Evaluation of the healthy median nerve elasticity
Feasibility and reliability of shear wave elastography

Bihui Zhu, BS\textsuperscript{a}, Feng Yan, PhD\textsuperscript{b}, Ying He, BS\textsuperscript{a}, Liyun Wang, BS\textsuperscript{a}, Xi Xiang, BS\textsuperscript{a}, Yujuan Tang, BS\textsuperscript{a}, Yujia Yang, BS\textsuperscript{a}, Li Qiu, MD\textsuperscript{a,∗}

Abstract
The present study applied the shear wave elastography (SWE) to the median nerve in order to investigate the feasibility and reliability of its use in 40 healthy volunteers. Shear wave velocities of the median nerve on bilateral forearms and right carpal tunnel were obtained with relaxing or stretching conditions. The inter- and intraobserver agreement coefficients and differences of nerve elasticity among groups were evaluated using intraclass correlation coefficients, the paired t test, and the Wilcoxon signed-rank test, respectively. The stiffness of the site was expressed by 3 types of values: mean, minimum, and maximum shear-wave velocities. The inter- and intraobserver agreement coefficients were excellent (0.852–0.930) on the right forearm. No differences were detected between the bilateral forearm (mean: $P = .14$), while the values of different body sites and postures were statistically different ($P < .001$). SWE, as a noninvasive and objective tool, reached a good consistency in evaluating the healthy median nerve. Further studies are essential to investigate the detailed influencing factors and provide an insight of SWE to estimate both the normal nerve and peripheral neuropathy.

Abbreviations: ARFI = acoustic radiation force impulse elastography, EUS = elastography ultrasound, ICC = intraclass correlation coefficients, ROI = region of interest, SWE = shear wave elastography, US = ultrasonography.

Keywords: elasticity, inter- and intraobserver agreements, median nerve, shear wave elastography

1. Introduction
In the peripheral nervous system, the connective tissue is constituted of 3 layers: the epineurium, the perineurium, and the endoneurium. The axon, basic component of peripheral nerves, is wrapped by the endoneurium. Groups of these axons form the nerve fascicles surrounded by the perineurium that contains collagen fibers, fibroblasts, and vessels, which in turn are joined together within another layer known as the epineurium. The anatomy endows peripheral nerves with viscoelasticity, and this mechanical property may protect the nerve to resist mechanical stress, as well as provide abundant information about diagnosis and classification of peripheral nerve pathologies.\cite{1–5} Peripheral neuropathies refer to a group of disorders and can be divided broadly into traumatic and nontraumatic neuropathies, including entrapment, inflammation, neoplasm,\cite{4} and complication of systemic diseases.\cite{6–7}

Previous studies have investigated the value of existing diagnostic methods of peripheral nerve pathologies. The diagnosis is initially on the basis of characteristic symptoms, but an asymptomatic presentation can occur in patients.\cite{16,7} Electrophysiological test is considered the reliable method for peripheral neuropathies, but just efficiently for the abnormalities of large nerve fibers, and cannot detect small fiber neuropathy because the absence or reduced myelin of small fibers results in slow conduction velocities that are beyond the resolution of these studies.\cite{8–10} In addition, this assay is as time-consuming and expensive as magnetic resonance imaging.\cite{11–14} Since the first report of the application of ultrasonography (US) for carpal tunnel syndrome in 1992, US examinations have been used as a complementary test for peripheral nerve pathologies.\cite{11} The peripheral nerve has a relatively mixed hyperechoic and hypoechoic appearance in US, which provides a noninvasive assessment of peripheral nerve pathologies with respect to morphology and localization.\cite{15,16} Although there are advantages of the nerve US, the qualitative result and wide range sensitivity and specificity limit the potential development.\cite{14}

Thus, utilizing the elastography ultrasound (EUS) to quantitatively assess the elasticity of the peripheral nerve may serve as an alternative method. The structure and composition of the tissue determine its deformation and rehabilitation capability, which is characterized by the elasticity. EUS is a technique based on this biomechanical property that evaluates the elasticity of the tissues after an external or internal stimulus imposed on the target tissues.\cite{15} Currently, several elastography techniques are applied, such as strain EUS, shear wave EUS (SWE), acoustic radiation force impulse EUS (ARFI), and transient EUS.\cite{17} Although strain EUS is the most common and cost-effective technique, the result is qualitative and largely dependent on the examiners.\cite{18} ARFI is an alternative type of strain EUS that does not use any mechanical pressure. It generates a shear wave in the
target area by focused ultrasound beam and acquires a quantitative result with shear wave velocities. SWE is equipped with both color-coded qualitative elastograms and quantitative maps of shear wave velocity. This method is based on the different physical principles stating that the shear wave is caused by the ultrasound impulse. In addition, the shear wave velocity, such as ARFI, is calculated automatically in a region of interest (ROI) in this map for the tissue stiffness. Simultaneously, the Young module of elasticity is obtained by the formula \( E = \frac{3 \times V^2}{2} \), where \( E \) is Young module in kPa and \( V \) is the shear wave velocity in m/s.

Although several studies describe EUS for the evaluation of the peripheral nerves in peripheral neuropathies, such as carpal tunnel syndrome or diabetic peripheral neuropathy, SWE is considered more objective than strain EUS and still less utilized. The present study used SWE to explore the reliability and feasibility of measuring the median nerve elasticity in healthy volunteers. In order to gain a better understanding of SWE in the detection of nerve elasticity and provide the methodological basis for the further study of peripheral nerves in pathological conditions, the intra- and interobserver reproducibility, the difference in nerve stiffness of different postures, the difference between right wrist and right forearm, and the difference in the bilateral forearms were investigated.

2. Materials and methods

2.1. Participants

A total of 40 healthy subjects were enrolled in the present study from November 2016 to April 2017. Volunteers were excluded if they presented a history of systemic neurological disorders, post-traumatic changes to nerves, nerve tumors, nerve entrapment syndromes, musculoskeletal disorders, or other systemic metabolic disease. The study was approved by the West China Hospital of Sichuan University Ethics Committee, and informed consent was obtained from all participants.

2.2. Positioning

During examinations, the room was temperature-controlled and silence maintained. For imaging of the median nerve, each subject was asked to sit facing the examiner with the arm extended. Initially, the elbow was flexed 90°, the forearm was in the supine position, and wrists relaxed on a flat surface with fingers semi-flexed (posture 1; Fig. 1A). Then, the subject was instructed to another posture, wherein the wrist was stretched maximally while maintaining the forearm on the flat surface (posture 2; Fig. 1D). This position was chosen owing to the lengthening of the median nerve. The examined limb was carefully maintained in a neutral position without any movement.

2.3. Equipment and SWE measurement

All elastography examinations were performed by Aixplorer ultrasound scanner (SuperSonic Imaging, Aix-en-Provence, France) with a 4 to 15-MHz linear array probe. Light contact was applied to the transducer onto the skin surface using the coupling agents, avoiding a compression effect. The transverse imaging plane of the nerve with B-mode was identified initially. Then, the transducer was rotated 90° to obtain the longitudinal imaging plane, which is a parallel orientation to the nerve, followed by the SWE mode. During preliminary studies, we found that reliable elasticity data could not be acquired in transverse orientation. A superficial musculoskeletal setting was chosen during the elastographic evaluation. Considering the anisotropy of nerve, shear wave velocities were determined for the nerve stiffness that does not alter with different modes and scale in the case of a completely filled square ROI as described previously. And the range of velocities that can be measured by this US system is 0 to 16.3 m/s. For the best image quality, the scale was adjusted to 600 kPa with “standard” or “penetration” mode, the size of ROI was kept as 2 mm, and the depth was fixed at 2 cm. Figure 2 represents the typical SWE images.

In this study, the median nerve was assessed over the bilateral mid-forearm and proximal inlet of the carpal tunnel on the right side. Two sonographers, trained in SWE, conducted the full examinations, respectively. The median nerve images were obtained by sonographer A, and sonographer B measured the median nerve on the right mid-forearm for interobserver repeatability. Within 1 week after the first examination, the same subjects were rechecked by sonographer A, and the data were used to calculate the intraobserver repeatability. Twenty healthy volunteers were randomly chosen to be examined for the inter- and intraobserver repeatability. The 2 sonographers were blinded to the results assessed by another expert. All measurements were carried out 3 times and the average of mean, minimum, maximum velocities (m/s) data (which is Vmean, Vmin, Vmax) were analyzed for statistical significance.

2.4. Statistical analysis

Statistical analyses were performed using SPSS software (Version 20.0; IBM, NY). Data were expressed as mean ± standard
deviation. The Shapiro–Wilk test was used for normal distribution data. The differences in age and body mass index in volunteers were evaluated using the Mann–Whitney U test. A paired t test was used for evaluating the difference in the nerve stiffness of bilateral forearm. The median nerve shear-wave velocities of right forearm in different positions, as well as, the difference in nerve stiffness of right wrist and forearm were compared using the Wilcoxon signed-rank test, the intra- and interobserver agreements were assessed with single-measure intraclass correlation coefficients (ICCs) calculated using a 2-way random effects model. An ICC > 0.75 was indicative of excellent agreement.\textsuperscript{[21]} Pearson correlation was used in the correlation analysis. \(P < .05\) was considered as the statistically significant difference.

3. Results

3.1. Demographic data

Table 1 summarizes the baseline demographic data of the study participants. The mean age of the participants was 31.20 ± 8.92 (range, 20–52) years and the mean body mass index was 21.72 ± 2.67 (range, 16.8–28.37) kg/m\(^2\). Statistical analysis did not reveal any significant difference in age, although males had a significantly higher body mass index than females.

3.2. Inter- and intraobserver repeatability of median nerve measurements

The results of inter- and intraobserver repeatability of SWE measurement in 20 volunteers are presented in Tables 2 and 3, respectively. Figure 3 shows the correlation of ICCs. As ICCs analyzed for the median nerve in the right forearm ranged from
0.852 to 0.930, an excellent inter- and intraobserver agreement was noted. \( R^2 \) ranged from 0.560 to 0.775, indicating a good correlation. All the \( P \) values were <.001.

3.3. Difference in elasticity values of median nerve on bilateral forearms

With respect to the median nerve stiffness in the same individual, the difference of nerve shear wave velocities (\( V_{\text{mean}}, V_{\text{min}}, V_{\text{max}} \)) between bilateral forearms was calculated as \( D \) values; no statistical significance was observed (\( P > .05 \)) (Table 4).

3.4. Difference in the same median nerve stiffness of different body sites

Average shear wave velocities of the same median nerve in the different body sites are summarized in Table 5. The median nerve of the right wrist was significantly stiffer than that of the right forearm (\( P < .001 \)).

3.5. Difference in right forearm postures on median nerve stiffness

Shear wave velocities for the median nerve in the right forearm were obtained with 2 postures. A significant effect of the different nerve postures was observed, and the median nerve in the tension condition had a higher stiffness than that in the slack condition (\( P < .001 \)). The data are illustrated in Fig. 4.

4. Discussion

The SWE has been extensively employed to assess the liver, breast mass, and musculoskeletal tissues,\(^{18,20,22,23}\) and increasingly used in the peripheral nerves in recent years.\(^{14,24}\) However, the feasibility and reliability of using SWE for peripheral nerves have

![Figure 3. Inter- and intraobserver reliability of shear wave elastography. (A–C) The interobserver reliability of mean, minimum, and maximum elasticity values in the right mid-forearm. (D–F) The intraobserver reliability of mean, minimum, and maximum elasticity values in the right mid-forearm.](image)

![Table 4](image)

![Table 5](image)
Previous literatures seldom investigated the same median nerve stiffness of different body sites. In this study, the median nerve on the right carpal tunnel and mid-forearm were compared; the shear wave velocities were found to differ significantly between the 2 body sites ($P < .001$); the nerve stiffness of the wrist was higher. In contrast to the forearm, the structure of the carpal tunnel is believed to be complicated, and nerve stiffness may be easily influenced by surroundings where the nerve approaches the bone surface,\(^{33}\) which could be one of the factors contributing to the present phenomenon. In addition, the median nerve depths on the 2 sites were different. Although the probe pressure was similar, the superficial probe might exert excess pressure, partially explaining the difference. Also, the nerve elasticity value on the carpal tunnel was dependent on the measurement location,\(^{34}\) which gave it more variability than that on the forearm. This finding suggests that the nerve stiffness of different body sites may be different and selecting the suitable site for SWE-based measurement of peripheral nerve may provide reliable results.

The nerve elasticity demonstrated an increase in stretching conditions in this study. Under tension condition, the mean shear wave velocity for the right forearm was $7.85 \pm 0.87$ m/s, which is 2-fold that of the relaxing posture. Greening and Dilley\(^ {35}\) talked about the movement-evoked changes of the nerve shear wave velocities, and the conclusion confirmed our result. However, they just mentioned the mean value, we got the minimum and maximum elasticity values showing the same increase, which more comprehensively proved the influence of the limb posture. It was also consistent with the literature\(^ {36}\) wherein the stiffness of resting and contracting muscle was attributed to the phenotype of the anisotropic tissue. Thus, the significant variation in median nerve elasticity in different limb positions suggests that caution should be exerted with limb postures during examination for precise outcomes. In addition, this study compared bilateral median nerve before and no significant difference was observed. This would help patients with restricted limb posture to be examined using contralateral side, which other literatures seldom considered.

Nevertheless, our study has several limitations. First, the study population is small and consists of only healthy volunteers. Although comparing the disease with normal condition is crucial, it mainly explores the methodological basis of peripheral nerves for further studies. In addition, with respect to the peripheral neuropathy, not only peripheral nerves of upper arms but also of lower limbs are affected. In the current study, we performed measurements on the median nerve, and hence, it is essential to discuss the tibial nerve elasticity assessment in depth.

5. Conclusion

The present study evaluated the feasibility and reliability of the median nerve elasticity with SWE and acquired high reproducibility and reliability. Moreover, the obvious changes were detected for different body sites and postures. However, no significant difference was observed between bilateral median nerves and contralateral nerve, which might be used as the internal control. These results could provide a methodological basis for further studies, which are essential to investigate the detailed influencing factors of nerve stiffness and evaluate both the normal nerve and peripheral neuropathy.

Author contributions

Methodology: Bihui Zhu, Liyun Wang, Li Qiu.
Project administration: Li Qiu.
Resources: Ying He, Li Qiu.
Writing – original draft: Bihui Zhu.
Writing – review & editing: Feng Yan, Xi Xiang, Yuanjiao Tang, Yujia Yang, Li Qiu.

References

[1] Kowalska B, Sudol-Szopinska I. Normal and sonographic anatomy of selected peripheral nerves. Part I: Sonohistology and general principles of examination, following the example of the median nerve. J Ultrasound 2012;12:120–30.

[2] Rosso G, Young P, Shahin V. Implications of Schwann cells biomechanics and mechanosenstivity for peripheral nervous system physiology and pathophysiology. Front Mol Neurosci 2017;10:345.

[3] Belin S, Zuloga KL, Potelion Y. Influence of mechanical stimuli on Schwann cell biology. Front Cell Neurosci 2017;11.

[4] Garg K, Aggarwal A, Srivastava DN, et al. Comparison of different sequences of MRI and ultrasound with nerve conduction studies in peripheral neuropathies. World Neurosurg 2017;108:185–200.

[5] Yagi I, Kenis-Coskun O, Ozsoy T, et al. Increased stiffness of median nerve in systemic sclerosis. BMC Musculoskelet Disord 2017;18:434.

[6] Won JC, Park TS. Recent advances in diagnostic strategies for diabetic peripheral neuropathy. Endocrinol Metab (Seoul) 2016;31:230–8.

[7] Rubino A, Rousculp MD, Davis K, et al. Diagnosis of diabetic peripheral neuropathy among patients with type 1 and type 2 diabetes in France, Italy, Spain, and the United Kingdom. Primary care diabetes 2007;1:129–34.

[8] Azadeh A, Vasaghi A, Jalli R, et al. Comparison of inching electro-diagnosis method and ultrasonographic findings in the determination of median nerve entrapment site in carpal tunnel syndrome. Am J Phys Med Rehabil 2017;96:869–73.

[9] Hu G, Zhai F, Mo F, et al. Effectiveness and feasibility of nailfold microcirculation test to screen for diabetic peripheral neuropathy. Diabetes Res Clin Pract 2017;131:42–8.

[10] Terkelson AJ, Karlsson P, Lauria G, et al. The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes. Lancet Neurol 2017;16:934–44.

[11] Ishibashi F, Taniguchi M, Kojima R, et al. Elasticity of the tibial nerve assessed by sonoelastography was reduced before the development of neuropathy associated with the severity of neuropathy in patients with type 2 diabetes. J Diabetes Invest 2016;7:404–12.

[12] Ghajarzadeh M, Dadgostar M, Sarraf P, et al. Application of ultrasound elastography for determining carpal tunnel syndrome severity. Jpn J Radiol 2015;33:273–8.

[13] Dikici AS, Ustabsioglu FE, Delil S, et al. Evaluation of the tibial nerve with shear-wave elastography: a potential sonographic method for the diagnosis of diabetic peripheral neuropathy. Radiology 2017;282:494–501.

[14] Kantarcı F, Ustabsioglu FE, Delil S, et al. Median nerve stiffness measurement by shear wave elastography: a potential sonographic method in the diagnosis of carpal tunnel syndrome. Eur Radiol 2014;24:434–40.

[15] Kowalska B, Sudol-Szopinska I. Ultrasound assessment on selected peripheral nerve pathologies. Part I: Entrapment neuropathies of the upper limb: excluding carpal tunnel syndrome. J Ultrasound 2012;12:307–18.

[16] Park G-Y, Kwon DR. Application of real-time sonoeastlography in musculoskeletal diseases related to physical medicine and rehabilitation. Am J Phys Med Rehabil 2011;90:875–86.

[17] Xiang X, Yan F, Yang Y, et al. Quantitative assessment of healthy skin elasticity: reliability and feasibility of shear wave elastography. Ultrasound Med Biol 2017;43:445–52.

[18] Sigrist RMS, Liao J, Kaffas AE, et al. Ultrasound elastography: review of techniques and clinical applications. Theranostics 2017;7:1303–29.

[19] Paluch L, Navrocks-Laskus E, Wieczorek J, et al. Use of ultrasound elastography in the assessment of the musculoskeletal system. Pol J Radiol 2016;81:240–6.

[20] Pawlus A, Sokolowska-Dabek D, Szymanska K, et al. Ultrasound elastography–review of techniques and its clinical applications in pediatrics–part I. Adv Clin Exp Med 2015;24:537–43.

[21] Miyamoto H, Halpern EJ, Kaslunger M, et al. Carpal tunnel syndrome: diagnosis by means of median nerve elasticity–improved diagnostic accuracy of US with sonoelastography. Radiology 2014;270:481–6.

[22] Creze M, Timoh KN, Gagey O, et al. Feasibility assessment of shear wave elastography to lumbar back muscles: a radioanatomic study. Clin Anat 2017;30:774–80.

[23] Siu W-I, Chan C-H, Lam C-H, et al. Sonographic evaluation of the effect of long-term exercise on Achilles tendon stiffness using shear wave elastography. J Sci Med Sport 2016;19:883–7.

[24] Andrade RJ, Nordez A, Hug F, et al. Non-invasive assessment of sciatic nerve stiffness during human ankle motion using ultrasound shear wave elastography. J Biomech 2016;49:326–31.

[25] Berg WA, Cosgrove DO, Doré CJ, et al. Shear-wave elastography improves the specificity of breast US: the BEI multinational study of 939 masses. Int J Med Radiol 2012;62:435–9.

[26] Dillman JR, Chen S, Davenport MS, et al. Superficial ultrasound shear wave speed measurements in soft and hard elasticity phantoms: repeatability and reproducibility using two ultrasound systems. Pediatr Radiol 2015;45:376–85.

[27] Baumer TG, Davis L, Dischler J, et al. Shear wave elastography of the supraspinatus muscle and tendon: repeatability and preliminary findings. J Biomech 2017;53:201–4.

[28] Hatta T, Giambini H, Uehara K, et al. Quantitative assessment of rotator cuff muscle elasticity: reliability and feasibility of shear wave elastography. J Biomech 2015;48:3853–8.

[29] Mathevon L, Michel F, Aubry S, et al. Two-dimensional and shear wave elastography ultrasound: a reliable method to analyse spastic muscles? Muscle Nerve 2018;57:222–8.

[30] Samarawickrama MB. A study of anatomical variations of median nerve formation and its relation to the arteries in the axilla and arm. Int J Morphol 2017;35:698–704.

[31] Andresen G, White LM, Kassner A, et al. Evaluation of diffusion tensor imaging and fiber tractography of the median nerve: preliminary results on intrasubject variability and precision of measurements. AJR Am J Roentgenol 2010;194:65–72.

[32] Lee SY, Cardones A, Doherty J, et al. Preliminary results on the feasibility of using ARF/SWELI to assess cutaneous sclerotic diseases. Ultrasound Med Biol 2013;41:2806–19.

[33] Bortolotto C, Turpin E, Felsaz P, et al. Median nerve evaluation by shear wave elastosonography: impact of “bone–proximity” hardening artifacts and inter-observer agreement. J Ultrasound 2017;20:293–9.

[34] Shen ZL, Vince DG, Li ZM, In vivo study of transverse carpal ligament stiffness using acoustic radiation force impulse (ARFI) imaging. Pls One 2013;8:e68169.

[35] Greening J, Dilley A. Posture-induced changes in peripheral nerve stiffness measured by ultrasound shear wave elastography. Muscle Nerve 2017;55:213–22.

[36] Shinohara M, Sabra K, Gennisson JL, et al. Real-time visualization of muscle stiffness distribution with ultrasound shear wave imaging during muscle contraction. Muscle Nerve 2010;42:438–41.