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Comparison of acoustic radiation force impulse imaging (ARFI) to liver biopsy histologic scores in the evaluation of chronic liver disease: A pilot study

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ABSTRACT

Background and aims. Acoustic Radiation Force Impulse Imaging (ARFI) is a novel non invasive technique studying the localized mechanical properties of tissue by utilising short, high intensity acoustic pulses (shear wave pulses) to assess the mechanical response (tissue displacement), providing a measure of tissue elasticity. The aim of this study is to investigate the feasibility of ARFI imaging as a non-invasive method for the assessment of liver fibrosis compared to liver biopsy scores. **Materials and methods.** A prospective blind comparison study of ARFI elastography (Virtual Touch Imaging™, ACUSON S2000 Ultrasound Unit, Siemens, Mountain View CA) in a consecutive series of patients who underwent liver biopsy for assessment of fibrosis in chronic liver disease. ARFI shear-wave propagation velocity was measured in meters per second. Mean ARFI velocities were compared with both Batts-Ludwig (F0 to F4) and Modified Ishak scores (F0 to F4) for fibrosis in liver biopsy findings. Twenty-one patients with chronic liver disease (Hepatitis C (HCV) =16, Hepatitis B (HBV) = 1, both HCV and HBV = 1 Alcoholic liver disease (ALD) = 1, others = 2) underwent ARFI and liver biopsy on the same day. **Results.** The Spearman correlation coefficients between the median values of the ARFI measurements and the histological fibrosis stage of the Modified Ishak score and Batts-Lud- ≥ wig score were both highly significant ($p < 0.01$) with rho = 0.69 and rho = 0.72 respectively. The median ARFI (total 180 replications; minimum 5, maximum 10 measurements per patients) velocities for our study population range from 0.92 to 4.17 m/sec. Areas under the receiver operating characteristic curve for the accuracy of ARFI imaging was 1.00 and 0.35, for the diagnosis of moderate fibrosis (histologic fibrosis stage, $F \geq 2$) and 0.85 and 0.85 respectively for Ishak and Batts-Ludwig score, for the diagnosis of cirrhosis. **Conclusion.** ARFI imaging has a strong correlation with the fibrosis stage of both Batts-Ludwig and shak score in chronic liver disease. It's accuracy in prediction of severe fibrosis and cirrhosis is maximal in comparison with earlier stages.

Key words. Chronic Liver Disease. Liver Biopsy. Non-invasive. ARFI. Acoustic Radiation Force Impulse Imaging.

INTRODUCTION

Early diagnosis of chronic liver disease and the negative sequelae of organ transplantation are crucial for optimal management. Histology remains the gold standard but percutaneous biopsy is not without complications, such as bleeding and infection. Acoustic radiation force impulse imaging (ARFI) is a new non invasive ultrasound based technique which has shown promising *in vivo* results suggesting that it may be useful clinically in the management of chronic liver disease although clinical studies are few and the technology is currently not licensed. Preliminary result of this study has been compared ARFI imaging with histology as the gold standard in patients with chronic liver disease.

BACKGROUND

In fibrosis and cirrhosis of the liver; pathological changes in tissue mechanical properties are known to be accompanied by stiffness changes[1]. Elastography is a relatively new ultrasound technique, which provides non-invasive information (complementary to diagnostic ultrasound and histological assessment of tissue) about the mechanical properties of tissue

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by measuring local displacements, which occur during global tissue compression.

The feasibility of established elasticity imaging methods, **i**.e. Fibroscan® (Echosens, Paris France) is well recognized, and has shown significant promise for assessment of diffuse liver disease.[2] Moreover, the technology is commercially licensed in Canada and throughout the world. However there is little data to date regarding the novel technology of ARFI compared to a gold standard histological reference standard.

ARFI is a newer technique providing non invasive information about the localized mechanical properties of tissue by utilizing short, high intensity acoustic pulses (shear wave pulses) to locally displace tissues while conventional B-mode ultrasound is used to assess the mechanical response (tissue displacement) thereby providing a measure of tissue elasticity.[3] ARFI imaging is different to elastography in that it does not depend on operator-induced compression as it uses a shear wave pulse from the transducer to compress the tissue.[4] Moreover, ARFI technology is a component of an ultrasound unit (Virtual Touch Imaging™, ACUSON S2000 Ultrasound Unit, Siemens, Mountain View, CA**)** and will allow for conventional ultrasound imaging in addition to ARFI determinations unlike the current commercially licensed elasticity technology (i.e. Fibroscan®, Echosens, Paris France).

The primary end-point of this preliminary pilot study was to determine if ARFI imaging correlated with liver biopsy histology scores in patients with chronic liver disease.

MATERIALS AND METHODS

The study was designed as a prospective blind pilot comparison study of ARFI elastography in a consecutive series of patients who underwent liver biopsy for assessment of fibrosis in chronic liver disease at the Vancouver General Hospital.

Ethics approval was obtained from the University of British Columbia Clinical Ethics Research Board.

Eligibility criteria

- **Inclusion criteria.** All patients attending for an ultrasound guided liver biopsy with a history of chronic liver disease as determined necessary by the referring physicians who were able to understand and give full informed consent.
- **Exclusion criteria**. Patients who were pregnant or breast feeding or had abnormal coagulation parameters precluding percutaneous core liver biopsy (as per internal departmental protocol: platelet count < 50,000/mL and INR > 1.4).

Ultrasound Protocol

Patients were prepared according to the Radiology Department protocol for ultrasound guided percutaneous biopsy. Patients fasted for 6 hours prior to the study. A qualified ultrasound technologist performed a standard abdominal ultrasound. ARFI imaging measurements were obtained at the same ultrasound visit and a single 18G core liver biopsy was performed.

Wherever possible the same radiologist performed the biopsies and ARFI imaging measurements in each study patient. All ultrasounds with ARFI were performed in the Ultrasound Department of the Vancouver General Hospital using an ARFI ultrasound unit (Virtual Touch Imaging™, ACUSON S2000 Ultrasound Unit, Siemens, Mountain View, CA). Radiologists had full access to the clinical history and previous imaging findings.

ARFI shear-wave propagation velocity was measured in meters per second. Ten ARFI measurements were taken on an average per patient and the average score was used.

An experienced liver histopathologist (D.O.) has been blinded to the clinical diagnosis and examined the liver histology. Each specimen has been classified according to the Batts-Ludwig and Modified Ishak scoring systems.[5,6] Mean ARFI velocities were compared with both Batts-Ludwig (F0 to F4) and Modified Ishak scores (F0 to F4) for fibrosis in liver biopsy findings.

Statistical Analysis

Statistical significance was evaluated at the conventional $\alpha = 0.05$ probability level. The ARFI measurements are presented as Mean ± Standard Deviation, and Range (also Median) in table 1. Comparative p-values by the parametric independent One-sample t-tests were used to compare the differences between mean values of the ARFI measurements of each patient and the non-replicated [one measurement per liver] histological reference standards; namely Butts-Ludwig inflammation score [B1], Butts-Ludwig fibrosis score [B2], Ishak modified inflammation grade[I1]and Ishak modified stage [I2]. The parametric Paired t-tests and Pearson's correlations (2-tailed) were applied to compare the

Table 1. Patient data including primary liver disease, ARFI measurements and histologic scores.

Patient#	Diagnosis	n	ARFI-Mean	ARFI-Median	B1	B2	I1	I2
1	AIH/PBC	10	3.412	3.290	2	4	7	4
2	HCV	10	1.135	1.035	1	1	2	1
3	HCV	10	1.110	0.970	2	2	6	1
5	HCV	10	1.489	1.510	2	2	5	1
6	AIH	10	1.369	1.415	1	1	4	1
7	HCV	10	1.375	1.375	1	1	3	1
8	HCV	6	1.050	1.075	2	2	2	1
9	HBV/HCV	9	2.088	1.340	2	2	4	1
10	HCV	10	2.390	1.995	3	3	7	3
11	HCV	6	3.795	3.935	3	3	9	2
13	HCV	6	2.125	2.255	3	3	9	3
14	HCV	5	3.294	4.170	2	3	6	2
18	HCV	9	1.718	1.740	3	4	8	4
19	HCV	10	1.432	1.425	2	2	1	1
20	HCV	10	1.236	1.165	1	1	2	1
22	HCV	10	0.848	0.920	1	1	4	1
23	HBV	7	1.267	1.220	1	0	2	0
24	HCV	6	1.197	1.190	2	1	2	1
25	ALD	6	3.318	3.390	3	4	9	4
26	HCV	10	1.311	1.310	3	3	6	3
27	HCV	10	1.096	1.130	2	1	3	1

HCV: Hepatitis C. HBV: Hepatitis B. ALD: Alcoholic liver disease. AIH: Auto immune hepatitis. PBC: Primary biliary cirrhosis. **P#:** Case Identification, serial number/liver. **n:** number of replications. **ARFI-Mean:** Value of the Mean of Acoustic Radiation Force Impulse Imaging measurements per liver. **ARFI-Median:** Value of the Median of Acoustic Radiation Force Impulse Imaging measurements per liver. **B1:** BATTS-LUDWIG: Grade (inflammation score) - ONE measurement/liver No replications were done; [scale 0-4]. **B2:** BATTS-LUDWIG: Stage (fibrosis score) - ONE measurement/liver No replications were done; [scale 0-4]. **I1:** ISHAK score: Grade only - Test value: ONE measurement/liver No replications were done; [scale 0-18]. **I2:** ISHAK score: Modified stage - ONE measurement/liver No replications were done; [scale 0-4].

Mean ARFI measurements with the histological gold standards [B1, B2, and I1, I2]. Non-parametric Spearman correlations (2-tailed) were also used to compare the Median ARFI measurements with the three histological gold standards.

The diagnostic Accuracy of the Median ARFI measurements values were experimented with the Receiver Operating Characteristics Curve (ROC) and evaluated as the areas under the curves for various fibrosis stages. Statistical analyses were performed with the SPSS version 17.0 software package (SPSS Inc. Chicago, Illinois).

RESULTS

Twenty one patients with chronic liver disease (Hepatitis C (HCV) =16, Hepatitis B (HBV) =1, both HCV and HBV = 1 Alcoholic liver disease (ALD) = 1, others = 2) underwent ARFI and liver biopsy on the same day (Table 1). The Spearman correlation coefficients between the median values of the ARFI measurements and the histological fibrosis stage of the Modified Ishak score and Batts-Ludwig score were both highly significant ($p < 0.001$) with rho = 0.69 and rho = 0.73 respectively. The median ARFI (total 180 replications; minimum 5, maximum 10 measurements per patients) velocities for our study population range from 0.92 to 4.17 m/s. Areas under the receiver operating characteristic curve for the accuracy of ARFI imaging was 1.00 and 0.35, for the diagnosis of moderate fibrosis (histologic fibrosis stage, $F \geq 2$) and 0.85 and 0.85 respectively for Ishak and Batts-Ludwig score, for the diagnosis of cirrhosis. For inflammation scores the correlation rho = 0.56 ($p = 0.008$). The value of the correlation was lower than fibrosis scores with Batts-Ludwig or with Modified Ishak scoring system, but it was still statistically significant. Due to the relatively small numbers of patients enrolled in this preliminary pilot study, threshold ARFI values for the different histologic scores were not determinable.

DISCUSSION

Imaging and histopathological assessment play a major role in the clinical assessment of patients with chronic liver disease and the complications of

organ transplantation. Early identification of significant target organ damage (i.e. advanced fibrosis) in this diverse group of patients is essential to initiate appropriate clinical decision making. Liver biopsy is the current gold standard for the assessment of chronic liver disease but is not without problems: a small but significant risk of severe complications and false negative results (reported in high as 30% of biopsy samples).[8] Ultrasonography has a reported accuracy of 82-88% in the diagnosis of hepatic fibrosis and cirrhosis.[9] Newer imaging techniques, such as elastography (ie. Fibroscan® and ARFI) have been developed to provide an alternative non invasive and accurate method of assessment of liver fibrosis.

Unlike Fibroscan® the current clinical experience with ARFI in liver disease is still very limited. Preliminary quantitative *in vivo* results, however, suggest that the ARFI method may be useful clinically.[10] The utility of ARFI imaging has been demonstrated for abdominal applications,[11] and in particular in the assessment of diffuse liver disease,[11] particularly chronic viral hepatitis. Recent data suggests that it may have a diagnostic accuracy comparable to that of transient elastography.[12] It is also suggested that ARFI imaging improves visualization of malignancies in the liver and kidney compared to the use of conventional US alone.[11] The experience with ARFI in terms of correlation with liver histology, however, is still very much in its early stages, hence our decision to undertake this pilot study to determine the potential feasibility of ARFI at our hospital with "real world" patients drawn from clinical practice. We note that the ability to measure bulk liver stiffness whilst simultaneously screening for focal lesions of the liver/abdomen with conventional ultrasound imaging, as well as intra-abdominal doppler flow studies, is one potential advantage not currently associated with any other ultrasound-based methods of imaging tissue elasticity.[11] If ARFI is determined to be reliable, then a combined ARFI, conventional diagnostic imaging at a single patient encounter would allow for greater clinical convenience to both the patient and health care providers than the need to undergo both transient elastography (Fibroscan®) and a conventional ultrasound imaging on separate occasions. It may also be more cost effective for centres to acquire an ultrasound machine with ARFI technology than to acquire both transient elastography and conventional diagnostic ultrasound units.

CONCLUSION

In our preliminary pilot study, ARFI imaging appears to have a significant correlation with the fibrosis stage of both Batts-Ludwig and Ishak score in chronic liver disease. Future studies are needed to determine threshold ARFI values for each histologic, especially fibrosis, stage.

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DISCLOSURES

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