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Ultrasound in Med. & Biol., Vol. ■, No. ■, pp. 1–8, 2015

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2015.05.006

- *Original Contribution*

IMPACT FACTORS AND THE OPTIMAL PARAMETER OF ACOUSTIC STRUCTURE QUANTIFICATION IN THE ASSESSMENT OF LIVER FIBROSIS

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(*Received* 16 *December* 2014; *revised* 30 *April* 2015; *in final form* 5 *May* 2015)

Abstract—The aims of the present study are to assess the impact factors on acoustic structure quantification (ASQ) ultrasound and find the optimal parameter for the assessment of liver fibrosis. Twenty healthy volunteers underwent ASQ examinations to evaluate impact factors in ASQ image acquisition and analysis. An additional 113 patients with liver diseases underwent standardized ASQ examinations, and the results were compared with histologic staging of liver fibrosis. We found that the right liver displayed lower values of ASQ parameters than the left (p = 0.000–0.021). Receive gain experienced no significant impact except gain 70 (p = 0.193–1.000). With regard to different diameter of involved vessels in regions of interest, the group ≤2.0 mm differed significantly with the group 2.1–5.0 mm (p = 0.000–0.033) and the group >5.0 mm (p = 0.000–0.062). However, the region of interest size (p = 0.438–1.000) and depth (p = 0.072–0.764) had no statistical impact. Good intra- and inter-operator reproducibilities were found in both image acquisitions and offline image analyses. In the liver fibrosis study, the focal disturbance ratio had the highest correlation with histologic fibrosis stage ($r = 0.67, p < 0.001$). In conclusion, the testing position, receive gain and involved vessels were the main factors in ASQ examinations and focal disturbance ratio was the optimal parameter in the assessment of liver fibrosis. (E-mail: wangw73@mail.sysu.edu.cn) © 2015 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Acoustic structure quantification, Morphology, Ultrasound, Elastography, Liver fibrosis.**

Early diagnosis of liver fibrosis is important for the prognosis and clinical management of patients with chronic liver diseases (EASL 2012, 2014). Because of its ease of use and wide availability, ultrasound (US) provides an ideal non-invasive assessment of liver fibrosis. A major advance in predicting the stage of fibrosis has been the development of elasticity-based US techniques (Berzigotti and Castera 2013; Piscaglia et al. 2014), including transient elastography, acoustic radiation force impulse elastography and shear wave elastography. As surrogate markers of fibrosis, they have paved the way to quantitatively assess liver stiffness (Castera et al. 2008; Piscaglia et al. 2014). High diagnostic accuracy for fibrosis (especially for cirrhosis) has been reported (Ferraioli et al. 2012; Friedrich-Rust et al. 2008; Zhang et al. 2015).

Liver stiffness is a biological and mechanical property correlated with its pathologic process (Gao et al. 1996; Wells and Liang 2011) but not the fibrosis itself. Morphologic changes, including the formation of septa and nodules, are considered major factors in the pathologic scoring systems for fibrosis (Goodman 2007). Therefore, beyond what is provided by elastography, morphologic US technology can provide new and valuable information for liver fibrosis assessment. However, conventional B-mode US techniques for evaluating liver morphologic characteristics have limited accuracy in detecting mild to significant fibrosis (Aube et al. 1999; Kudo et al. 2008).

A recently developed real-time US-based technique, acoustic structure quantification (ASQ) software, may provide a better measure of morphology. ASQ is based on the statistical processing of scattered echo signals to estimate the local heterogeneity of the liver structure

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(Toyoda et al. 2009). To our knowledge, only three studies in English literature have been published on ASQ of liver fibrosis (Kramer et al. 2014; Ricci et al. 2013; Toyoda et al. 2009). Preliminary studies found a positive correlation between ASQ parameters and the METAVIR stages of fibrosis (Ricci et al. 2013; Toyoda et al. 2009). However, the standardization of scanning and analysis procedures was not defined, such as specifications for the definition of large vessels and the transmit focus and imaging depth. Furthermore, several new parameters are now available in the latest version of the ASQ software and it is necessary to attempt to define the optimal parameter.

The objectives of this prospective study were twofold: (i) to assess the factors important to establish a standard methodology for ASQ and (ii) to define the optimal parameter of ASQ in fibrosis assessment, with the histologic stages of fibrosis as the reference standard.

MATERIALS AND METHODS

Patients

From January to February 2013, 20 healthy volunteers, which included hospital staff and college students, visiting the hospital for a medical checkup were recruited. The volunteers had no significant medical history of liver disease and systemic disease. They also had no history of chronic drug abuse or excessive alcohol consumption (defined as >30 g/d for men and >20 g/d for women).

From March to August 2013, 161 consecutive adult patients scheduled for liver biopsy or partial liver resection were prospectively recruited. The exclusion criteria were as follows: (i) presence of the focal liver lesion on segment V or VI of the liver (n = 40); (ii) presence of dilated intrahepatic bile duct (>2.0 mm) in the right lobe of the liver (n = 4); and (iii) inadequate liver biopsies (n = 4). The final cohort comprised 113 patients. All patients underwent clinical examinations, US examinations and biological tests within 2 wk before liver biopsy or surgery.

The study protocol was approved by the ethics committee in our hospital, and written informed consent was obtained from all participants.

B-mode US examination

All participants, lying in dorsal decubitus with right arm in maximal abduction, underwent a standard-care US examination including an extra standardized acquisition of US images for ASQ analysis. Each scan was performed with an Aplio 500 ultrasound scanner (Toshiba Medical Systems, Osaka, Japan) and a frequency of 3.7–5.5 MHz convex transducer (PVT-375 BT, Toshiba Medical Systems). For ASQ examination, the image depth and transmit focus were fixed at 6 cm and 4 cm, respectively. The transducer was applied on the same cross-section of liver for an interval of 3 s during breath-holding, and a video including a series of 21 consecutive US images would be recorded digitally with raw data. During the measurement, intrahepatic vessels and the gallbladder were avoided.

ASQ analyses

Offline analysis was performed through its own program in Version 1.11R001 (Fig. 1). Up to four regions of interest (ROIs) could be drawn on one image so that large structures would be avoided. The detailed principles of ASQ imaging are described in previous studies and the manufacturer's documentation (Kuroda et al. 2012; Toyoda et al. 2009). ASQ is based on the statistical χ^2 test of receiving echo signals of raw data (Toyoda et al. 2009). Normal liver tissue structures are smaller than the wavelength of the US signals used in clinical examination, and the echo amplitude in normal liver is statistically approximated to a Rayleigh distribution (Toyoda et al. 2009). However, fibrotic structures, including cirrhotic nodules, develop to become larger than the US wavelength. Consequently, the echo signals from fibrotic liver tend to be inconsistent with the Rayleigh distribution (Toyoda et al. 2009; Tuthill et al. 1988). Therefore, differences in the statistical measures obtained using ASQ could be used to quantitatively assess morphologic changes caused by liver fibrosis. Once a primary ROI is set manually on the image, hundreds of second ROIs are automatically set sweeping the primary ROI to complete the analysis. The basic analysis parameter, defined as C_m^2, measures the difference between the theoretical and observed distributions of echo amplitude. It is calculated according to all samples within a second ROI, and all the results for C_m^2 were plotted on a histogram. The C_m^2 occurrence histogram consists of a red line representing focal structures homogeneous or diffuse inhomogeneous, and a blue line standing for focal inhomogeneous. Final analysis data contain peak, average and standard deviation (SD) of the C_m^2 values, expressed as total mode, total average, red mode, red average, red SD, blue mode, blue average and blue SD. Focal disturbance (FD) ratio is defined as the ratio of the area under the blue line and red line.

Study design

We studied various impact factors in 20 healthy volunteers, including the testing position of the liver, receive gain, involved vessels and ROI size and depth and set the standardized testing condition as described in the following section. The intra- and inter-operator reproducibility in both image acquisitions and offline images analyses was also studied. Another 113 patients were