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Electrical Impedance Myography in Facioscapulohumeral Muscular Dystrophy

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Abstract

Introduction—We determined the reliability and validity of electrical impedance myography (EIM) in facioscapulohumeral muscular dystrophy (FSHD).

Methods—We performed a prospective study of EIM on 16 bilateral limb and trunk muscles in 35 genetically defined and clinically affected FSHD patients (reliability testing on n=18). Summary scores based on body region were derived. Reactance and phase (50 and 100 kHz) were compared to measures of strength, FSHD disease severity, and functional outcomes.

Results—Participants were mostly men, mean age 53.0 years, and included a full range of severity. Limb and trunk muscles showed good to excellent reliability [intraclass correlation coefficients (ICC) 0.72-0.99]. Summary scores for the arm, leg, and trunk showed excellent reliability (ICC 0.89-0.98). Reactance was the most sensitive EIM parameter to a broad range of FSHD disease metrics.

Discussion—EIM is a reliable measure of muscle composition in FSHD which offers the possibility to serially evaluate affected muscles.

Keywords

Muscular dystrophy; Facioscapulohumeral Muscular Dystrophy; Electrical Impedance Myography; Muscle Composition; Outcome Measures

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Author's Contributions

Jeffrey Statland, Kate Eichinger, Chad Heatwole, and Rabi Tawil contributed to drafting/revising the manuscript for content; study concept or design; analysis or interpretation of data; acquisition of data; and statistical analysis.

Disclosures

Dr. Statland is a consultant for Cydan and Third Rock Ventures, and served on the advisory board for Bristol Myers Squibb and Sarepta.

Kate Eichinger reports no disclosures.

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Rabi Tawil is a consultant for Acceleron and aTyr, and served on the DSMB for Novartis for a non FSHD trial.

Introduction

Facioscapulohumeral muscular dystrophy (FSHD) is among the most common muscular dystrophies and causes progressive loss of motor function. Approximately 20% of people require a wheelchair over age 50.^{1,2} FSHD is notable for marked side-to-side asymmetry. Although considerable variability exists between patients, there is a characteristic pattern of progression involving the muscles of the face and shoulders, then later distal lower extremity, and finally the hip girdle muscles. In addition, patients may have debilitating involvement of abdominal and paraspinal muscles.^{3,4} Although the individual experience of the disease may suggest periods of rapid worsening followed by periods of stability, the largest natural history study to date showed a slow but progressive loss of strength over time.^{5,6} Recent advances in our molecular understanding of FSHD have identified potential therapeutic targets for future clinical trials, and the focus of the research community is shifting towards clinical trial planning.⁷ Traditional measures of strength testing would require long follow up periods or large numbers of participants to demonstrate halt of progression, but more importantly there are not well validated techniques for quantifying changes in muscles which are particularly affected by FSHD, for example the facial, abdominal, or paraspinal muscles.⁵ Recent international FSHD meetings have identified the need for a biomarker of muscle structure or function for clinical trials.⁷

Impedance has long been used to assess body composition, because tissues, such as muscle and fat, have different impedance to current flow. Electrical impedance myography (EIM) is an adaptation of this technique which uses subthreshold electrical current to determine the resistance to current flow through a particular muscle. EIM has been shown in preclinical studies to reflect changes in muscle structure, and techniques have been optimized to be more sensitive to muscle than underlying skin or fat.^{8,9} EIM has shown good reliability and relationship to disease severity in diverse neuromuscular diseases, including spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD), and it is responsive to disease progression in amyotrophic lateral sclerosis.¹⁰⁻¹²

Here we determine the reliability of EIM and its association with known measures of disease severity in FSHD. In particular, we examine the performance of EIM in muscles particularly affected in FSHD, including the face, abdominal, and paraspinal musculature.

Material and Methods

We performed a prospective cross-sectional observational study of genetically confirmed and clinically affected FSHD patients at the University of Rochester Medical Center conducted from 2012 to 2015. The study was approved by the Human Subjects Committee, and written and informed consent was obtained from all participants.

Participants

FSHD participants were between 18 and 75 years of age, were clinically affected as determined by investigator examination, were independently ambulatory, and had genetically confirmed FSHD type 1 or 2.^{13,14} Participants were recruited from our neuromuscular research database or neuromuscular clinic using inclusion criteria reflecting the spectrum

disease severity for a typical, early phase trial. Participants completed a baseline visit, then local participants (or participants able to extend their stay) returned for a subsequent repeat visit within 3 weeks of the baseline assessment for reliability testing. Evaluations included EIM, standardized physical evaluation, manual and quantitative strength testing, and a battery of standard functional assessments.

Outcomes and assessments

The EIM device was obtained from Skulpt, Inc (Boston, MA, Figure 1A,B) and consists of a laptop computer with a connection to a portable hand-held sensor.¹⁵ Evaluators were trained in technique and standard recording positions during a 1 day training session (Figure 1 C,D). Pediatric sensors were used for muscles of the face, as they have a smaller surface area, and are more appropriate for facial muscles.¹¹ The impedance is measured at each frequency by applying low-intensity electrical current (<1 mA) via surface electrodes embedded in a single hand-held sensor, and measuring the resulting voltage signals using a second set of surface electrodes embedded in the same sensor, converting them into 3 impedance parameters, the resistance (R) the reactance (X), and the Phase [arctangent (X/R)]. While the device records 41 frequencies ranging between 1 kHz and 10 MHz, 50 and 100 kHz were chosen for this analysis, as they are thought to be more sensitive to biological tissues. The 50 kHz phase is commonly utilized in neuromuscular disease.¹⁶ We compared values for phase and reactance. Three recordings of each muscle were obtained, and the 2 most closely aligned measurements were averaged (Figure 1B). Recordings were made from the following bilateral muscle groups: orbicularis oris, deltoid, biceps, triceps, abdominals, vastus lateralis, tibialis anterior, and thoracic paraspinals. Recordings took approximately 20 minutes for each subject. Summary scores were created by averaging the bilateral arm muscles, leg muscles, and trunk muscles.

The FSHD Clinical Score is a 15-point clinical severity scale composed of scores for different body regions: face, shoulder, arms, abdomen, and legs (0=unaffected, 15=severely affected).¹⁷

Quantitative myometry was performed using a fixed myometry testing system (QMA, Gainesville, GA) with standardized positions in 14 bilateral muscle groups: shoulder abductors, external rotators, elbow flexors and extensors, knee extensors, ankle dorsiflexors, and handgrips.¹⁸ Manual muscle testing was performed by a trained physical therapist on 28 muscle groups: bilateral shoulder abductors, shoulder external rotators, elbow flexors, wrist flexors, wrist extensors, hip flexors, hip abductors, knee extensors, hip extensors, knee flexors, elbow extensors, ankle dorsiflexors, and plantar flexors, plus neck extensor and neck flexors.¹⁸

The 6-minute walk test (6MWT) is a test of strength and cardiopulmonary reserve and determines the distance walked using casual gait in 6 minutes. This test has been shown previously to have high test-retest reliability in Duchenne/Becker muscular dystrophy, where it was reliable and responsive to change over time.¹⁹⁻²¹ Additional standard functional tests included: time to ascend 4 stairs; timed supine to sit; and time to don/doff a jacket.^{22,18}

Statistical Considerations

Distributions for all parameters were tested for normality visually, and by performing the Shapiro-Wilk test. Descriptive statistics were used to describe all parameters (mean and standard deviation, median, and quartiles). Test-retest reliability was determined using the intra-class correlation coefficient based on a mixed effects model, with lower 95% confidence limits. To ensure technical consistency for reliability testing, outliers with leverage were identified from the linear regression plots using RStudent and CooksD. Outliers were removed if visual inspection of the tracing record showed technical inconsistencies with measurements. Additionally negative values at 10 kHz were used to identify recordings where probe contact was less than optimal. To determine the relative sensitivity of phase versus reactance to other measures of FSHD severity, correlation plots of the Pearson correlation versus EIM parameter at both 50 and 100 kHz were created. Fifty kHz reactance was determined to be the most sensitive measure and was used for subsequent analysis. The relationships with other known measures of FSHD disease (clinical severity, strength, and functional measures) were determined using Pearson correlations. All statistical tests were 2-sided, and *P*-value cut offs were adjusted for multiple testing (*P*<0.01 for tables 2 & 4, and *P*<0.007 for table 3).

Results

Thirty-five participants were included, and 18 returned within 3 weeks for test-retest reliability. Participants were mostly men (Table 1), adults, and moderately affected, but covering the range of disease severity from mild to moderately-severe. Most participants were FSHD type 1 (mean *D4Z4* fragment size 25.2 kb), except for 2 with SMCHD1 confirmed FSHD type 2.

Reliability was good to excellent for major muscle groups (deltoid, biceps, triceps, vastus lateralis, and tibialis anterior) with ICCs ranging from 0.72-0.99 (Supplementary Table S1, available online). Reliability for the abdominals and thoracic paraspinals was also acceptable (ICCs 0.71-0.98). There appeared to be a learning effect for the evaluator for recordings over the orbicularis oris; there were side-to-side differences in reliability likely due to the order of testing, with the right side tested first and ICCs <0.5, and the left side showing acceptable ICCs of 0.84-0.91. This was also likely complicated by technical limitations due to facial hair, and slightly longer recording times with the smaller pediatric sensors. Overall summary scores showed higher reliability due to the reduced variability in averaging across multiple muscles with ICCs for trunk, arm, and leg between 0.89 and 0.98.

Sample tables were made for the biceps, vastus lateralis, and thoracic paraspinal muscles to test the relationship of resistance, reactance, and phase to FSHD severity measures. The parameter that showed the strongest overall correlation with FSHD disease measures was reactance at 50 kHz, which was chosen for this study (Table 2). The 50 kHz reactance showed broad moderate to strong correlations with other FSHD disease measures, which made sense for the particular muscle being tested. For example the EIM value for the right vastus lateralis correlated with strength on MMT and QMT, as well as functional tasks like time to ascend 4 stairs or the 6 minute walk distance (Tables 3 & 4). The summary scores demonstrated tighter and more significant correlations with clinical severity and functional

measures than the individual muscle scores, likely reflecting the ability of the summary measures to serve as surrogates for overall disease state. The actual relationship between reactance and disease severity in FSHD was inverse: as severity increases, reactance decreases (Figure 2).

The relationship of EIM reactance with age was driven by disease duration, which can be seen by stratifying participants based on their age of diagnosis; a stronger correlation was seen for participants with longer disease duration (Figure 3A). Evaluating for differences due to known groups is underpowered for this study; women are known to be diagnosed later and to be less severely affected per age than men, but no clear difference in reactance or phase was seen here. Participants with *D4Z4* residual fragments <20 kb also tend to have more severe disease and demonstrated lower reactance values in some muscles (Figure 3B,C).^{2,23}

Discussion

EIM of major muscle groups and summary scores were reliable in FSHD, for both phase and reactance. Reactance appeared to be most sensitive to changes in other measures of FSHD disease severity, with moderate to strong correlations with other disease measures across a broad variety of assessments for FSHD. Of particular interest is the reliability and concordant validity of EIM recordings from muscles normally excluded from FSHD assessments, such as abdominal and paraspinal muscles. EIM of facial muscles may ultimately prove to be useful in FSHD if the technical hurdles that affect reliability can be overcome.

Prior studies in EIM have focused on the phase at 50kHz, as this was felt to be the most sensitive EIM metric. But this was largely based on the early work in motor neuron diseases, ALS and SMA.^{10,16,24} Studies designed to assess the impact of different tissue compartments on EIM measurements suggested reactance was particularly sensitive to muscle and less sensitive to skin or fat, likely due to the inherent permittivity to current flow in muscle tissue.⁸ Resistance is felt to reflect changes in skin and fat. Ultimately the decision to use 1 electrical parameter or another depends on the reliability of the measurements and the relationship to a feature of interest in the disease. Phase as a derived measure, which incorporates both reactance and resistance, may provide more stability. However to the degree stability in phase is due to resistance it may dilute the association with disease metrics of interest, because resistance is highly dependent on skin and subcutaneous fat. Here, although the phase was slightly more reliable in FSHD, there was a strong relationship with disease metrics when we used reactance. Thus, the increase in validity to disease metrics of interest should be weighed against any increase in variability of the measurement.

In the DMD literature, a couple of approaches to optimize EIM parameters have been used. In one the relative correlation to skin fold measurements versus correlation with the 6MWT to pick the frequency which gave the highest correlation to the functional measure, while minimizing the correlation to skin fold was used.¹² We did not optimize based on skin fold here, but the broad correlations with FSHD disease metrics suggest that 50 kHz reactance measures a metric of interest to FSHD by providing a value that relates to not only overall

severity but individual muscle strength and function. Future studies can look at further optimizing this metric, either by evaluating different frequency ranges or ratios of reactance to phase.²⁵ Many things argue for using the current approach at this stage of development. We have demonstrated acceptable reliability. Recordings at 50 kHz occur in a stable portion of the reactance versus frequency curve profile. Reactance already shows promising correlations to a broad set of FSHD disease measures. Ultimately it is the longitudinal relationships to change which will need to be used to determine optimized scores. What is desired from any outcome is reliability, concordant validity, and responsiveness. Caution must be used when trying to optimize EIM to cross-sectional data, as what is optimal in a cross sectional association may not prove to be optimal when gauging responsiveness.

EIM should be considered in the context of recent studies of MRI in FSHD. Muscle MRI studies in FSHD demonstrated fatty infiltration and structural changes, which could be quantified and followed over time.^{26,27} These structural changes demonstrate moderate baseline correlations with measures of strength or function. In addition, certain muscles demonstrated characteristic T2/STIR hyperintensities consistent with inflammation in otherwise ultrastructurally normal appearing muscle, which raises the possibility of identifying muscles at risk for future decline.^{26,28} However, MRI as a clinical outcome tool has a number of limitations: 1) MRI is not universally available and requires dedicated facilities; 2) there are significant site-to-site differences in equipment and technique; 3) MRI can take up to 40 minutes for a single limb; 4) MRI remains an expensive recurring cost; and 5) some patients with FSHD would be excluded from having a MRI due contraindications (e.g. metal in the body).

The advantages of EIM are readily apparent when collecting the measurements. It is painless, requires minimal training, and does not require specific expertise in post-processing. Preclinical data have shown good relationships with muscle structure. Muscles that are not typically tested can be included, in particular facial, abdominal, and paraspinal muscles. Lastly, the technology can allow measurements from the home, outside of formal study visits. The current commercial price for the complete system used here is \$18,000, and there is a \$50 per sensor recurring cost. Linear arrays used for tongue measurements may ultimately prove to be useful for measurements of facial muscles.²⁹ Both MRI and EIM may prove useful in FSHD. They may be complimentary in evaluating changes in response to therapeutics and allow better understanding of the natural history of disease in FSHD. For example, MRI could be used at baseline to stratify patients, and EIM could be used to follow individual muscles over time.

Limitations to this study include the sample size and inclusion of ambulatory subjects. EIM may also be useful for interventions in non-ambulatory patients, and the ability to reliably measure more affected muscles is not determined here. Whether EIM ultimately proves more responsive to disease progression needs to be determined.

EIM is a fast, commercially available, and simple technique for quantifying muscle composition and function. It expands our ability to measure muscles particularly affected in FSHD. Future directions will include determining the responsiveness to change in FSHD, optimizing recordings for clinical trials, and piloting home measurements of EIM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DMD	Duchenne muscular dystrophy
EIM	electrical impedance myography;
FSHD	facioscapulohumeral muscular dystrophy;
kHz	kilohertz
MHz	megahertz;
6MWT	six minute walk test;
SMCHD1	structural maintenance of hinge domain 1;
ICC	intra-class correlation;
MMT	manual muscle testing;
QMT	quantitative myometry;
ALS	amyotrophic lateral sclerosis;
SMA	spinal muscular atrophy;
MRI	magnetic resonance imaging.

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Figure 1.

A) The EIM device consists of a simple laptop computer connected to a portable hand-held sensor. B) Sample recording from the right biceps muscle showing the relationship of reactance to frequency range. The lines represent 3 different trials. Dotted lines represent the frequencies used in this study, which occur on the most stable portion of the reactance versus frequency curve. (C, D) Examples show EIM measurement locations for the biceps (C) and orbicularis oris (D).

Figure 2.

There is an inverse relationship between reactance and disease severity. As reactance goes down disease, severity goes up for FSHD. Rvl_x50 = 50 kHz reactance for the right vastus lateralis; FSHD_CS = FSHD clinical severity score.

Figure 3.

A) The relationship of leg 50 kHz reactance to age was largely driven by an association with longer disease duration; B) There was no clear difference for 50 kHz reactance for the right vastus lateralis in women; C) EIM values were lower for participants with *D4Z4* residual fragments ≤ 20 kb, a group thought to be more severely affected.

Table 1

Demographics.

Parameter	Value
Number	35
Men/Women (%)	27 (77.1)/8 (22.9)
Age, years (range)	53.0 (22-68)
Symptom Onset, years (range)	26.0 (10-55)
Disease Duration, years (range)*	14.1 (1, 41)
FSHD1 (%)	33 (94.3)
FSHD1 D4Z4 Residual Fragment kb (range)	25.2 (13-41)
FCS: 0=unaffected, 15=severe (range)	7.3 (2-12)

Kb=kilobase; FCS = FSHD Clinical Score.

* Disease duration is defined as the difference in age minus age of diagnosis.

Table 2

Sample for sensitivity analysis for right vastus lateralis shows a strong signal for the reactance value (n=35).*

	50 kHz			100 kHz		
Comparator	Phase	Reactance	Resistance	Phase	Reactance	Resistance
FSHD Clinical Severity Score	-0.26 (0.14)	-0.60 (0.0003)	-0.13 (0.47)	-0.27 (0.13)	-0.63 (0.0001)	-0.10 (0.59)
Combined LEXT MMT	0.37 (0.03)	0.57 (0.0004)	0.03 (0.85)	0.36 (0.04)	0.59 (0.0002)	0.00 (0.99)
Knee Extensor Right QMT Std	0.32 (0.07)	0.49 (0.003)	0.04 (0.82)	0.32 (0.06)	0.49 (0.003)	0.01 (0.94)
6 Minute Walk Test	0.50 (0.002)	0.69 (<0.0001)	-0.12 (0.49)	0.50 (0.003)	0.66 (<0.0001)	-0.16 (0.38)

LEXT = lower extremity; MMT = manual muscle testing; QMT = quantitative myometry; Std = standardized score.

*
P<0.01 considered significant.

Table 3

EIM 50 kHz reactance correlations with FSHD disease severity and function (n=35). *

Parameter	Age	Disease Duration	FSHD Clinical Score	6MWT	Ascend 4 Stairs	Don/Doff Coat	Supine to Sit
Right Vastus Lateralis	-0.22 (0.22)	-0.39 (0.02)	-0.60 (0.0003)	0.69 (<0.0001)	-0.65 (<0.0001)	-0.58 (0.0003)	-0.64 (<0.0001)
Right Biceps	-0.38 (0.03)	-0.41 (0.02)	-0.50 (0.003)	0.38 (0.02)	-0.39 (0.02)	-0.60 (0.0002)	-0.50 (0.002)
Right Thoracic Paraspinal	-0.33 (0.05)	-0.44 (0.008)	-0.51 (0.002)	0.37 (0.03)	-0.42 (0.01)	-0.49 (0.003)	-0.50 (0.002)
Leg	-0.39 (0.02)	-0.52 (0.001)	-0.72 (<0.0001)	0.74 (<0.0001)	-0.65 (<0.0001)	-0.65 (<0.0001)	-0.69 (<0.0001)
Arm	-0.33 (0.06)	-0.55 (0.0008)	-0.53 (0.001)	0.45 (0.007)	-0.53 (0.002)	-0.70 (<0.0001)	-0.58 (0.0002)
Trunk	-0.41 (0.01)	-0.41 (0.02)	-0.54 (0.001)	0.48 (0.004)	-0.47 (0.006)	-0.54 (0.0007)	-0.53 (0.001)
Face	-0.37 (0.04)	-0.34 (0.05)	-0.43 (0.02)	0.30 (0.10)	-0.25 (0.19)	-0.22 (0.24)	-0.26 (0.15)

MMT = manual muscle testing; UEXT = upper extremity; LEXT = lower extremity; QMT = quantitative myometry; PP = percent predicted normal; 6MWT = 6 minute walk test; REF = right elbow flexor, RKE = right knee extensor.

* P<0.007 considered significant.

Table 4

EIM 50 kHz reactance correlations with FSHD muscle strength (n=35). *

Parameter	Combined MMT	MMT UEXT	MMT LEXT	RKE QMT PP	REF QMT PP
Right Vastus Lateralis	0.63 (<0.0001)	0.46 (0.006)	0.57 (0.0004)	0.49 (0.003)	0.50 (0.005)
Right Biceps	0.54 (0.0007)	0.62 (<0.0001)	0.33 (0.05)	0.09 (0.59)	0.68 (<0.0001)
Right Thoracic Paraspinal	0.54 (0.0009)	0.51 (0.002)	0.43 (0.01)	0.05 (0.77)	0.37 (0.05)
Leg	0.76 (<0.0001)	0.60 (0.0002)	0.70 (<0.0001)	0.48 (0.003)	0.54 (0.002)
Arm	0.63 (<0.0001)	0.71 (<0.0001)	0.38 (0.03)	0.09 (0.62)	0.57 (0.001)
Trunk	0.56 (0.0004)	0.51 (0.002)	0.47 (0.004)	0.04 (0.82)	0.40 (0.03)
Face	0.40 (0.02)	0.30 (0.09)	0.40 (0.02)	0.32 (0.08)	0.16 (0.44)

MMT = manual muscle testing; UEXT = upper extremity; LEXT = lower extremity; QMT = quantitative myometry; PP = percent predicted normal; REF = right elbow flexor, RKE = right knee extensor.

* P<0.01 considered significant.