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● *Original Contribution*

NORMAL LIVER STIFFNESS IN HEALTHY ADULTS ASSESSED BY REAL-TIME SHEAR WAVE ELASTOGRAPHY AND FACTORS THAT INFLUENCE THIS METHOD

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Abstract—Real-time shear wave elastography (SWE) is a novel two-dimensional elastographic method that is used to estimate the severity of liver fibrosis. However, the normal range of liver stiffness (LS) and the possible factors that influence SWE are not well understood. The aims of the current study are to define the normal range of LS in healthy subjects and to explore the factors that may affect SWE. A total of 509 healthy subjects underwent SWE to determine the stiffness of their livers, and the effects of gender, age and body mass index (BMI) on LS were analyzed. The effects of different factors on SWE, including the testing position, measurement depth and size of the region of interest (ROI), were analyzed in 137 subjects. SWE imaging was successfully performed in 502 healthy subjects (98.6%, 502/509). The mean value of the SWE measurements in 502 individuals was 5.10 ± 1.02 kPa, and the 95% confidence interval was 5.02–5.19 kPa (range: 2.4–8.7 kPa). We found that the detective position within the liver had a significant impact on the liver stiffness measurement (LSM), and the lowest coefficient of variation (CV = 8%) was obtained for LSMs made at segment V. LS was greater at a depth >5 cm (5.78 ± 1.66 kPa) compared with depths ≤5 cm (4.66 ± 0.77 kPa, $p < 0.001$); LS was also greater in men than in women (5.45 ± 1.02 kPa vs. 4.89 ± 0.96 kPa, $p < 0.001$). However, there were no significant differences in the LS values regarding the size of the ROI, age or BMI (all $p > 0.05$). The mean LS value in all 502 healthy subjects was 5.10 ± 1.02 kPa. The mean LS value obtained by SWE was not influenced by the size of the ROI, age or BMI, but the mean value was significantly influenced by the different segments of the liver, the detection depth and gender. (E-mail: zhengrq@mail.sysu.edu.cn) © 2014 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Liver stiffness measurement, Elastography, Shear wave elastography, Normal, Non-invasive diagnosis, Liver fibrosis, Healthy volunteers.**

INTRODUCTION

Liver fibrosis is a progressive process that advances from all types of chronic liver diseases, including chronic viral hepatitis, chronic alcoholic liver disease, and non-alcoholic fatty liver syndrome (Abdel-Hady and Kelly 2013; Basaranoglu et al. 2013; Verbeek et al. 2013). Successfully detecting and managing liver fibrosis at an early phase can significantly improve the prognosis of patients in clinical practice (Belongia et al. 2008; de Franchis et al. 2003); therefore, accurately assessing the degree of fibrosis when the disease is at an early stage is extremely important. Currently, liver biopsy is the "gold standard" for diagnosing liver fibrosis and cirrhosis, but biopsy is invasive and has a potential risk of causing bleeding and infection. In addition, liver biopsy has the following shortcomings (Grizzi et al. 2006; Persico et al. 2002; Ratziu et al. 2005; Vuppalanchi et al. 2009): The tissue biopsy specimen can be too small to minimize sampling error, and there is often a difference between different observers regarding the diagnosis. Thus, non-invasive methods that are expected to replace liver biopsy have recently been developed, including transient elastography (TE), acoustic radiation force impulse (ARFI), real-time tissue elastography (RTE) and real-time shear wave elastography (SWE). SWE is the newest of these methods and has the following advantages: real-time two-dimensional (2-D) imaging, simple operation and quantitative measurements. (Bavu et al. 2011). Some

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Conflicts of interest: None of the authors has a financial relationship with any commercial entity that has an interest in the subject of this manuscript.

studies have indicated that SWE performs well in the non-invasive diagnosis of liver fibrosis (Bavu et al. 2011; Ferraioli et al. 2012). However, few studies have investigated the normal range of liver stiffness measurements (LSMs) (Sirli et al. 2013).

Therefore, the primary aim of this study is to define the normal range of LS in healthy livers and to explore the factors that may influence SWE, including the testing position, body position, measurement depth and size of the region of interest (ROI); the secondary aim is to determine the effects of gender, age and BMI on liver stiffness (LS).

MATERIALS AND METHODS

Subjects

After providing a complete description of the study to all potential subjects, written informed consent was obtained in accordance with the National Health and Medical Research Council guidelines. This study was approved by the ethics committee at the Third Affiliated Hospital of Sun Yat-sen University. From April 2010 to December 2012, 705 subjects, which included patients, hospital staff and college students, were recruited from the physical examination center at the Third Affiliated Hospital of Sun Yat -sen University. No volunteer had a history of liver disease or systemic disease. All subjects underwent clinical examination, ultrasound examination, and laboratory examinations. Laboratory examinations included tests for viral markers (hepatitis B virus [HBV], hepatitis C virus [HCV]), serum aspartate aminotransferase and alanine aminotransferase (AST and ALT), total bilirubin, serum albumin concentrations, platelet counts and prothrombin activity. A total of 196 subjects were excluded because of alcohol abuse, abnormal laboratory tests or evidence of liver disease on ultrasound examination (fatty liver, n = 43; liver tumor, n = 5) (Fig. 1).

We evaluated the LSMs in 502 healthy subjects (7 subjects were excluded because of technical failures) and analyzed the effects of age, sex and BMI on the LSM. A subset of subjects (n = 137) were included to study multiple factors that could influence SWE, such as the test position, body position, measurement depth and size of the ROI.

B-mode ultrasound examination

All participants underwent a B-mode liver ultrasound scan before the SWE examination. The exams were conducted by two experienced ultrasound physicians (Z.P.H. and J. Z.). Each scan was performed with a Supersonic Imagine Aixplorer ultrasound system (Aix-en-Provence, France) that was equipped with an SC6-1 convex array probe with a frequency of 1–6 MHz. The software version was 4.2.18123.

SWE examination

The same scanner and transducer was used for the SWE examinations. All subjects fasted for more than 8 h before the examinations. The subjects raised their right arms from a supine or left decubitus position, and they were required to hold their breath for 3–5 s before the SWE examination. During the measurement, intrahepatic vessels and the gallbladder were avoided. The color SWE images were captured and frozen, and the circular quantitative sampling frame was initiated to measure the elastic modulus of the liver in the ROI. The system automatically calculated the mean value of the elastic modulus (unit: kPa) within the ROI. The detection was repeated three times under various conditions, and the mean values of the elastic modulus were recorded for the statistical analysis. The ROI diameter was set to 20 mm.

Study design

We studied various impact factors in 137 subjects, including segment, depth, body position and ROI size. Based on the best segment for assessment, we expanded the study to include another 365 subjects, for a total of 502 subjects. For these subjects, the testing conditions were standardized as described in the following section.

Study of testing conditions (n = 137). The following conditions were tested. (1) Different segments: With the subjects in a supine position, six liver segments were measured, including the left lateral lobe (segments II or III), segment IV, segment V, segment VI, segment VII and segment VIII. (2) Depth: With the subjects in a supine position, the right lobe was selected, and the depth was measured in two groups based on the distance from the liver capsule (≤5 cm and >5 cm). (3) Body position: Liver segment VI was detected with the subjects in a supine position followed by a left decubitus position. (4) ROI size: With the subjects in a supine position, liver segment V was selected, and the detection was performed in two groups selected based on the diameter of the ROI (10 mm and 20 mm).

Study of normal values of LSM, age, gender and BMI (n = 502). Based on the previously described impact factor study, we chose segment V as the best site for collecting consistent data, the best distance from the liver capsule as ≤5 cm and the best position of the subjects as a supine position. The subjects were divided into five groups according to age: 18–29 years, 30–39 years, 40–49 years, 50–59 years and older than 60 years. The subjects were divided into three groups according to BMI (WHO Expert Consultation 2004): underweight with a BMI < 18.5, normal weight with a BMI between 18.5 and 24.9, and overweight with a BMI between 25 and 29.9.