Ultrasound in Med. & Biol., Vol. ■■, No. ■■, pp. ■■–■■, 2017

0301-5629/$ - see front matter

https://doi.org/10.1016/j.ultrasmedbio.2017.08.1885

● *Original Contribution*

TRANSTEMPORAL INVESTIGATION OF BRAIN PARENCHYMA ELASTICITY USING 2-D SHEAR WAVE ELASTOGRAPHY: DEFINITION OF AGE-MATCHED NORMAL VALUES

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(*Received* 26 *July* 2017; *revised* 23 *August* 2017; *in final form* 28 *August* 2017)

Abstract—The goal of our research was to assess the possibility of reliable investigation of brain tissue stiffness using ultrasonographic brain parenchyma elastography with an intact temporal bone. We enrolled 108 patients after exclusion of intracranial pathology or healthy volunteers. All patients were subdivided by age into groups: 20–40, 40–60 and >60 y. For statistical analysis, the χ^2 test and *t*-test were used. The mean values, regardless of age and other parameters, were 3.34 kPa (SD = 0.59) on the left side and 3.33 kPa (SD = 0.58) on the right side. We found no correlation between the values, body mass index (r = 0.07, *p* = 0.48) and sex (t = –0.11, *p* = 0.91), but we observed a highly significant correlation between the values and age (r = 0.43, *p* < 0.0001). We found ultrasonographic brain parenchyma elastography to be a valid, reproducible and investigator-independent method that reliably determines brain parenchyma stiffness. Normal values should serve as a reference for studies on various intracranial lesions. (E-mail: Michael.Ertl@klinikum-augsburg.de) © 2017 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: **2-D- shear wave elastography, Brain elastography, Transtemporal ultrasound, Stroke.**

INTRODUCTION

Ultrasonographic shear wave elastography measures local tissue stiffness, analyzing ultrasound-induced shear wave propagation. The ultrasound probe generates a localized radiation force, which induces shear waves that propagate from that focal point directly in the tissue of interest. Propagation speed of shear waves is directly related to the elasticity of tissues. This propagation is slower in soft tissue than in a stiff region (Bamber et al. 2013). This technique is already used in a variety of medical disciplines: to determine the grade of liver cirrhosis (Sandrin et al. 2003); in the staging of prostate carcinomas (Sarvazyan et al. 2011); or in the investigation of various pathologies of the thyroid gland (Vorlander et al. 2010), the lymph nodes (Xu et al. 2011) or the breast parenchyma (Garra et al. 1997).

The importance of brain parenchyma elastography has been evaluated in various types of brain pathologies—for example, neoplastic (Shiroishi et al. 2016), inflammatory (Enzinger et al. 2015) or degenerative (Wang et al. 2013) processes—using magnetic resonance elastography, although data about ultrasound elastography remain scarce. A few studies have investigated brain tissue elasticity by ultrasound brain parenchyma elastography (uBPE), mainly in the neurosurgical field, where various entities of brain tumors (*e.g.,* meningiomas, low-grade gliomas, high-grade gliomas and metastases) were studied intra-operatively (Chauvet et al. 2016), with the surrounding bone having been removed earlier. These preconditions lead to a restriction in applicability for patients in need of surgery. Recently, normal values were established from various brain regions of neonates, applying the slightly different approach of acoustic radiation force impulse imaging. Of course, the neonates were examined *via* the fontanelles without the obstruction caused by the skull. Values were dependent on age and brain region (Su et al. 2015).

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To the best of our knowledge, no scientific findings report the possibility of reliable investigation on brain tissue, applying uBPE in the presence of an intact skull. Few, but encouraging, data are available from animal research (Xu et al. 2013), with values of healthy brain tissue ranging 4.32–4.49 kPa.

The objective of this study was to evaluate whether brain parenchyma elasticity can be measured reliably in persons with an intact temporal bone. Possible applications of uBPE might be the preclinical discrimination of hemorrhagic and ischemic strokes to accelerate clot-dissolving therapy according to the *time is brain* concept and the evaluation of the compression of vital brain tissue by mass lesions, such as intra-cerebral bleedings.

MATERIALS AND METHODS

The study protocol was approved by the medical institutional review board at the Clinic of Augsburg (No 2016-23) in accordance with the guidelines of the Declaration of Helsinki. All patients or their legal representatives provided written informed consent before enrollment.

Study population

Between September 2016 and March 2017, patients and healthy volunteers were enrolled in this prospective study. In total, 108 subjects were examined. For patient inclusion, the presence of a relevant intra-cranial pathology had to be excluded by sufficient cerebral imaging (computed tomography [CT] or magnet resonance imaging [MRI]). Only patients with exclusively peripheral neurologic symptoms were eligible. We recruited 11 patients. Their diagnoses and numbers were as follows: benign paroxysmal positional vertigo (n = 3), vestibular neuritis (n = 1), Guillain-Barré-syndrome (n = 2), Miller-Fisher-syndrome (n = 1), myopathy (n = 1), thoracic-outlet syndrome (n = 1) and conversion disorder (n = 2). Not included in the study were 3 patients with confirmed hemorrhagic (n = 1) and ischemic (n = 2) stroke. They were used as examples for values in damaged brain tissue. Neuroimaging evaluations were conducted by specialized neuroradiologists.

Transtemporal ultrasound brain parenchyma elastography

For ultrasound examination a 1.5–4.4 MHz convex ultrasound transducer (Model C5-1, Philips, Amsterdam, Netherlands), normally used for abdominal ultrasound, was employed because our standard sector transducers, normally used for transcranial ultrasound, were not equipped for tissue elastography analysis. For shear wave elastography, the specific mode of the Philips iU22 machine was applied. The transducer was placed on the temporal margin of the patient's skull for evaluation of the transtemporal bone window. In the presence of a proper bone window, the usual landmarks for identification of the midbrain plane were clearly visible. Elastography measurements (EMs) were only performed if all the relevant landmarks for the identification (*e.g.,* visualization of the midbrain peduncules) were on display. Patients with no proper bone window were excluded from the study. B-mode and shear wave elastography images were acquired bilaterally, if possible.

To ensure exact and reproducible measurements of brain parenchyma, a standardized examination depth of 3–4 cm in the midbrain plane was defined to gain information about subcortical brain tissue. This region was selected because it was most easily accessible through the transtemporal bone window. During data acquisition, patients were asked to hold their breath to ensure as few artifacts as possible. For EMs, a box with fixed dimensions of 1.0×0.5 cm was used, predefined in the elastography settings of the ultrasound machine.

In every case, measurements were either performed by a single experienced examiner accredited by the German Medical Ultrasound Society or supervised by this specialist. To reduce measuring intolerances, the examination was repeated at least two times by the same examiner. For illustration of exemplary values in damaged brain tissue (three patients), EM was also performed in regions of ischemic and hemorrhagic strokes, predefined by alternative imaging (CT).

Safety considerations

As noted earlier, 2-D shear wave elastography is already in widespread use for other parenchymatous organs without any relevant risks and is recommended by the respective guidelines (Barr et al. 2015, 2017; Cosgrove et al. 2017; Ferraioli et al. 2015; Shiina et al. 2015). Additionally, reliable data for the use in brain tissue were supplied by experimental animal studies (Li et al. 2016). No adverse effects were reported in neurosurgical investigations with the protective scull having been removed (Chauvet et al. 2016). Investigations were performed according to the *as low as reasonably achievable* (ALARA)-radiation safety principle (Toms 2006).

Statistical analysis

Statistical analysis was performed, using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). As not all patients had a sufficient temporal bone window on both sides, there were 9 patients who could only be investigated unilaterally. These patients were included with the available data. Structural equality of patients evaluated by each investigator were compared with respect to sex and age group (20–40 y, 40–60 y and >60 y), using a Chi-square test. Age and body mass index (BMI) were analyzed using *t*-tests, and Pearson's correlation coefficient was used for showing correlation of age and BMI with EM values. Possible influence of the sequence and the side of measurements were evaluated by a mixed model for