personnes CPP Ile de France III No. 08003), and by the ethical comittee of the Cochin Hospital. This study includes 67 men and 75 women, from 21 to 84 years old (mean age 55 ± 11.9 years), with a mean biomass index of 24.0 ± 3.8 kg.m^{-2}. 104 patients with successful measurements (blood samples, liver biopsy, FS and SSI) were included in statistical study. The patients were classified following the METAVIR score [28] ($n_{F0F1} = 42$, $n_{F2} = 22$, $n_{F3} = 18$, $n_{F4} = 22$), determined from histological analysis of LB and surrogate marker tests by two experienced pathologists blinded from SSI and FS measurements in order to keep this reference score unbiased.

B. Bidimensional transient elastography using SSI

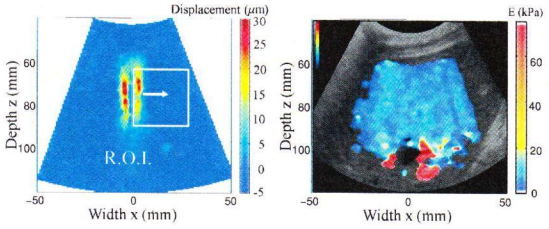
The SSI technique is based on the combination of the acoustic radiation force imaging technique and an ultrafast echographic imaging approach, allowing to assess a quantitative elasticity map of biological tissues in a single ultrasonic sequence, and has been described in detail in previous publications [29]–[31].



(a) (b)

Fig. 1. (a) Probe positioning for the SSI liver elasticity measurement - (b) Generation of a conical shear wave from pushing beams at increasing depths

The present work is the first clinical application of the SSI mode with a curved ultrasonic probe (C4-2 ATL, Seattle, WA, USA, central frequency 2.5 MHz, 128 elements). Measurements on each patients were performed on the right lobe of the liver (Fig.1(a)). The conventional curved probe generates several "pushing beams" in the intercostal space, at increasing depths of the liver tissues. A pushing beam corresponds to a remote acoustic radiation force resulting from a focused ultrasonic beam. By successively focusing beams at 5 increasing depths, a shear wave is generated and propagates in the tissues (Fig.1(b)). The operator positions the probe using a conventional realtime B-mode image in order to locate a large liver imaging area. When the target area is located, the operator launches the SSI sequence measurement, and the depth of the first pushing beam is adjusted for each patient in order to avoid pushing in the intercostal muscle region. After this remote excitation, the ultrafast echographic device acquires at a high frame rate (4000 frames/s.) IQ data using the same curved ultrasonic probe. The tissues displacement field induced by the propagation of the shear waves is then derived from these IQ data (Fig.2(a)).



(a) (b)

Fig. 2. (a) Liver tissues displacement measurement and region of interest for the shear wave dispersion calculation - (b) Corresponding elasticity map

The SSI sequence is repeated successively in 3 different directions. The 3 sequences last less than 2 s. of experiment. This results in a set of 3 propagation movies that are used to assess the liver elastic modulus ($E = \rho v_s^2$) which is directly derived from the propagation velocity(Fig.2(b)). The SSI measurement is achieved on a large bandwidth (60 Hz - 600 Hz), and the shear wave spectroscopy method [32] provides the shear wave velocity dispersion law derived from the propagation movies in the region of interest (Fig.2(a)). The all measurement, which lasts less than 1 s., is reproduced 5 consecutive times for each patient in order to test the intraoperator reproducibility. The whole examination lasts less than 3 mn.

III. Results and Discussion

A. Liver stiffness mapping

Young's modulus mapping of 4 patients liver tissues are presented in Fig.3. The stiffness is calculated from the displacements induced in the liver tissues. The elasticity mapping are superimposed with the corresponding B-mode images on which the fat and muscle region are well differentiated from the liver region, and the elasticity is only mapped in the liver region. Fig 3 *(a)*, *(b)*, *(c)* and *(d)* show respectively the elasticity mapping for patients who have been staged on fibrosis levels F1, F2, F3, and F4 using blood samples and liver biopsy. The median elasticity derived from these maps are equal to 4.78 ± 0.83 kPa for the patient with F1, 10.64 ± 1.10 kPa for patient with F2, 14.52 ± 2.20 kPa for patient with F3, and 27.43 ± 2.64 kPa for the patient with F4. The mean surface of the region in which the global elasticity is assessed for these 4 patients equals to 16.39 ± 2.77 cm^2. When compared to the size of liver stiffness evaluation using a linear probe with SSI (≤ 10 cm^2) [24], this shows that the curved array is more suitable for liver tissues than a linear probe. The curved probe introduces less biases in the measurement because it allows to image the liver tissues elasticity on a much wider and deeper area, which is a great advantage for obese patients. Furthermore, the liver heterogeneities observed in the maps are less likely to introduce biases in the elasticity measurement with SSI than with FS since the global elasticity is assessed on a much larger area (2D vs 1D).

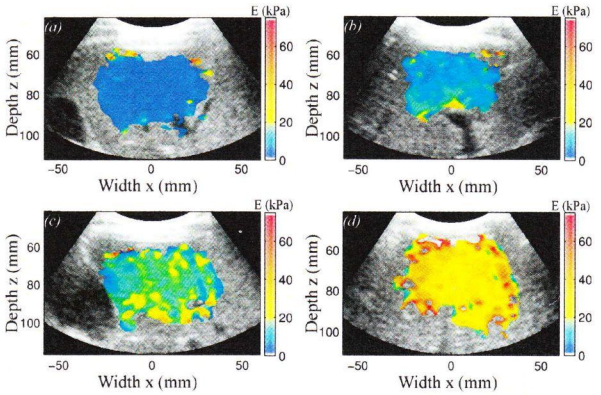
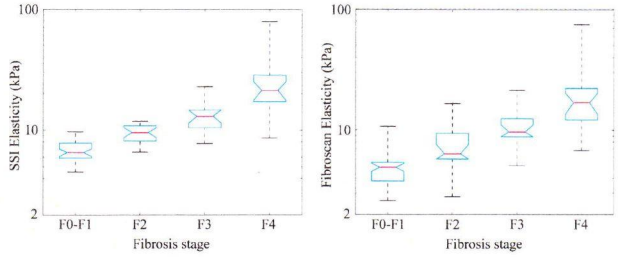


Fig. 3. Bidimensional liver elasticity maps assessed using the SSI technique superimposed to the corresponding B-Scan. The Young's modulus is represented in color levels. *(a)*: Patient 59 - F1 *(b)*: Patient 51 - F2 *(c)*: Patient 39 - F3 *(d)*: Patient 22 - F4

B. Fibrosis level staging

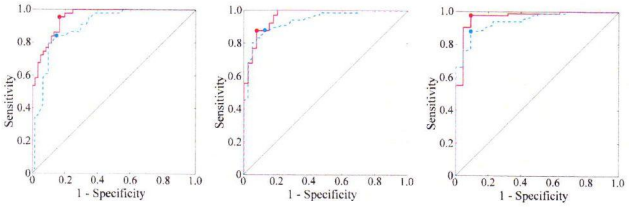
Figure 4 shows box and whisker plots of SSI elasticity values (assessed from shear wave group velocity) and FS elasticity values for each fibrosis stage for the 104 patients included in the study. The corresponding one-way Anova analysis gives a p-index of $4.44 \cdot 10^{-16}$ for SSI and $7.21 \cdot 10^{-12}$ for FS.



(a) SSI - $p = 4.44 \cdot 10^{-16}$ (b) Fibroscan - $p = 7.21 \cdot 10^{-12}$

Fig. 4. Box and whisker plots of SSI (a) and FS (b) values for each fibrosis stage.

As a consequence, SSI allows to stage fibrosis levels with a smaller variance than FS. Figure 5 shows ROC curves for different degrees of fibrosis. This Figure shows that SSI has better performances for liver fibrosis level staging than Fibroscan, for each fibrosis levels, both for specificity and sensitivity analysis. This result is confirmed by the indicators computed from the ROC analysis (Table I). As shown in Table I, the FS examination gives worse AUROCs for each fibrosis level than SSI. SSI has also a better Youden's index for each fibrosis threshold. Furthermore, the SSI method remains less biased than the FS examination, since the misclassification rate is much smaller for each fibrosis level. SSI appears to be a fast, simple, and reliable method for non-invasive liver fibrosis staging, which has better staging performances than FS for each fibrosis level, especially for intermediate stages of liver fibrosis. This analysis suggests SSI could be an efficient complementary routine examination, and avoid a liver biopsy for many patients.



(a) $F \leq 1$ vs $F \geq 2$ (b) $F \leq 2$ vs $F \geq 3$ (c) $F \leq 3$ vs $F = 4$

Fig. 5. ROC curves for SSI (red solid line) and FS (blue dashed line) for each fibrosis threshold.

Value	Method	$F \geq 2$	$F \geq 3$	$F = 4$
AUROC	SSI	0.95	0.96	0.97
	FS	0.90	0.93	0.94
Youden's index	SSI	0.79	0.81	0.89
	FS	0.69	0.75	0.78
Misclassification rate	SSI	0.11	0.09	0.03
	FS	0.15	0.12	0.11

TABLE I
AUROC, YOUDEN'S INDEX AND MISCLASIFICATION RATE FOR EACH METAVIR THRESHOLD USING SSI AND FS.

C. Shear wave spectroscopy

On contrary to FS, SSI allows a large bandwidth measurement. The shear wave dispersion law can be assessed from displacement movies using SSS in a region of interest of the liver. The SSS method consists in converting the space-time representation of the shear wave displacement into a *phase velocity* representation [32] (Fig.6*(a)-(b)*).

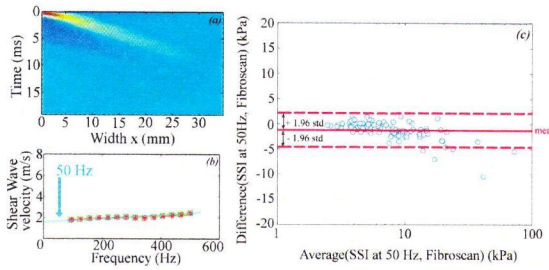


Fig. 6. *(a)* Space-time representation of the shear wave dispersion, derived from the tissues displacement movie (Fig.2(a)-(b)) Corresponding shear wave velocity dispersion, with a linear fit - *(c)* Bland-Altman analysis between SSS fitted at 50 Hz and FS measurement

The global elasticity measurement from SSI method results from the broadband (60-600 Hz) characteristic of the mechanical excitation generated using the acoustic radiation force [24], [32], whereas FS acts at a central frequency of 50 Hz, with a much smaller frequency bandwidth [22]. Thus, the global elasticity assessed by SSI makes use of higher frequency content and is also determined by the dispersive properties of the liver tissues. This emphasizes the fact that SSI provides more information than FS, because it measures the full mechanical response of the liver tissues over a large bandwidth.

Furthermore, as shown in Fig.6*(b)*, SSS allows to study the liver elasticity at each frequency, because SSI and SSS methods give access to the shear wave *phase velocity*. This information is of crucial importance when comparing the elasticity values assessed by FS and those assessed by SSI, because SSS allows to fit the shear wave dispersion at 50

Hz. This linear fit of the shear wave velocity dispersion curve was performed for each patient (Fig.6*(b)*). The corresponding liver stiffness distributions assessed by SSS fitted at 50 Hz are compared to FS measurements on Fig.6*(c)* using a Bland-Altman representation. This multivariate analysis shows a good correlation ($\chi = 0.9605$, $p < 10^{-5}$) and a good agreement (offset:, -1.23 ± 1.77kPa) between the two methods. Furthermore, the large bandwidth measurement of SSI gives to this method a strong advantage when comparing with FS.

IV. Conclusions

As a conclusion, SSI appears to be a fast, simple, reproducible and reliable method for non-invasive liver fibrosis staging. This method allows liver elasticity mapping in a large and deep area, preventing biases due to fibrosis heterogeneities, on contrary to Fibroscan. Furthermore, the large liver area mapped using a large frequency bandwidth allows better diagnostic accuracy for each fibrosis stages than Fibroscan, which is a 1D measurement that acts at a 50Hz. This suggests that SSI could be an efficient complementary examination and avoid a liver biopsy for many patients since it has good diagnosis performances for early,intermediate, and advanced stages of fibrosis. SSS is currently under strong development for liver activity staging as a complement to SSI fibrosis staging.

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