Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 27 (2017) 214–220

www.elsevier.com/locate/nmd

Effects of Duchenne muscular dystrophy on muscle stiffness and response to electrically-induced muscle contraction: A 12-month follow-up

Lilian Lacourpaille [a,*,1], Raphaël Gross [a,1], François Hug [a], Arnaud Guével [a], Yann Péréon [b], Armelle Magot [b], Jean-Yves Hogrel [c], Antoine Nordez [a]

[a] *Laboratory (Movement, Interactions, Performance) (EA 4334), Faculty of Sport Sciences, University of Nantes, France*
[b] *CHU Nantes, Centre de Référence Maladies Neuromusculaires Nantes-Angers, University of Nantes, Nantes, France*
[c] *Institute of Myology, GH Pitié-Salpêtrière, Paris, France*

Received 12 July 2016; received in revised form 24 November 2016; accepted 4 January 2017

Abstract

The present study aimed to assess the ability of muscle stiffness (shear modulus) and response to electrically-induced muscle contraction to detect changes in muscle properties over a 12-month period in children with Duchenne muscular dystrophy (DMD). Ten children with DMD and nine age-matched healthy male controls participated in two experimental sessions (T_0 and $T_{+12months}$) separated by 12.4 ± 0.9 months. Two contractions of the *biceps brachii* were electrically-induced during which an ultrasound probe was placed over the muscle. The resting shear modulus was measured using elastography from six muscles. Evoked maximal torque was increased at $T_{+12months}$ in controls (+11.2 ± 7.6%, $P < 0.001$) but was not modified in children with DMD ($P = 0.222$). Electromechanical delay (+12.9 ± 11.3%, $P < 0.001$) and its force transmission component (+10.1 ± 21.6%, $P = 0.003$) were significantly longer at $T_{+12months}$ than T_0 for children with DMD. The results revealed an increase in muscle stiffness at $T_{+12months}$ in children with DMD for *tibialis anterior* (+75.1 ± 93.5%, $P = 0.043$), *gastrocnemius medialis* (+144.8 ± 180.6%, $P = 0.050$) and *triceps brachii* (+35.5 ± 32.2%, $P = 0.005$). This 12-month follow-up study demonstrates that electromechanical delay and elastography may help detect subtle muscle impairments in patients with DMD. These sensitive outcomes may improve the follow-up of innovative therapeutic interventions within the field of DMD.

Keywords: Elastography; Ultrafast ultrasound; Evoked muscle force; Electromechanical delay; Myopathy

1. Introduction

Promising therapeutic options are being developed for children with Duchenne muscular dystrophy (DMD) [1,2]. Because some therapies aim to target a specific muscle or limb region [3,4], the development of non-invasive and sensitive methods to locally assess both muscle function and muscle biomechanics is needed. Recent studies have revealed the potential of two approaches that have the advantage of obviating voluntary and maximal contraction by the patients [5,6].

The first approach is the electromechanical delay (EMD), defined as the time lag between the onset of muscle activation and onset of force production [7]. EMD can be assessed during electrically-induced contractions using very high frame rate ultrasound (up to 5 kHz) [8–10]. The first part of the EMD is the delay between muscle electrical stimulation and the onset of muscle fascicle motion, which is mainly attributed to electrochemical processes such as the excitation–contraction coupling. Its second part is the delay between the onset of fascicle motion and the onset of force production, which is attributed to the force transmission processes. By determining the time required for the electrochemical and mechanical processes this technique provides information on both the function and the biomechanics of a targeted muscle. Applying this method to children with DMD, Lacourpaille et al. [5] reported a longer EMD in patients with DMD compared to healthy age-matched participants. This was mainly explained by an increased time required for the force to be transmitted to the skeleton (+75%). In addition, the electrically-evoked torque was lower in children with DMD.

Second, resting muscle stiffness can be reliably estimated in DMD using ultrasound shear wave elastography [6,11]. Although an increased stiffness was found in these patients for

* Corresponding author. Laboratory (Movement, Interactions, Performance) (EA 4334), University of Nantes, 25 bis Boulevard Guy Mollet, BP 72206, Nantes 44322 CEDEX 3, France. Fax: +33(0)251837045.
E-mail address: lilian.lacourpaille@univ-nantes.fr (L. Lacourpaille).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.nmd.2017.01.001
0960-8966/

five muscles *(tibialis anterior*, *gastrocnemius medialis*, *vastus lateralis*, *biceps brachii* and *triceps brachii),* there was no change for the distal *abductor digiti minimi* muscle (hand muscle) [6]. This latter result is in line with previous works showing that DMD progresses according to a proximal-distal pattern [12].

The assessment of both muscle stiffness and responses to electrically-induced contractions (EMD and torque amplitude) can provide important information related to muscle function and structure with potential relevance to clinical and therapeutic assessments. In order to bring new arguments for the use of these innovative biomechanical approaches, the present study aimed to assess their ability to detect changes in muscle properties over a 12-month period in children with DMD. We hypothesized that both muscle stiffness and the electromechanical delay would be increased after a 12-month period in patients with DMD.

2. Materials and methods

2.1. Participants

Ten DMD patients (genetically confirmed) and nine age-matched healthy controls volunteered to participate (Table 1). The experimental procedures were approved by the local ethics committee (Nantes Ouest IV – CPP-MIP-004) and all of the procedures conformed to the declaration of Helsinki. All the control subjects and patients with DMD have been previously reported elsewhere [5,6]. These prior articles dealt with the effects of DMD on muscle stiffness and response to electrically-induced muscle contraction whereas in this manuscript we report their ability to quantify the degenerative effects of DMD over a 12-month period.

2.2. Measurements

Elbow flexion force. Participants were seated with their right shoulder abducted (90°), elbow flexed at 90° with their wrist in a neutral position. To measure the force produced during elbow flexion, a force transducer (SML-50, Interface, USA; range: 0–50 lbf, sensitivity: 2 mV/V) was incorporated in a homemade ergometer and connected with Velcro straps to the wrist to ensure constant contact. The force signal was digitized at a sampling rate of 5 kHz (MP36, Biopac, Goleta, USA).

Electrical stimulation. Percutaneous electrical stimulation was applied over the *biceps brachii* to elicit its contraction. A constant-current stimulator (Digitimer DS7A, Digitimer, Letchworth Garden City, UK) delivered a single electrical pulse (pulse duration = 200 μs, 400 V) through two electrodes (2 × 1.5 cm, Compex, Annecy-le-Vieux, France) placed on the main motor point (previously determined as the location inducing the strongest twitch with the lowest electrical stimulation) and on the distal portion of the *biceps brachii* muscle. To determine the stimulation intensity required to induce the maximal elbow flexion force (Imax), the output current was increased by steps of 5 mA until a maximum force output or a maximum tolerable current output was reached.

Ultrasound. A very high frame rate ultrasound scanner (Aixplorer, version 7, Supersonic Imagine, Aix-en-Provence, France), coupled with a linear transducer array (4–15 MHz, SuperLinear 15–4, Vermon, Tours, France), was used in "research" mode to acquire raw radio-frequency signals at 4 kHz. Force and ultrasound data were synchronized using transistor–transistor logic pulses, as previously described [10,13].

Muscle stiffness. An Aixplorer ultrasound scanner (Aixplorer, version 7, Supersonic Imagine, France) coupled with a linear transducer array (4–15 MHz) was used in shear wave elastography mode [11]. This technique provides a 2-dimensional map of shear modulus (*i.e.*, index of muscle stiffness) of a localized area in real-time at one sample/s. Good reliability of this technique has been demonstrated [14]. For each muscle and each position, ten successive shear elastic measurements were averaged to obtain a representative value [14].

2.3. Protocol

DMD patients and healthy participants participated in two experimental sessions (T_0 and $T_{+12months}$) separated by 12.4 ± 0.9 months.

Electrically-induced contractions. Electrically-induced contractions were used to assess the amplitude of the elbow flexion torque and the electromechanical delay. To determine the minimal stimulation intensity required to induce the maximal elbow flexion force (Imax), the output current was incrementally increased (incremental step of 5 mA) until a maximum force output was reached [13]. The maximal elbow flexion force produced at Imax was used to calculate the evoked maximal torque. Two selective contractions of the *biceps brachii* were elicited by means of percutaneous electrical stimulation at 70% of Imax, with 15-s rest in between. This submaximal intensity was chosen to limit the discomfort associated with the stimulation and because we previously demonstrated that the EMD was not affected by an increase in stimulus intensity above 70% of Imax [13]. During these two electrically-evoked contractions, the ultrasound probe was placed over the thickest part of the *biceps brachii* muscle belly, parallel to the muscle fascicles [5]. Participants were instructed to be fully relaxed prior and during the stimulations.

Table 1
Individual data for DMD patients.

DMD patients (#)	Age	ACE	Corticosteroids	Thiocolchicoside	Calcium	Vitamin D
1	10			X	X	X
2	12				X	X
3	8	X			X	X
4	10					
5	7					
6	23	X				
7	8		X		X	X
8	22	X				
9	22	X				
10	14		X		X	

For each DMD patient, both age and medications provided as part of their standard care management are depicted. ACE, angiotensin-converting enzyme.