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Inter-session reliability of electrical impedance myography in children in a clinical trial setting

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HIGHLIGHTS

- Electrical impedance myography (EIM) is highly reliable in children even when measurements are made days apart and by different evaluators.
- EIM reliability is high whether evaluating single muscles or multiple muscles in combination.
- The reliability of EIM in healthy children and those with Duchenne muscular dystrophy is similar.

ABSTRACT

Objective: High reliability is a prerequisite for any test to be useful as a biomarker in a clinical trial. Here we assessed the reproducibility of electrical impedance myography (EIM) in children by comparing data obtained by different evaluators on separate days.
Methods: Healthy boys and boys with Duchenne muscular dystrophy (DMD) aged 2–14 years underwent EIM of multiple muscles performed by two evaluators on two visits separated by 3–7 days. Single and multifrequency data were analyzed. Reliability was assessed via calculation of the percent relative standard deviation (% RSD), Bland–Altman analysis, and the intraclass correlation coefficient (ICC).
Results: For both individual muscle data and data averaged across muscles, intra-evaluator measurements showed high repeatability for both 50 kHz phase and 50/200 kHz phase ratio values, with ICCs generally above 0.90 and % RSD below 10%. Inter-evaluator results showed very similar ICC and % RSD values as those obtained by the same evaluator.
Conclusions: Both the 50 kHz phase and 50/200 kHz phase ratio are reliable measures both across time and evaluators and in both health and disease.
Significance: These results support the concept that EIM can serve as a reliable measure in clinical therapeutic trials in a pediatric population.

1. Introduction

Better measures that can serve as reliable biomarkers of disease severity and drug effect in neuromuscular disease clinical trials are needed. For example, recent and ongoing clinical therapeutic trials in Duchenne muscular dystrophy (DMD) have relied on the 6-min walk test or muscle biopsy as the major outcome measures of drug efficacy (Finkel et al., 2013; McDonald et al., 2013). However, such measures are limited for many reasons. The 6 min walk test can be utilized in only a subset of boys – namely those who are ambulatory above the age of 5 years, requires considerable training for investigators to perform well, and has sufficient variability to have negatively impacted the results of at least two recent clinical trials (Hoffman and Connor, 2013). Although muscle biopsy for dystrophin staining has also been used especially in early-stage trials, it is impractical in larger trials and its relationship to functional improvement remains uncertain.

Electrical impedance myography (EIM) is a measure that is showing promise for the quantification of neuromuscular disease severity (Rutkove, 2009). In EIM, a weak, electrical current at multiple high frequencies (generally over 10 kHz) is applied to a localized area of tissue and the consequent surface voltages are measured. From these voltages, the complex impedance can be calculated, which includes the reactance (X), the resistance (R) from

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which the major outcome variable phase (θ) is derived via the trigonometric relationship: $\theta = \tan^{-1}\left(\frac{X}{R}\right)$.

To date, EIM parameters have proven to be very sensitive to disease status in a variety of disorders including amyotrophic lateral sclerosis (ALS), spinal muscular atrophy, and DMD (Tarulli et al., 2009; Rutkove et al., 2010, 2014). The alterations in EIM values are due to a variety of factors, including changes in muscle fiber size, organization, and the development of increasing connective tissue and intramuscular fat (Ahad et al., 2009; Li et al., 2014a). Recently, work has also shown that EIM is very sensitive to disease status in the muscular dystrophy (mdx) mouse, showing substantial differences compared to wild type animals at even young age (Li et al., 2014a). Importantly, EIM is very different from whole body bio-impedance techniques, which are mainly geared to the assessment of body composition, and thus provide no information on individual muscles or body regions. Also, unlike whole body bio-impedance analysis, EIM is relatively insensitive to hydration status (Li et al., 2014b) and can provide anisotropic (directional dependent) data on muscle condition (Garmirian et al., 2009).

Given the potential value of EIM for assessing neuromuscular disease, we recently initiated a longitudinal study assessing EIM changes over time in children with DMD and their relationship to standard functional measures. Indeed, early cross-sectional analysis of that baseline data has shown important correlations between function, age, and EIM data (Rutkove et al., 2014). However, before evaluating the value of these measures in assessing disease progression, it is critical that we establish the reliability of the measures in children. In this study, we describe a detailed analysis of the reliability of the technique in both healthy boys and those with DMD by comparing data obtained several days apart by the same and different evaluators.

2. Methods

Boston Children's Hospital Institutional Review Board approved the protocol, and parents and children provided written consent and verbal assent, respectively. Both healthy boys and those with DMD aged 2–14 years were recruited into the study through the neuromuscular clinic at Boston Children's Hospital with the plan to follow them for up to 2 years. Subjects were excluded if they had a pacemaker or other implanted electrical device. All subjects with DMD had genetic confirmation of disease or had a consistent history and were a brother of a family member with a genetically confirmed diagnosis. DMD subjects were excluded if they were involved in an ongoing clinical trial (outside of a natural history study) or if they had a concomitant neuromuscular or another medical condition that substantially impacted health. Healthy subjects had no history of neuromuscular disease or other disorder that would substantially impact muscle health and were recruited via advertisement and word-of-mouth. For all subjects, the analysis presented here comes from data obtained at the baseline visit as well as at a second visit designed specifically to assess the technique's reproducibility, 3–7 days after the initial visit.

2.1. EIM measurements

EIM measurements were obtained with the Imp SFB7 (Impedimed, Inc., Sydney Australia), using a custom hand-held array previously described (Narayanaswami et al., 2012). Three different probe sizes were used depending on the child's size (small: 4×1.5 cm, medium: 5×2 cm, large: 7×2.5 cm). Unilateral measurements were performed on 6 muscles/muscle groups on the dominant side: deltoid, biceps brachii, forearm flexors compartment, quadriceps (rectus femoris), tibialis anterior, and medial gastrocnemius. Placement of the probe was established by measuring the distance between anatomical landmarks that coincide with the connections of tendon to bone for each muscle. EIM measurements were performed both longitudinally and transversely to the major muscle fiber direction.

Importantly, all 6 muscles were measured by the same evaluator on the two separate visits to obtain intra-rater reliability; however, in the interest of time, only 2 muscles, biceps brachii and quadriceps, were evaluated by the second evaluator. Thus, only 2-muscle comparisons were available for inter-rater reliability.

2.2. Evaluators

The evaluators, all of whom were research assistants with no previous training in radiological or electrophysiological testing, were taught how to perform the EIM measurements by one of the senior authors. They were shown where to place the probes and what data was technically sound based on the appearance of the multi-frequency resistance and reactance curves on the device's screen (e.g., absence of low frequency artifacts due to poor electrode contact or negative values). No ongoing oversight was provided outside of this basic training, so as to be consistent with what would occur typically in a clinical trial in which this test was being utilized.

2.3. EIM procedure

For each measurement, children were placed in a sitting position with their arms and legs resting at a 90° angle at the elbow and knee. The skin was moistened with saline and the probe placed over the muscle of interest. Repeated measurements were made for all muscles at both the initial visit and at a second visit 3–7 days later by the same evaluator. For the biceps brachii and quadriceps only, a second evaluator made measurements as well on both days. An example of the testing being performed on a boy with DMD is shown in Fig. 1.

2.4. Data analysis

For both longitudinal and transverse measurements, the 50 kHz phase and recently developed 50/200 phase ratio (Schwartz et al.,

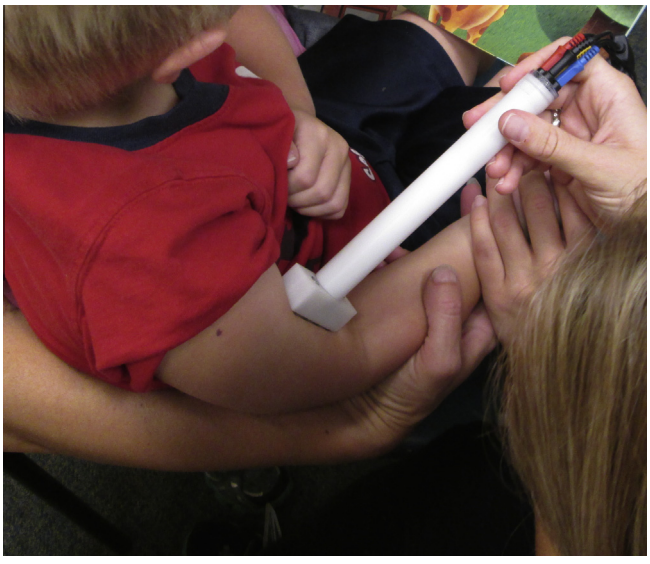

Fig. 1. EIM being performed on the biceps of a young boy with Duchenne muscular dystrophy. The array is placed longitudinally along the muscle. The connectors/wires at the end of the tube attach to the impedance-measuring device (not shown).