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MUSCLE SHEAR WAVE ELASTOGRAPHY IN INCLUSION BODY MYOSITIS: FEASIBILITY, RELIABILITY AND RELATIONSHIPS WITH MUSCLE IMPAIRMENTS

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Abstract—Degenerative muscle changes may be associated with changes in muscle mechanical properties. Shear wave elastography (SWE) allows direct quantification of muscle shear modulus (MSM). The aim of this study was to evaluate the feasibility and reliability of SWE in the severely disordered muscle as observed in inclusion body myositis. To explore the clinical relevance of SWE, potential relationships between MSM values and level muscle impairments (weakness and ultrasound-derived muscle thickness and echo intensity) were investigated. SWE was performed in the biceps brachii at 100°, 90°, 70° and 10° elbow flexion in 34 patients with inclusion body myositis. MSM was assessed before and after five passive stretch-shortening cycles at 4°/s from 70° to 10° elbow angle and after three maximal voluntary contractions to evaluate potential effects of muscle pre-conditioning. Intra-class correlation coefficients and standard errors of measurements were >0.83 and <1.74 kPa and >0.64 and <1.89 kPa for within- and between-day values, respectively. No significant effect of passive loading–unloading and maximal voluntary contractions was found (all p values >0.18). MSM correlated to predicted muscle strength (all Spearman correlation coefficients (ρ) > 0.36; all p values < 0.05). A significant correlation was found between muscle echo intensity and muscle shear modulus at 70° only ($\rho = 0.38$, $p < 0.05$). No correlation was found between muscle thickness and MSM (all ρ values > 0.23 and all p values > 0.25, respectively). Within- and between-day reliability of muscle SWE was satisfactory and moderate, respectively. SWE shows promise for assessing changes in mechanical properties of the severely disordered muscle. Further investigations are required to clarify these findings and to refine their clinical value. (E-mail: d.bachasson@institut-myologie.org)

Key Words: **Skeletal muscle, Shear wave elastography, Quantitative muscle ultrasound imaging, Myositis, Neuromuscular disorders, Muscle stiffness, Muscle elasticity, Passive muscle mechanics.**

INTRODUCTION

In the skeletal muscle, passive and active mechanical properties may be affected by structural alterations induced by disuse and pathological processes (Wisdom et al. 2015). Measuring these properties may help to assess and monitor disease-induced muscle changes (Bilston and Tan 2015; Brandenburg et al. 2014).

Ultrasound elastography techniques provide an opportunity for direct quantification of passive and active muscle elasticity in real time (Dubois et al. 2015; Eby et al. 2013; Gennisson et al. 2013). In comparison with previous ultrasound-based techniques for elastography, shear wave elastography (SWE) has been found to exhibit superior reliability (Bavu et al. 2011; Brandenburg et al. 2014). Assessments of muscle stiffness using SWE have been reported to be particularly relevant for investigating mechanisms underlying limitations in range of motion in conditions involving muscle/tendon retraction and/or spasticity, such as cerebral palsy (Brandenburg et al. 2016), stroke (Lee et al. 2015) and Duchenne muscular dystrophy (Lacourpaille et al. 2015). Good agreement between fibrosis staging using biopsy and elasticity assessed from SWE has been repeatedly reported in liver (Deffieux et al. 2015), highlighting the great potential of this technique to characterize tissue-level changes. However, studies that have investigated relationships between local muscle

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elasticity and the severity of degenerative muscle changes are particularly scarce (Bilston and Tan 2015). For instance, the muscle pathology in inclusion body myositis (IBM, *i.e.,* the most common acquired inflammatory myopathy after 50 y of age) combines inflammation and myofiber degeneration, leading to severe muscle atrophy, fatty infiltration, fibrosis and edema. It is unclear whether these changes affect passive mechanical muscle properties when they co-occur (Virgilio et al. 2015; Wisdom et al. 2015). In addition, data regarding within- and between-day reliability of measurements using SWE in the severely disordered muscle are scarce.

Therefore, this study was aimed at assessing the feasibility and reliability (within- and between-day) of use of SWE in the severely disordered muscle that may be observed in patients with neuromuscular diseases such as IBM. The acute effect of stretching and muscle contraction was also evaluated. To explore the clinical relevance of SWE, potential relationships between MSM values and level muscle impairment (weakness and ultrasound-derived muscle thickness and echo intensity) were investigated.

METHODS

Participants

A total of 34 patients diagnosed with IBM volunteered to participate in this study (18 men: age = 67.5 ± 7.6 y, height = 172 ± 6 cm, weight = 78 ± 12 kg; 16 women: age = 61.9 ± 8.5 y, height = 161 ± 6 cm, weight = 63 ± 11 kg). All patients had definite IBM; that is, pathological examination of their biopsies revealed fibers invaded by lymphocytes, vacuoles and amyloid deposits (Benveniste and Hilton-Jones 2010). Symptom onset was 7.6 ± 4.5 y, and time since diagnosis was 2.6 ± 2.6 y. The mean IBM weakness composite index (Benveniste et al. 2011) was 60 ± 18 (maximal score = 100). Patients had no history of traumatic event in their right upper limb. This study conformed to the Declaration of Helsinki and was approved by the local ethics committee. All patients gave written informed consent.

Muscle shear modulus assessment

Patient setup. Participants sat (85° hip flexion) on an ergometer (Biodex, Biodex Medical, Shirley, NY, USA) with the right upper limb positioned as follows: 90° shoulder flexion, 20° shoulder abduction, 0° shoulder rotation, 90° elbow flexion, 0° supination. The upper body was stabilized with straps across the thorax and the abdomen.

Muscle SWE. Measurements were performed in the short head of the right biceps brachii because of its longitudinal architecture (Lieber and Ward 2011) and because it is variably affected in patients with IBM (Cox et al. 2011). SWE measurements in biceps brachii have also been found to be feasible and reliable in healthy subjects (Lacourpaille et al. 2012). Muscle shear modulus (MSM) was assessed at different elbow joint angles. Measurements were performed using an Aixplorer Ultrasound scanner (V9.2, Supersonic Imagine, Aix-en-Provence, France) driving a 4- to 15-MHz linear transducer array (SL15-4, 256 elements, pitch = 0.2 mm). Settings were defined as follows: supersonic shear imaging mode enabled; musculoskeletal pre-set, penetration mode enabled; tissue tuner at 1540 m/s; gain at 40%; dynamic range at 80 dB. MSM was calculated assuming a linear elastic behavior in muscle tissue (Bercoff et al. 2004) as:

$$\mu = \rho V_s^2 \tag{1}$$

where ρ is the density of muscle (1000 kg/m^3), and V_s is the shear wave speed.

A generous amount of water-soluble transmission gel was used during scanning for optimal acoustic coupling, and minimal pressure was applied to the transducer to limit tissue deformation. The belly of the short head of the biceps brachii was identified during transverse scanning in B-mode at two-thirds of the distance between the acromion and antecubital fossa. Then the probe was rotated and carefully aligned with the direction of muscle fascicles as recommended by Gennisson et al. (2010). Appropriate transducer alignment was achieved when several fascicles were continuously visible. A > 5-s delay was used before capturing all clips to obtain stabilized acquisition. During all measurements, participants were asked to keep their whole upper limb as relaxed as possible, and elastograms and B-mode images were carefully monitored. Clips were discarded if subtle movement and/or contraction was detected. Typical recordings for one patient are illustrated in Figure 1.

Post-processing of SWE data. Each frame of the 10-s clips was processed using a custom software developed in MATLAB (The MathWorks, Natick, MA, USA) (Dubois et al. 2015; Vergari et al. 2014). A rectangular region of interest (ROI) was manually defined on the first frame as large as possible between the superficial and the deep aponeurosis in the muscle belly, and focal penetration defects or fibrous septa were carefully avoided. The ROI was tracked over other frames to evaluate the same region all over the measurement. MSM was computed as the mean of shear modulus values within whole ROIs. A normalized shear modulus was computed for each individual by dividing values at all tested joint angles by the value obtained at 100°.

Within- and between-day reliability

For all measurements, two clips were consecutively acquired after re-positioning the probe to assess within-

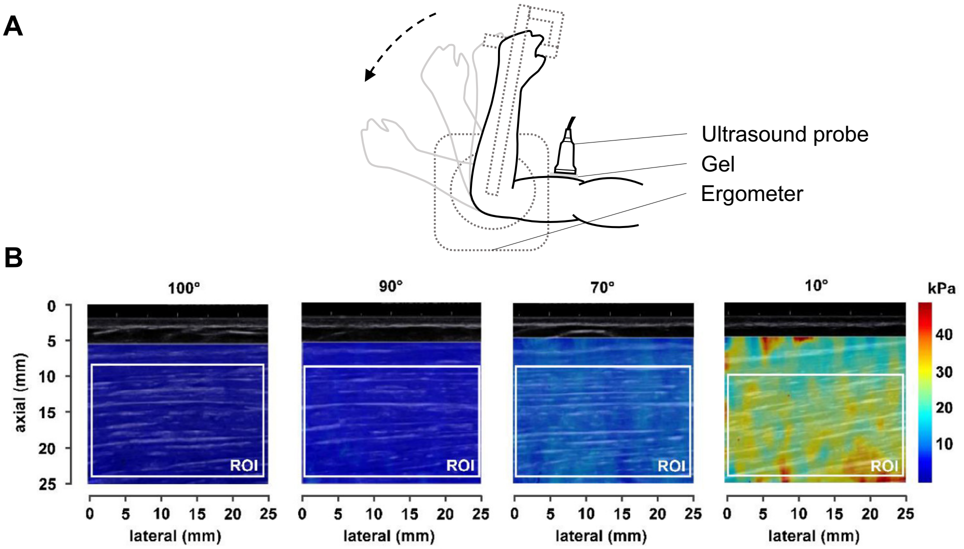

Fig. 1. (a) Lateral view of the experimental setup. (b) Typical recordings of shear modulus measurements using shear wave elastography in the short head of the biceps brachii at 100°, 90°, 70° and 10° elbow joint angles in one patient with inclusion body myositis. ROI = region of interest for post-processing of elastograms.

day reliability for all elbow flexion positions (100°, 90°, 70° and 10°). A sub-sample of 15 patients came on a second visit 1 week apart to evaluate between-day reliability of MSM measurements. To evaluate the between-day reliability, the first of the two measurements was used.

Acute effect of muscle pre-conditioning and assessment of maximal voluntary strength

Passive muscle stiffness has been reported to be affected by the muscle's previous history of length changes and contractions (Lacourpaille et al. 2014; Whitehead et al. 2001). Therefore, MSM at 100°, 90°, 70° and 10° elbow flexion was re-assessed immediately after five passive stretch-shortening cycles at 4°/s from 70° to 10° elbow angle using the Biodex ergometer in 19 patients. In 8 patients, MSM was reassessed immediately after a set of voluntary contractions of the elbow flexors at 90° elbow flexion. Clips were acquired after probe re-positioning for both stretch-shortening cycles and voluntary contractions. The set of contractions consisted of three increasing 5-s submaximal contractions followed by three 5-s maximal voluntary contractions with 1 min of rest between maneuvers. This set of voluntary contractions was performed in all subjects to assess maximal voluntary strength. Maximal peak torque over 500 ms was expressed as a percentage of predicted value using previously published predictive equations (Harbo et al. 2012).

Quantification of muscle echo intensity and muscle thickness

To evaluate muscle echo intensity, a gray-scale index (GSI) ranging from 0 to 1 was defined as follows for B-mode images (8-bit resolution, resulting in a number between 0 and 255, where black = 0 and white = 255) acquired transversally to muscle fascicles at 90° elbow flexion (2):

$$\text{gray-scale index} = 1 - \frac{\frac{1}{(n \cdot m)} \sum_{i=1}^{n \cdot m} I_i}{255} \qquad (2)$$

with I_i the intensity of the pixel i in a ROI of $n \times m$. A lower GSI value corresponds to greater muscle echo intensity (Dubois et al. 2018). As mentioned above, gain and all other ultrasound settings were kept constant for all subjects (Caresio et al. 2015). Thickness of the biceps brachii was measured with electronic calipers as previously described (Arts et al. 2010).

Statistical analysis

Data within text and tables are expressed as the mean ± standard deviation (SD) or mean (95% confidence interval [lower 95% CI, upper 95% CI]). The assumptions of normality and sphericity were confirmed using the D'Agostino *K*-squared and Mauchly tests, respectively. To assess within- and between day reliability, change in mean and paired *t*-tests were used for detection of systematic bias. Standard error of measurement (SEM) was used to study absolute reliability. Relative reliability was assessed with the intra-class correlation coefficient (ICC) with 95% confidence interval. Regression analysis and Bland–Altman plots were also performed. When available, data from the second visit were analyzed jointly with data from the first visit to evaluate within-day reliability. A two-way analysis of variance (ANOVA,

Table 1. Within-day reliability of muscle shear modulus in patients with inclusion body myositis (n = 49)

Angle	Test (kPa)	Re-test (kPa)	CIM [95% CI] (kPa)	SEM [95% CI] (kPa)	ICC [95% CI]
All	11.58 ± 6.52	11.51 ± 6.47	−0.07 [−0.29, 0.14]	1.04 [0.95, 1.17]	0.97 [0.97, 0.98]
100°	7.66 ± 1.46	7.74 ± 1.58	0.07 [−0.12, 0.27]	0.47 [0.39, 0.59]	0.90 [0.84, 0.94]
90°	8.38 ± 1.63	8.36 ± 1.76	−0.03 [−0.26, 0.21]	0.53 [0.44, 0.68]	0.90 [0.83, 0.95]
70°	9.76 ± 2.69	9.67 ± 2.45	−0.10 [−0.53, 0.34]	1.07 [0.89, 1.34]	0.83 [0.72, 0.90]
10°	22.13 ± 5.87	21.85 ± 6.17	−0.28 [−1.08, 0.52]	1.74 [1.42, 2.24]	0.92 [0.85, 0.96]

CIM = change in mean; SEM = standard error of measurement; ICC = intra-class correlation coefficient.

trial × condition) were conducted to test main and interaction effects on changes in MSM induced by passive conditioning. A one-way ANOVA was used to assess the effect of maximal voluntary contractions. Tukey's honest significant difference (HSD) *post hoc* tests were conducted when a significant main and/or interaction effect was found. We hypothesized monotonic relationships between variables, but we did not assume that these relationships would be linear. Therefore, Spearman's rank-order correlation coefficients (ρ) were computed to assess relationships between variables. All analyses were performed in the computing environment R Version 3.2.3. Statistical significance was set at $p < 0.05$ for all tests.

RESULTS

Within- and between-day reliability of muscle SWE values

Within- and between-day reliability data of measurements performed at each tested angle are summarized in Tables 1 and 2, respectively. No systematic bias was detected for both within-day (all $p > 0.44$) and between-day (all $p > 0.30$) measurements. For within-day values, the ICC and SEM were >0.83 and <1.74 kPa, respectively. Regarding between-day values, the ICC and SEM were >0.64 and <1.89 kPa, respectively. Regression analysis and Bland–Altman plots are displayed in Figure 2. Lower and upper limits of agreements were –2.97 and 2.82 kPa for within-day measurements and −4.23 and 2.89 kPa for between-day measurements, respectively.

Effect of elbow joint angle and passive loading–unloading cycles on muscle shear modulus

Normalized shear moduli at each tested angle during the first measurement are illustrated in Figure 3. Normalized MSM at 10° was significantly greater than shear moduli at all other angle (all p values < 0.05). There were no significant differences between 100° and 90° ($p = 0.77$) or between 90° and 70° ($p = 0.57$).

Absolute values of muscle shear moduli at all elbow joint angles measured before and after passive loading/unloading cycles are illustrated in Figure 4A. MSM at 10° was significantly greater than values at all other angles ($p < 0.001$). There were no significant differences between 100° and 90° ($p = 0.96$) or between 90° and 70° $p = 0.97$). No significant effect of trial or trial × angle interaction was found ($p = 0.54$ and $p = 0.68$, respectively).

Effect of maximal voluntary contractions on muscle shear modulus

Maximal elbow flexor isometric strength was 25.7 ± 11.1 N · m, corresponding to 70.1 ± 25.7% of predicted values. Measurements of MSM at 90° before and after maximal voluntary contractions are illustrated in Figure 4B. No significant effect of maximal voluntary contractions was found ($p = 0.18$).

Relationships between muscle shear modulus, muscle strength, muscle echo intensity and muscle thickness

Muscle shear moduli at all angles significantly correlated with muscle strength expressed as a percentage of predicted values (at 100°: $\rho = 0.39$, $p < 0.05$; at 90°: $\rho = 0.36$, $p < 0.05$; at 70°: $\rho = 0.46$, $p < 0.01$; at 10°: $\rho = 0.53$, $p < 0.01$). Individual data points are illustrated in Figure 5. No significant correlation was found between normalized MSM and muscle strength expressed as a percentage of predicted values (at 90°: $\rho = -0.03$, $p = 0.87$; at 70°: $\rho = 0.13$, $p = 0.47$; at 10°: $\rho = 0.32$, $p = 0.07$). Muscle thickness was 1.37 ± 0.37 cm and correlated with

Table 2. Between-day reliability of muscle shear modulus in patients with inclusion body myositis

Angle	Day 1 (kPa)	Day 2 (kPa)	CIM [95% CI] (kPa)	SEM [95% CI] (kPa)	ICC [95% CI]
All	12.07 ± 6.72	11.41 ± 6.09	−0.67 [−1.13, −0.20]	1.28 [1.09, 1.56]	0.96 [0.93, 0.97]
100	7.65 ± 1.43	7.32 ± 1.61	−0.33 [−100, 0.33]	0.85 [0.62, 1.34]	0.69 [0.30, 0.88]
90	8.11 ± 1.63	7.78 ± 1.41	−0.34 [−1.12, 0.45]	0.92 [0.66, 1.51]	0.64 [0.18, 0.87]
70	9.38 ± 2.26	9.10 ± 1.97	−0.28 [−0.97, 0.42]	0.96 [0.71, 1.46]	0.80 [0.54, 0.92]
10	22.30 ± 4.29	20.64 ± 3.87	−1.66 [−3.08, 0.24]	1.89 [1.39, 2.92]	0.73 [0.39, 0.89]

CIM = change in mean; SEM = standard error of measurement; ICC = intra-class correlation coefficient.

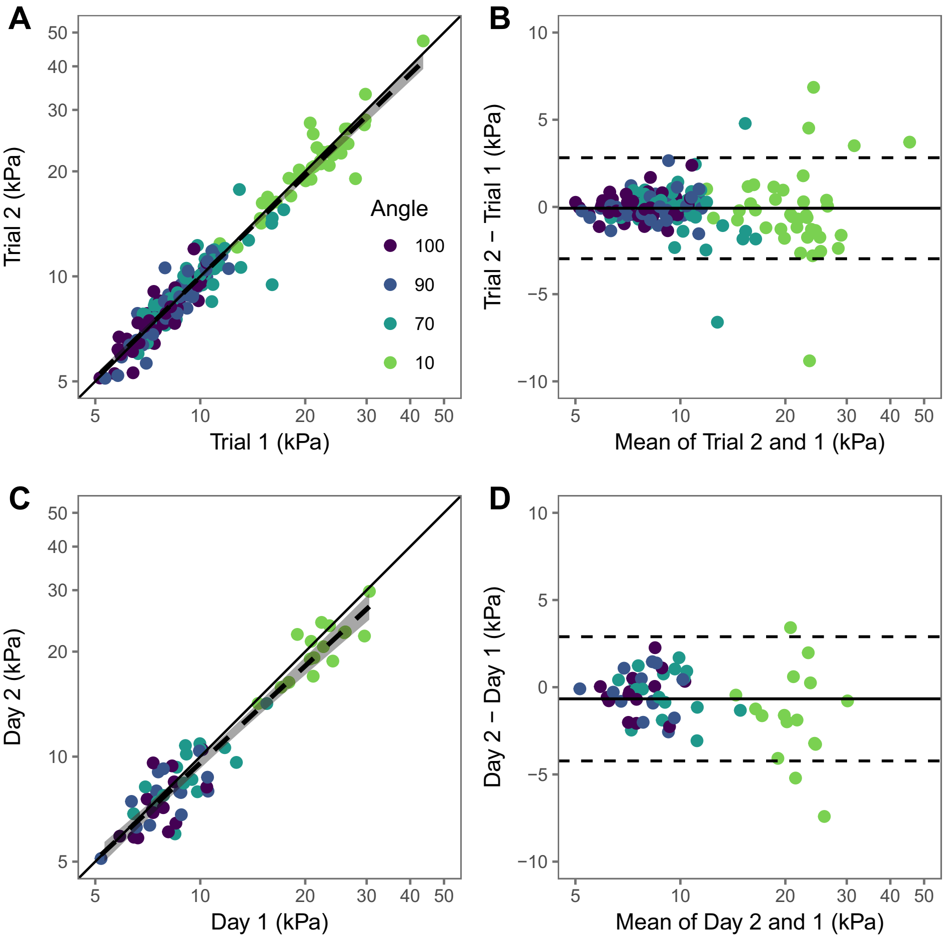

Fig. 2. Regression analysis (a, c) and Bland–Altman plots (b, d) for within- and between day reliability of measurements. (a, b) Regression analysis and Bland–Altman plot for within-day measurements. (c, d) Regression analysis and Bland–Altman plot for between-day measurements. In (a) and (c), the *solid line* represents the identity line, and the *dashed line* indicates the linear regression line with shaded 95% confidence region. In (b) and (d), the *solid line* indicates the mean difference between the measurements, and the *dashed lines* represent the 95% limits of agreement.

absolute strength ($\rho = -0.43$, $p < 0.01$). GSI was 0.70 ± 0.07 and correlated with predicted muscle strength ($\rho = 0.46$, $p < 0.01$). GSI also correlated with MSM at all angles except 10° (at 100°: $\rho = 0.49$, $p < 0.05$; at 90°: $\rho = 0.54$, $p < 0.05$; at 70°: $\rho = 0.62$, $p < 0.01$; at 10°: $\rho = 0.17$, $p = 0.23$).

DISCUSSION

The aim of the present study was to investigate the feasibility and relevance of muscle shear modulus assessment using ultrasound shear wave elastography in the biceps brachii of patients with IBM. Main results are as follows: (i) Within-day reliability of MSM measurements was satisfactory. (ii) Agreement of between-day MSM measurements was moderate. (iii) Passive loading/unloading cycles and maximal voluntary contractions did not significantly affect MSM values. (4) Lower muscle stiffness was associated with more severe muscle weakness.

Muscle stiffness and stretch-stiffening behavior

As repeatedly demonstrated using SWE (Lacourpaille et al. 2014) and conventional stress-strain tests (Eby et al. 2013), our data revealed an increase in MSM with increasing tensile load, illustrating the typical non-linear length–tension behavior of muscle tissue when subjected to tensile strain. Our data indicated substantial dispersion at the longest muscle length tested (*i.e.,* 10° elbow angle) suggesting inter-individual differences in the passive force–length relationship (as estimated here using SWE) that may result from muscle remodeling and/or anatomic variations (Fig. 2). In healthy subjects, the elbow joint angle corresponding to the slack length of the biceps brachii has been reported to occur at ~85°–95° (Lacourpaille

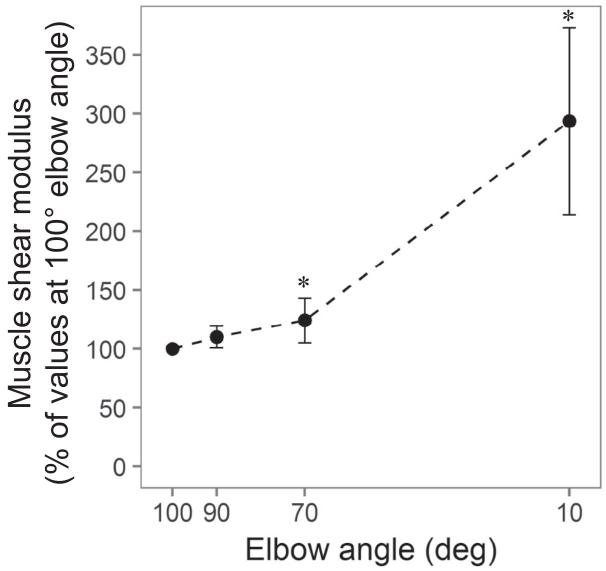

Fig. 3. Muscle shear modulus at different muscle lengths. Muscle shear modulus assessed with shear wave elastography in the short head of the biceps brachii at 100°, 90°, 70° and 10° elbow joint angles (n = 33). Values are normalized to values at 100°. *Significantly different from value at 100°.

and Hug 2013; Lacourpaille et al. 2014). This may thus explain the absence of significant differences between MSM at 100° and 90° for both normalized and absolute MSM values. Consequently, it is reasonable to consider that measurements performed at 100° elbow joint angle reflects intrinsic shear modulus of the muscle tissue without passive tension.

Within-day and between-day reliability of muscle SWE values

Mean SEMs expressed as coefficients of variation were <8.6% and ICCs were >0.92, indicating satisfactory agreement between within-day measurements of MSM. These data are in line with previous studies that reported similar results in biceps brachii in healthy subjects (*i.e.,* ICC = 0.87 and SEM = 0.17 kPa (Lacourpaille et al. 2012)), patients with stroke (*i.e.,* ICC = 0.93, coefficient of variation = 4.5% (Lee et al. 2015)) and Duchenne muscular dystrophy (ICCs ranging from 0.67 to 0.80 (Brandenburg et al. 2015)). Prior to the current study, within- and between-day reliability of muscle mean shear modulus using an identical experimental setup were assessed in 12 unmatched healthy subjects. The ICC and SEM were 0.98 and 0.90 kPa, respectively (unpublished data). In IBM patients, In the current work, within-day reliability was comparable between all tested angles; that is, when expressed as coefficients of variation, SEMs were 6.0%, 6.4%, 8.6% and 7.2% at 100°, 90°, 70° and 10° elbow angles, respectively. Collectively, these results support that SWE may be used to assess acute changes in passive muscle stiffness induced by various factors (*i.e.,* stretching, passive loading/unloading cycles, maximal voluntary contractions) and to investigate relationships between variables as performed in the present study.

Our data indicated moderate agreement on between-day MSM measurements as indicated by ICCs <0.80 and substantial SEMs (*i.e.,* SEMs expressed as coefficients of variation were 10.4, 10.6, 9.8 and 7.8% at 100°, 90°, 70° and 10°, respectively). There are several potential explanations for these findings. In the present work, probe

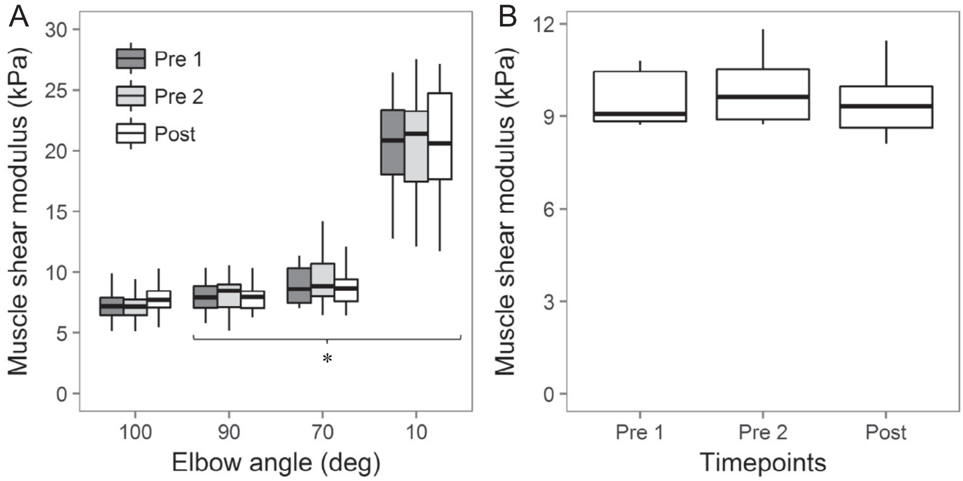

Fig. 4. Effect of passive loading–unloading and maximal voluntary contractions on muscle shear modulus. Muscle shear modulus was assessed with shear wave elastography in the short head of the biceps brachii at elbow joint angles of 100°, 90°, 70° and 10° before (Pre 1, Pre 2) and after (Post) five passive stretch-shortening cycles at 4°/s from 70° to 10° elbow angle (n = 19) (A) or three maximal voluntary isometric contractions of the elbow flexors (n = 8) (B). *Significantly different from value at 100°. No significant effect of passive conditioning or maximal voluntary isometric contractions was found.

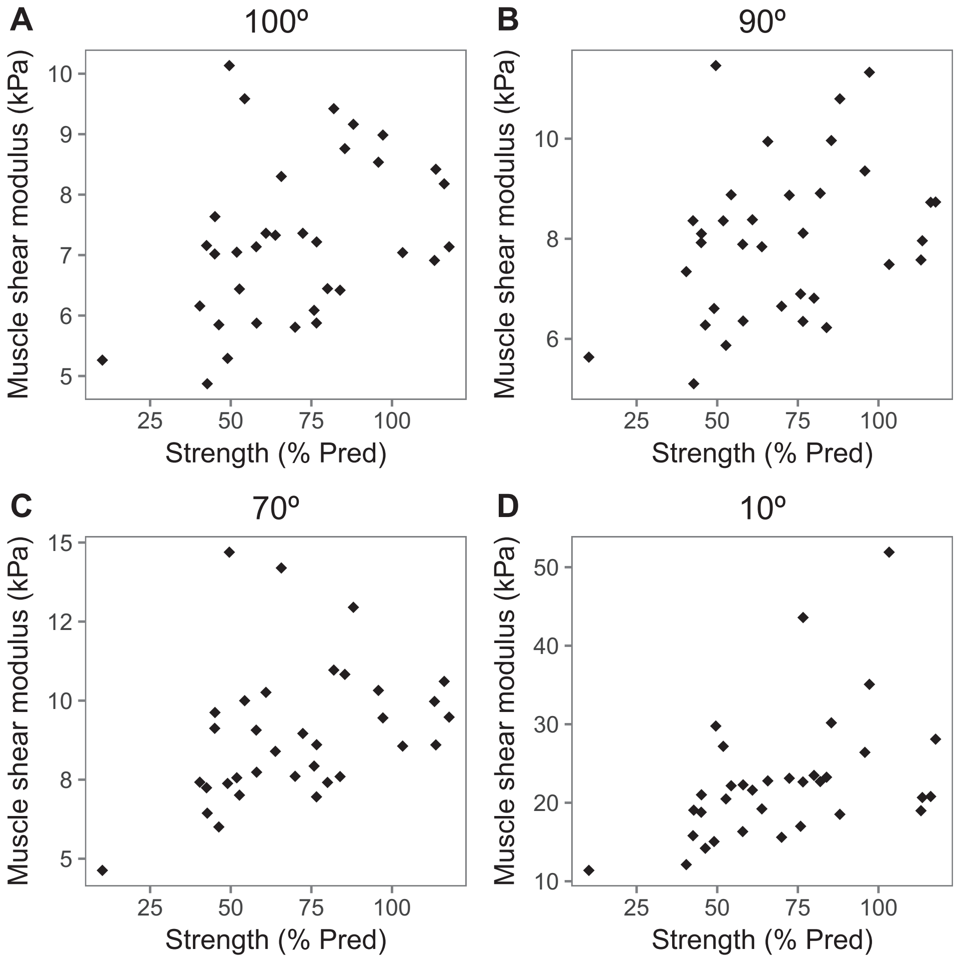

Fig. 5. Relationship between muscle shear modulus at different joint angles and maximal voluntary strengths expressed as a percentage of predicted value in patients with inclusion body myositis. Muscle shear modulus was assessed with shear wave elastography in the short head of the biceps brachii at elbow joint angles of 100° (A), 90° (B), 70° (C) and 10° (D) (n = 34). % Pred = percentage of predicted value. A moderate correlation was found between predicted muscle strength and biceps brachii short head muscle shear moduli at all angles.

positioning was based on anatomical landmarks and the skin was deliberately not marked between days to fit a clinical setting. Furthermore, patients studied in the present work exhibited severe muscle atrophy and heterogeneously distributed degenerative changes (*i.e.,* fatty infiltration, fibrosis, disrupted fascicles (Cox et al. 2011)) so that small positioning changes may result in more dramatic variations in MSM in comparison to healthy muscle. Probe pressure is also a critical factor (Kot et al. 2012). Experimental apparatus (*e.g.,* probe mounting jig, immersion of the probe in a silicon pool) have been proposed to bypass the confounding effect of probe pressure (Andonian et al. 2016; Koo et al. 2014). However, such experimental procedures question the feasibility of high-quality muscle SWE measurements within a clinical setting. The alignment of the probe with the direction of the fascicles is also critical factor (Gennisson et al. 2010; Maisetti et al. 2012). In a recent work, Miyamoto et al. (2015) reported a significant effect of the probe angle relative to the fascicle on the shear modulus in the biceps brachii. Although the difference was small (<1.3% of the measured values), for instance, as compared with the inter-observer reliability (around 9% according to Dubois et al. 2015), this may contribute to explaining the variability of the measurements observed in the current study.

Another important factor to consider is that exercise, particularly eccentric bout, may cause a long-lasting increase in muscle stiffness (Green et al. 2012; Lacourpaille et al. 2014). High relative intensity of muscle contraction level during daily-life activities because of weakness associated with high sensitivity to muscle damage may thus lead to substantial fluctuations of muscle stiffness in patients. These exercise-induced increases in muscle stiffness have also been reported to be more prominent at longer muscle length, mainly because sensitivity to Ca^{2+} increases as muscle is elongated (Stephenson and Williams 1982). Although between-day variability of MSM was not particularly greater at longer muscle length, this may contribute to explaining the limited agreement of MSM measurements in patients with IBM. Patient relaxation is also a critical aspect that can substantially reduce the reliability of measurements and may also vary between days.

Effect of passive loading/passive cycles and maximal voluntary muscle activation on muscle SWE values

Our data indicated no significant effect of the passive conditioning on MSM measurements. In a recent work investigating the time course effect of exercise-induced damage on muscle stiffness, Lacourpaille et al. (2014) reported no effect of passive loading/unloading cycles on the area under the loading curve before exercise. Conversely, 48 h after intense exercise, significant changes were seen for the first cycle only. In the current work, repeated maximal voluntary activation did not lead to significant acute changes in muscle stiffness. As mentioned above, intense exercise may lead to substantial changes in passive mechanical muscle properties (Green et al. 2012; Lacourpaille et al. 2014). These effects are observed mainly at muscle length greater than the slack length and appear to rely on calcium-dependent processes (Chen et al. 2007). Slack elasticity measurements may therefore be more relevant in characterizing the local elasticity of the muscle tissue while limiting the confounding effects of this phenomenon as well as those related to the inter-individual differences in the passive muscle length–tension relationship.

Relationships between muscle shear modulus, muscle strength, muscle echo intensity and muscle thickness

As expected and as reported previously, smaller muscle thickness was associated with smaller muscle strength observed, emphasizing the strong relationship between muscle size and muscle strength (Akagi et al. 2018; Jansen et al. 2012; Strasser et al. 2013). In line with previous work in neuromuscular disorders or in the elderly, greater muscle echogenicity was associated with more severe muscle weakness (Fukumoto et al. 2012; Jansen et al. 2012; Zaidman et al. 2010). Interestingly, our data also revealed moderate positive correlations between predicted muscle strength and muscle shear moduli at both slack and stretched lengths (Fig. 5). These findings are in line with a previous work that reported lower muscle stiffness in both upper- and lower-limb muscles of patients assessed with acoustic radiation force impulse ultrasound elastography (Botar Jid et al. 2012). Furthermore, significant correlations were found between MSM and echo intensity. Fibrous and particularly adipose tissue content within muscle has been reported as key explanatory factors of increased muscle echo intensity (Caresio et al. 2015; Reimers et al. 1993). Fatty infiltration has been reported to be a prominent feature of muscle alteration in IBM as assessed with nuclear magnetic resonance imaging (Cox et al. 2011; Morrow et al. 2016). Together, these data suggest that reduce lower muscle stiffness might be related to greater structural muscle impairments, that is, . greater muscle fat content. Therefore, further investigations allowing the comparison of muscle mechanical properties and muscle degenerative processes assessed with nuclear magnetic resonance imaging/spectroscopy must be conducted to clarify these findings and the clinical relevance of muscle SWE for diagnosis and follow-up.

Limitations

The absence of data for healthy controls in the present work limits the interpretation of findings. Post-processing of SWE data is an important factor for the reliability of measurements. In the present work, we used an advanced method to post-process SWE clips (Vergari et al. 2014). However, minor changes (size, location) when defining the ROIs may have occurred between days. Mechanical anisotropy is also a critical factor in the characterization of mechanical tissue properties (Green et al. 2013; Virgilio et al. 2015) and has been reported to be altered in muscle degeneration (Qin et al. 2014). Mechanical anisotropy estimation using SWE (Chino et al. 2017) should therefore be assessed in future studies. In addition, the dispersion of the shear waves may be studied from deeper exploitation of local tissue velocity maps acquired using SWE, allowing the quantification of muscle viscosity (Deffieux et al. 2009; Gennisson et al. 2010). The measurement of these complex viscoelastic and anisotropic mechanical properties will provide additional opportunities to characterize the diseased muscle.

CONCLUSIONS

Muscle SWE shows promise for the investigation of muscle degeneration in patients with muscle disorders such as those observed in IBM. Significant challenges remain to improve the applicability of muscle SWE in the severely disordered muscle and to clarify the complex interplay between biomechanical, structural and functional muscle changes in IBM and in a broader scope of muscle diseases. Further investigations will be aimed at comparing muscle mechanical properties (*i.e.,* shear modulus, shear viscosity and anisotropy) obtained using SWE and muscle changes quantified using nuclear magnetic resonance imaging/spectroscopy (*e.g.,* fatty infiltration, inflammation) in these populations.

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