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The effect of subthalamic stimulation on viscoelastic stiffness of skeletal muscles in patients with Parkinson's disease

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ABSTRACT

Background: Myotonometric evaluation of viscoelastic stiffness of skeletal muscles has been proposed to document the effect of surgical or pharmacological treatment on rigidity in patients with Parkinson's disease. The aim of the study was to analyze the changes of viscoelastic stiffness induced by deep brain stimulation.
Methods: Fifteen 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 Unified Parkinson's Disease Rating Scale was used for clinical assessment of the disease. Myotonometry was used to measure viscoelastic stiffness in the resting muscles before and directly after passive wrist movements, commonly used for clinical evaluation of rigidity. The measurements were repeated during the stimulation-on and stimulation-off periods and compared with fifteen healthy control persons.
Findings: The clinical scores for wrist rigidity improved from 3.0 (1–4) to 0.93 (0–2) ($P < 0.05$) due to brain stimulation. The mean values of viscoelastic stiffness were similar before and after passive wrist movements, but the differences between the patients with high vs. low rigidity values (354.9 vs 310.2 N/m; $P < 0.05$) and in stimulation-off vs. stimulation-on conditions (342.7 vs 310.5 N/m; $P < 0.05$) were significant only if the measurements had been performed after passive wrist movements.
Interpretation: Effective deep brain stimulation and increased rigidity can significantly change viscoelastic stiffness in the resting muscles in patients with Parkinson's disease, especially if evaluated after passive wrist movements. This paper supports the use of myotonometry for objective quantification of parkinsonian rigidity at rest.

1. Introduction

Parkinsonian rigidity is usually defined as an increased resistance to passive movement of a limb and the change in rigidity is subjectively quantified by passive flexion/extension movements of major joints according to the Unified Parkinson's Disease Rating Scale (UPDRS). Medical or surgical treatment of Parkinson's disease (PD) induces significant changes in muscular rigidity, which are useful for evaluation of treatment effectiveness. Unfortunately, the clinical evaluation of rigidity is substantially dependent on examiners' individual interpretations and this can limit the utility of the clinical quantification to observe the course of the disease and to assess the efficacy of different therapeutic interventions. Therefore a number of researchers have employed torque motors to measure the imposed force resistance to externally generated passive movements (Caligiuri, 1994; Kirollos et al., 1996; Lee et al., 2002; Teräväinen et al., 1989; Xia et al., 2006) or explored EMG recordings (Levin et al., 2009) to evaluate parkinsonian rigidity, however, none of the methods has been accepted for standard clinical utilization.

Parkinsonian rigidity is caused by neural-mediated abnormal muscle reflex responses combined with non-neural components (Dietz et al., 1981; Watts et al., 1986), which include viscoelastic (i.e., mechanical) properties of muscle fibers and passive connective tissues. The neural and non-neural mechanisms operate in parallel and the rigid muscles are stiffer than normal muscles even in totally relaxed state with no electromyographic activity present (Watts et al., 1986). Increased values of viscoelastic stiffness in resting muscles has been explained by adaptive structural alterations and atrophic changes in muscle fibers (Narici and Maganaris, 2006; Rossi et al., 1996) or by changed neuromuscular drive into the skeletal muscles of PD-patients (Takakusaki et al., 2003). Different researchers have tried to develop and validate non-invasive techniques with appropriate equipment to evaluate viscoelastic properties of skeletal muscles (Fukashiro et al., 2001; Horikawa, 2001; Leonard et al., 2003; Prochazka et al., 1997; Sepehri et al., 2007) and explored relations between viscoelastic stiffness and parkinsonian rigidity (Patrick et al., 2001; Prochazka et al., 1997; Sepehri et al., 2007; Tabbal et al., 2008). Myotonometry is one of the methods which has been used for evaluation of viscoelastic properties of the muscles or soft tissue (Bizzini and Mannion, 2003; Gavronski et al., 2007; Veldi et al., 2000, 2004; Viir et al., 2006) and it has also been tested in small groups of patients with PD (Marusiak et al., 2010, 2011, 2012; Rätsep

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and Asser, 2011). Myotonometry has been presented as a sensitive tool to show higher muscle passive stiffness in PD-patients as compared to healthy controls (Marusiak et al., 2010). However, effective deep brain stimulation (DBS) can induce a sudden decrease of parkinsonian rigidity, but significant change of viscoelastic properties of skeletal muscles due to DBS has not been detected in patients with PD (Rätsep and Asser, 2011). Furthermore, the utilization of myotonometry for evaluation of parkinsonian rigidity is still to be verified, especially as myotonometry evaluates viscoelastic properties in muscles at rest, but the clinical rigidity values are also affected by abnormalities in neural-mediated muscle reflex responses, like shortening reaction and stretch-induced inhibition (Xia, 2011). Nevertheless, the viscoelastic stiffness (assessed at rest with myotonometry) and rigidity (assessed clinically during passive joint movements) share similar mechanisms of muscle state regulation (Marusiak et al., 2012; Xia, 2011). Moreover, from the methodological point of view, it has been suggested that, in order to better reflect the clinical scores, the novel methods should not differ significantly from the clinical examination (Prochazka et al., 1997), which has routinely used passive joint movements for evaluation of rigidity. As the myotonometric measurements cannot be performed during passive movements due to muscle belly displacement, the rationale of performing the measurements in conjunction with passive joint movements is not clear. Still, the myotonometric measurements in PD-patients might be affected by coexisting tremor like muscle activity and to avoid this phenomenon, the common maneuver is to perform few passive joint movements before the measurements. However, so far there is no study comparing myotonometric measurements at rest before and after passive joint movements, to check the effect of this maneuver on myotonometric measurements of viscoelastic stiffness.

The aim of the study was: 1) to explore the utilization of myotonometry for objective quantification of parkinsonian rigidity; 2) to analyze the changes of viscoelastic stiffness induced by DBS of the subthalamic nucleus (STN) in patients with PD; 3) to compare the myotonometric measurements in the resting muscles performed before and directly after passive wrist movements (PWM), commonly used for the clinical assessment of rigidity according to UPDRS.

2. Methods

Fifteen patients (12 males, 3 females) in an advanced stage of PD participated in the study. Mean age of the patients was 63.1 years (range 44–75), mean disease duration 16.8 years (range 8–31) (Table 1). The Hoehn and Yahr scale (Hoehn and Yahr, 1967) and the UPDRS were used to evaluate the PD-patients: the average preoperative score in the UPDRS part III (motor evaluation) was 20.4 in the medication-on condition and 53.5 in the medication-off condition. The average total equivalent dose of antiparkinsonian medications in the presurgical period was 1435 mg/day (range 712.5–1950 mg/day). Our surgical technique has been described in detail elsewhere (Rätsep and Asser, 2011) and the surgical procedure for implantation of DBS has been performed as part of the clinical management of the patients. Before the study, the patients had been treated with STN-DBS for an average of 2.9 years (range 0.5–9). DBS parameters had a pulsewidth of 60 μs and a pulse rate of 130 Hz bilaterally in all patients. The mean amplitude of the stimulation was 3.1 V (range 2–5 V). Eleven patients received monopolar, two patients mono- and bipolar, and two bipolar stimulation (Table 1).

Fifteen healthy persons (12 males and 3 females, mean age 62.7 years, range 45–73) participated in the study as a control group. None of the healthy controls had a history of movement disorders, surgical procedures (including DBS) or medical treatment that could interfere with skeletal muscle properties.

The patients, as well as the control persons, gave their informed consent to the study and the project was approved by the Ethics Committee at the University of Tartu.

2.1. Myotonometry

The MyotonPro myotonometer (Müomeetria Ltd., Tallinn, Estonia) was used to measure viscoelastic stiffness of the skeletal muscles in patients as well as in control persons. The myotonometer provokes mechanical oscillations of the muscles by a constant mechanical impact made by the testing-end of the machine. The impact deforms the muscles under the probe and the following mechanical oscillations are governed by the viscoelastic properties of the tissue. The determined values of viscoelastic properties are calculated from the acceleration of the testing end during the measurements (Fig. 1, full details of the method are given elsewhere) (Gavronski et al., 2007; Veldi et al., 2000). Viscoelastic stiffness, as measured by myotonometry, reflects the resistance of the muscle to the force that changes its shape ($C = m \times a_{max}/\Delta l$). The higher this value is, the more energy is needed to modify the shape of the muscle.

Table 1
Patient characteristics.

Pt. n	Age	Gender	Hoehn- Yahr scale[a] postop. (preop.)	Dominant side	Post-surgical UPDRS item 22, medication-off		DBS parameters		Antiparkinsonian medication[b] (mg/day)
					DBS-on	DBS-off	Stim. level (V)	Electrode contacts	
1	52	M	2,5 (4)	R	1	3	3.0	3-, C+	750
2	67	M	2,5 (5)	R	0	3	3.0	0-, 1+	1820
3	71	F	3 (5)	R	1	3	3.0	0-, 1+	1205
4	64	F	4 (5)	R	1	2	2.2	2-, C+	1715
5	62	M	2,5 (4)	L	1	3	2.0	7-, C+	750
6	68	F	2 (3)	L	1	2	2.7	6-, C+	1560
7	75	M	2,5 (4)	L	1	3	4.5	5-, 6+	1000
8	71	M	2,5 (4)	R	1	3	2.5	2-, C+	840
9	70	M	3 (4)	L	2	4	4.0	5-, C+	–
10	56	M	3 (4)	R	1	3	3.0	1-, C+	750
11	50	M	2 (3)	L	0	1	5	4-, C+	500
12	68	M	3 (4)	L	0	3	2.2	7-, C+	680
13	61	M	2 (3)	L	1	4	3.0	6-, C+	550
14	44	M	3 (5)	R	2	4	2.1	1-, C+	1730
15	68	M	3 (5)	R	1	4	4.7	2-, C+	655

UPDRS = Unified Parkinson's Disease Rating Scale, DBS = deep brain stimulation.
[a] The postoperative Hoehn-Yahr scores are presented in DBS-on, medication-off conditions and the preoperative scores in medication-off conditions.
[b] Total equivalent dose of antiparkinsonian medications.