



Changes in viscoelastic properties of skeletal muscles induced by subthalamic stimulation in patients with Parkinson's disease

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ARTICLE INFO

Article history:

Received 16 May 2010

Accepted 21 September 2010

Keywords:

Myotonometry
Viscoelastic properties
Rigidity
Parkinson's disease
Deep brain stimulation

ABSTRACT

Background: Objective measurements would be useful to document the effect of deep brain stimulation in alleviating rigidity in patients with Parkinson's disease. The aim of the study was to examine the changes of viscoelastic properties in skeletal muscles as indicators of rigidity.

Methods: Six patients in an advanced stage of Parkinson's disease participated in the study. The study took place in the off-medication conditions after one night of drug withdrawal. The wrist rigidity was examined according to the Unified Parkinson's Disease Rating Scale in both sides. Myotonometry (Myoton) was used to determine stiffness and elasticity in extensor digitorum muscles bilaterally. The measurements were repeated and compared during the stimulation-on and stimulation-off periods.

Findings: A comparison of mean clinical motor scores revealed a significant improvement of parkinsonian symptoms due to brain stimulation. In particular, arm rigidity improved on average from 2.83 (1–4) in stimulation-off phase to 1.17 (0–2) in stimulation-on phase ($P < 0.05$). The mean values of elasticity and stiffness were not significantly different in stimulation-on and stimulation-off conditions. The patients with elevated clinical rigidity scores had higher mean values of stiffness (262.5 vs 211.0; $P < 0.05$) but the differences in elasticity were not significant.

Interpretation: Increased rigidity is associated with increased values of viscoelastic stiffness. This paper supports the use of myotonometry for objective quantification of rigidity and in the future, this tool could prove helpful for optimizing deep brain stimulation settings in patients with Parkinson's disease.

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1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is currently considered as the most important surgical option in the treatment of patients with advanced Parkinson's disease (PD) (Kleiner-Fisman et al., 2006). DBS improves most of the motor symptoms of PD, and reduces motor fluctuations and dyskinesias. Effective STN stimulation can induce a sudden decrease in muscle tone, which has been used for optimal programming of the stimulator settings.

Assessment of skeletal muscles is common in PD and the change in rigidity is usually subjectively quantified by passive flexion/extension movements around the wrist joint according to the Unified Parkinson's Disease Rating Scale (UPDRS) item 22. Unfortunately, the UPDRS score relies substantially on the clinical experience of the evaluators and the reliability between different raters can be poor (Prochazka et al., 1997). However, rigidity is frequently evaluated to assess the efficacy of pharmacological or neurosurgical therapies, or to observe the course of the disease. Objective measurements of rigidity are rather difficult to perform, still, simple and reliable methods of quantifying parkin-

sonian rigidity would be potentially very useful. Earlier a number of researchers have employed electromyogram (EMG) recordings and torque motors to evaluate rigidity in patients with PD (Caligiuri, 1994; Kirolos et al., 1996; Lee et al., 2002; Levin et al., 2009; Teräväinen et al., 1989; Xia et al., 2006). Recently, efforts have been made to document the effect of DBS on quantified measures of rigidity in patients with PD (Levin et al., 2009; Shapiro et al., 2007; Tabbal et al., 2008). Most of the studies have established good correlations with clinically examined rigidity, however, due to the complicated nature of these measurements, none of the methods has been accepted for standard clinical utilization.

The properties of the skeletal muscles consist of integrated functions of several structures (Bruton, 2002; Roberts, 2002; Schleip et al., 2006). The literature on muscle viscoelastic behaviour is sparse, however, human resting muscle tone is usually described as the passive tonus or tension of the skeletal muscle that derives from its intrinsic molecular viscoelastic properties (Masi and Hannon, 2008). Evaluation of skeletal muscle properties is accepted in clinical use to evaluate the treatment effect or progression of the pathology (Simons and Mense, 1998). Several researchers have tried to develop and validate noninvasive techniques with appropriate equipment to evaluate viscoelastic properties of skeletal muscles (Fukushiro et al., 2001; Hajrasouliha et al., 2005; Horikawa, 2001; Leonard et al., 2003;

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Prochazka et al., 1997; Sepehri et al., 2007). The Myoton myotonometer (Müomeetria Ltd., Tallinn, Estonia) is a simple handheld device for measuring viscoelastic properties of muscles by recording the damped mechanical oscillations. Several articles describe utilization of Myoton equipment for the evaluation of the viscoelastic properties of the skeletal muscles or soft tissue (Bizzini and Mannion, 2003; Gavronski et al., 2007; Veldi et al., 2000, 2004; Viir et al., 2006). There is only a limited amount of data on viscoelastic properties of skeletal muscles in patients with PD (Patrick et al., 2001; Sepehri et al., 2007). Myoton has never been used to evaluate patients with PD and the effect of DBS on the measurements has not been demonstrated. Viscoelastic stiffness has already been related to parkinsonian rigidity (Patrick et al., 2001; Prochazka et al., 1997; Sepehri et al., 2007; Tabbal et al., 2008) and it can be hypothesised that simple myotonometric measurements of rigidity could be useful for postoperative programming of DBS parameters in patients with PD.

The present study was performed to examine the relations between DBS-induced changes of the viscoelastic properties of skeletal muscles as compared to the changes of rigidity in patients with PD.

2. Methods

Six male patients in an advanced stage of PD participated in the study. Mean age of the patients was 61.3 years (range 44–68), mean disease duration 17.7 years (range 8–24). In the preoperative period patients were evaluated with the UPDRS: the average score in the UPDRS part III (motor evaluation) was 26.2 in the on condition and 53.7 in the off condition. The average total equivalent dose of antiparkinsonian medications in the presurgical period was 1315 mg/day (range 712.5–1750 mg/day). Patients gave their informed consent to the study and the project was approved by the Ethics Committee at the University of Tartu.

2.1. Surgery

Surgery was performed with the patient off-medication. A stereotactic frame (Leksell G frame, Elekta, Sweden) was placed under local anesthesia. Stereotactic localisation was performed using a combination of direct and indirect targeting based on preoperative magnetic resonance imaging and intraoperative stereotactic computed tomography. Our usual coordinates were 3 mm posterior to the mid AC–PC point, 4 mm inferior to the AC–PC plane, and 12 mm lateral to the midline. The DBS electrodes were implanted after electrophysiologic mapping. We used an array of up to three micromacroelectrodes (Inomed Medizintechnik GmbH, Teningen, Germany), separated by 2 mm, for physiological localization of the STN. The final location of the DBS electrodes was selected based on microelectrode recording and macrostimulation through the electrodes. The DBS electrode was

placed on the tract where we found the best stimulation parameters, i.e., the lowest current threshold producing a clinical improvement and high current threshold producing adverse effects. The DBS electrodes (DBS Medtronic 3387; Medtronic, MN, USA) were implanted bilaterally at 1 mm below the ventral border of the target structure. The electrodes were connected to a dual channel pulse generator (Kinetra, Medtronic, MN, USA) which was implanted into the infraclavicular fossa under general anesthesia on the same day.

Postoperative initial programming of pulse width, frequency and voltage, electrode contact, and polarity (mono or bipolar) was performed during the first weeks after the surgery. Stimulation parameters were set according to the results of the initial programming and adjusted during the follow-up reprogramming sessions until optimal antiparkinsonian effects were seen, without side effects. A concomitant change in medication was made according to the effects of long-term stimulation.

The patients had been treated with STN DBS, for an average of 1.5 years (range 1–2). DBS parameters had a pulse width of 60 μ s and a pulse rate of 130 Hz bilaterally in all patients. The mean amplitude of the stimulation was 3.0 V (range 2.2–5.0 V). All the patients received monopolar stimulation (Table 1).

Six healthy age-matched controls (mean age 59.0 years, range 45–65) also participated in the study. None of the controls had a history of movement disorders or was taking any drugs that could interfere with skeletal muscle properties.

2.2. Myotonometry

Myoton enables to examine mechanical oscillations of skeletal muscles provoked by a mechanical impact. The constant mechanical impact is made by the testing end of the machine which is placed perpendicularly on the surface of a muscle and then accelerated by an electromagnetic pole in the same direction. The testing end is connected to the acceleration transducer and acts also as a sensor for the tissue response. The impact causes the tissue under the probe to be deformed and after that the mechanical oscillations of the tissue occur governed by the viscoelastic properties of the tissue. The determined values are calculated from the acceleration of the testing end during the measurements (Fig. 1, for full details see Veldi et al., 2002 and Gavronski et al., 2007).

Elasticity is the ability of the body to recover its shape and it is characterized by the logarithmic decrement of the damped oscillations [$\vartheta = \ln(a_3/a_5)$]. It describes the loss of mechanical energy as the amplitude of the oscillations declines. During the contraction in normal muscle the decrement value decreases and the elasticity increases.

Stiffness reflects the resistance of the tissue to the force that changes its shape ($C = m \times a_{\max} / \Delta l$). The higher this value is, the more

Table 1
Patient characteristics.

Patient number	Age	Side	Post-surgical UPDRS item 22, medication-off		DBS parameters		Antiparkinsonian medication
			DBS-on	DBS-off	Stim. level (V)	Electrode contacts	
1	64	L	0	2	2.6	7-, C+	Carbidopa/levodopa CR 50/200, 3 tab Amantadine 100 mg, 2 tab
		R	1	3	2.6	3-, C+	
2	68	L	0	3	2.2	7-, C+	Carbidopa/levodopa CR 50/200, 8 tab Ropinirole 4 mg, 1 tab
		R	0	2	3.0	2-, C+	
3	61	L	2	4	3.0	6-, C+	Carbidopa/levodopa CR 25/100, 5 tab Pramipexole 0,7 mg, 1 tab Amantadine 100 mg, 1 tab
		R	1	4	4.0	1-, C+	
4	44	L	2	4	2.6	6-, C+	Carbidopa/levodopa CR 50/200, 7 tab Amantadine 100 mg, 2 tab Carbidopa/levodopa 50/200, 1 tab Pramipexole 0,7 mg, 4 tab
		R	2	4	2.1	1-, C+	
5	68	L	2	2	5.0	6-, C+	Carbidopa/levodopa CR 25/100, 5 tab Pramipexole 0,7 mg, 2 tab
		R	2	4	4.7	2-, C+	
6	63	L	1	1	2.2	5-, C+	Carbidopa/levodopa CR 25/100, 4 tab
		R	1	1	2.2	1-, C+	

UPDRS = Unified Parkinson's Disease Rating Scale, DBS = deep brain stimulation.

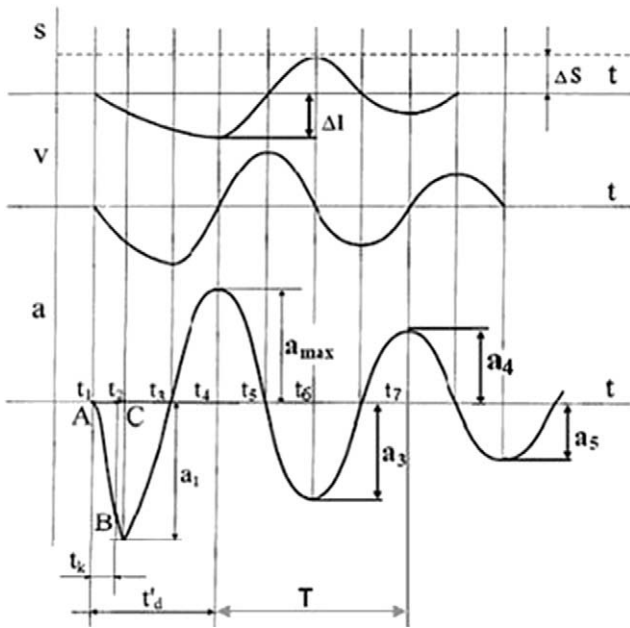


Fig. 1. The schematic graph depicting waveforms of acceleration (*a*), velocity (*v*), and displacement of the tissue (*s*), acquired in the process of damped natural oscillations in myotonometry. The t_k indicates the duration of the impact of the testing end on the tissue and *a* is the amplitude of the oscillations. The direct impact of the testing end on the tissue (t'_d) is considered terminated when the tissue deformation is the deepest (Δl —graph *S*), and the speed of the testing end is zero (graph *V*).

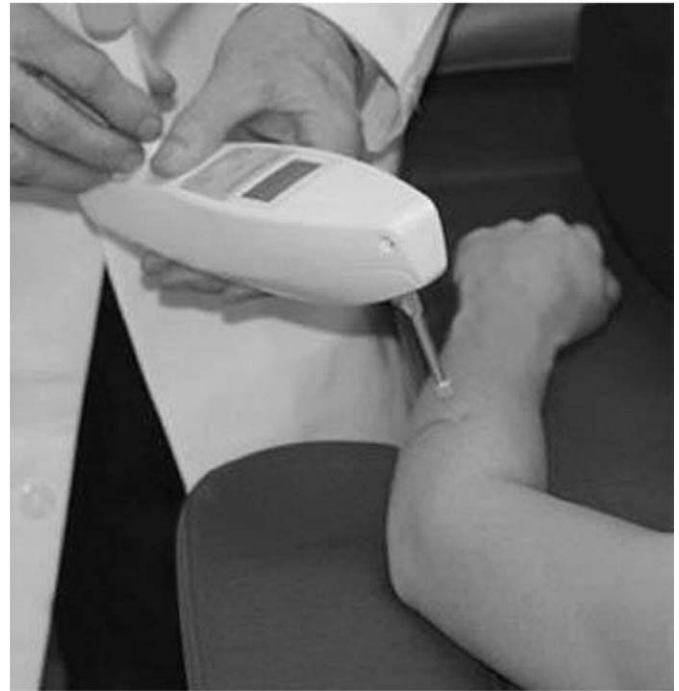


Fig. 2. Measurement of skeletal viscoelastic properties on *musculus extensor digitorum* with Myoton.

energy is needed to modify the shape of the tissue. During contraction in normal muscle the stiffness usually increases proportionally with the increase in the contraction force.

2.3. Experimental design

The study took place in an off-medication condition after one night of drug withdrawal. During the tests, the subjects were sitting relaxed on an examination chair with the upper extremity bended at elbow joint at 30–45° from the longitudinal axis of the upper arm and palm downwards. The experiments were performed by two examiners. The wrist rigidity was examined according to the UPDRS in both sides while the testing person was blinded for the assessment by the device. First, one examiner flexed and extended the joint as in a regular clinical examination for ten times and after that myotonometric measurements were performed by the second examiner on *m. extensor digitorum*. The location of the measuring point on *musculus extensor digitorum* was defined at the line of proximal one-third of the upper arm, ± 10 mm more proximally or distally, in the middle of the muscle belly. The muscle belly was identified by manual palpation. The testing end of the myotonometer was kept perpendicularly with the muscle's surface and was not moved horizontally during the impact. The myotometer's impact mechanism was started by slowly lowering the case of the myotonometer and the myotonometer was never inclined from the vertical direction more than ±30° to any direction. Ten consecutive measurements were made and then the procedure was repeated on the other hand. At the beginning, the measurements were carried out during the stimulation-on state. Then the DBS stimulator was switched off and the experiments were repeated after 2 h. Only the average values of the measurements were used for further analysis (Fig. 2).

2.4. Statistical analysis

Left and right sides were treated separately. The data was checked for normality using Shapiro–Wilk's *W* test. Data from patients and

control subjects was compared using one-way analysis of variance (ANOVA). The paired *t*-test was used to compare the viscoelastic parameters during stimulation-on and stimulation-off periods. For the purpose of statistical analysis, UPDRS motor score values were dichotomized for a low rigidity (UPDRS 0–2) and high rigidity (UPDRS 3–4). The ANOVA *t*-test for pairs of groups was used to compare the viscoelastic parameters of the tested muscles in the groups with high and low rigidity ratings. The Tukey–Kramer Honestly Significant Differences (HSD) test was used for *post-hoc* analysis. The analyses were performed with the use of JMP software (version 8.0.1, SAS Institute Inc., Cary, NC, USA). A *P*-value < 0.05 was considered statistically significant.

3. Results

All patients benefited substantially from the treatment. Mean UPDRS motor scores improved from 56 during stimulation-off – medication-off phase to 18.3 during stimulation-on – medication-off phase (*P* < 0.05). Arm rigidity improved at the same time from 2.83 (1–4) to 1.17 (0–2) (*P* < 0.05). Although tremor was significantly higher in the DBS-off phase (2.25; 0–4; UPDRS 20) than in the DBS-on phase (0.4; 0–2), the flexion/extension movements of the wrist during the examination considerably reduced tremor and the myotonometric measurements were performed with no obvious interference caused by tremor.

The mean values of elasticity and stiffness of the patients measured in the DBS-on conditions did not differ significantly from the values obtained in the DBS-off conditions (Table 2, Figs. 3 and 4).

High rigidity (UPDRS 3–4) was revealed during 7/24 (29%) of the evaluations. The values of stiffness were significantly higher in cases with high rigidity ratings as compared to the patients with low UPDRS values (Table 2, Fig. 3). Elevated rigidity ratings were not found to be significantly related to the changes in values of elasticity (Table 2, Fig. 4).

Only the mean values of muscle stiffness in the high rigidity group were significantly higher than the measurements performed in

Table 2
General effect of STN DBS and elevated rigidity on the viscoelastic parameters of the skeletal muscles.

	State	Stimulation-on	Stimulation-off	P-value
General effect of STN DBS	Decrement	1.31 (0.40)	1.35 (0.30)	NS
	Stiffness (N m^{-1})	220.0 (40.3)	232.5 (54.7)	NS
General effect of rigidity	Decrement	1.35 (0.35)	1.28 (0.36)	NS
	Stiffness (N m^{-1})	211.0 (40.8)	262.5 (45.4)	0.01 ^a

UPDRS = Unified Parkinson's Disease Rating Scale, DBS = deep brain stimulation, STN = subthalamic nucleus. Data are given as means (standard deviations).

^a Tukey–Kramer HSD test.

controls (262.5 (SD 45.4) vs 208.1 (SD 31.4)); the Tukey–Kramer HSD test, $P = 0.02$).

4. Discussion

In this study we described evaluation of viscoelastic properties of skeletal muscles in patients with PD using myotonometry (Myoton). The study was focused on the associations between DBS-induced changes in rigidity and changes in viscoelastic stiffness.

We found that increased rigidity is associated with increased values of stiffness. In 2007, Sepehri et al. designed a test rig to measure range of motion and viscous and elastic components of passive stiffness in patients with Parkinson's disease. The results showed significant correlation between viscous component of stiffness and UPDRS score. In 1997, Prochazka et al., introduced a device for the quantification of limb stiffness which was applied to the measurement of parkinsonian rigidity. This method quantifies the clinical examination and employs small sensors to monitor forces and angular displacements imposed by the clinician onto the limb segment distal to the joint being evaluated. Force and displacement data are used to calculate mechanical impedance (i.e., the vectorial sum of elastic and viscous stiffnesses). The reliability and validity of the device has been evaluated later and interexaminer agreement of measures of mechanical impedance in subjects with PD has been comparable to that of clinical UPDRS scores (Patrick et al., 2001). Tabbal et al., have used the impedance-based quantitative measurements to document the significant effect of STN DBS-on rigidity. We found that rigidity decreased significantly due to STN stimulation but the effect of DBS-on viscoelastic stiffness was significant only in comparison of groups with high and low rigidity values. Due to the subjective nature of UPDRS evaluations and small group of patients, it would have been

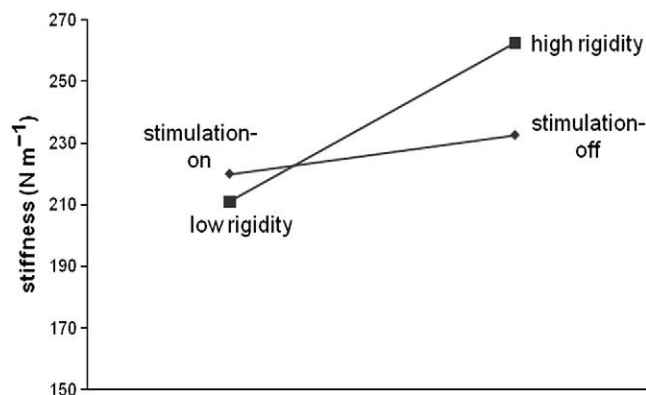


Fig. 3. Effects of DBS and clinical rigidity values on viscoelastic stiffness as measured with myotonometry (Myoton) in patients with PD. Mean values of stiffness are presented.

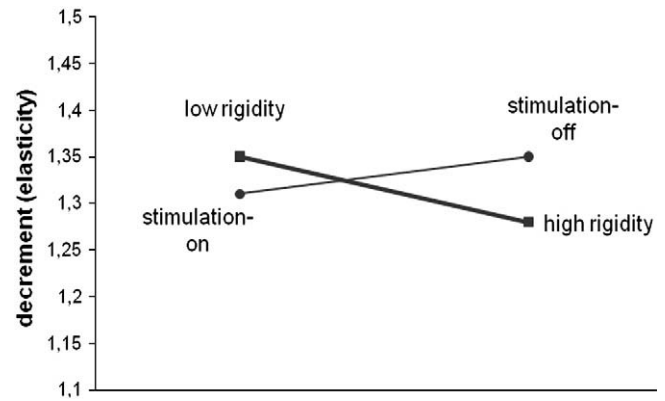


Fig. 4. Effects of DBS and clinical rigidity score on decrement (elasticity) as measured with myotonometry (Myoton) in patients with PD. Mean values of decrement are presented.

difficult to expect a direct correlation between UPDRS values and stiffness in our study. Unfortunately, due to the differences in the design of the measurement devices, the studies are not directly comparable, however, the methods seem to enable researchers to objectively describe the changes in rigidity in patients with PD.

We determined that the associations between the changes in elasticity and rigidity were not significantly related in our patients. In 2007, Gavronski et al., found that contracted muscles become generally more elastic and stiff at the same time. In normal muscles, it has been proposed, that as the elasticity of a muscle increases at contraction, the mechanical energy is released more efficiently for the movement with a minimum loss for plastic change in the shape of the muscle (Lindstedt et al., 2002). Sepehri et al. (2007), have earlier reported about better correlation between viscous component of stiffness and UPDRS score as compared to the elastic component in patients with PD. The decrease in elasticity has been observed in tongue muscles in patients with obstructive sleep apnea syndrome, and proposed to be associated with the relaxation and bursts of activity of tongue muscles during the sleep (Veldi et al., 2004). The pathophysiological basis of the changes in biomechanical properties of skeletal muscles in PD remains unclear, however, in these patients the decrease in elasticity might be related to the periodic muscular activity due to tremor.

We succeeded in performing the measurements of viscoelastic properties of skeletal muscles with Myoton equipment in patients with PD. With Myoton, the examiner needs to perform straightforward measurements and does not need complicated experimental setup, thus, it is easy to use in the hospital settings and during the routine patient evaluation. The method provides clear and simple numerical values and has been shown to have excellent interobserver repeatability and intraclass correlations (Bizzini and Mannion, 2003; Viir et al., 2006). Patients contributing in this research were not specially selected rigidity dominant patients, still, tremor did not interfere with the measurements. As far as we know, this is the first paper to examine the relations between the viscoelastic properties of the skeletal muscles, as characterized by myotonometry, and the changes of rigidity in patients with PD. Our results indicate that the method could potentially be very useful to quantify rigidity in PD patients and further studies in this field with larger patient groups are warranted.

We conclude that increased rigidity is associated with increased values of viscoelastic stiffness in patients with PD. Our results support the use of myotonometry as an objective method to evaluate rigidity in patients with PD. The method could be helpful for optimizing stimulator settings during DBS treatment. Larger patient groups are necessary to verify the results and to estimate the limits of stiffness on different degrees of rigidity due to PD.

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