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The effect of medication on vastus lateralis muscle activation patterns in Parkinson's disease patients

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ABSTRACT

The effect of levodopa on muscle activity patterns in Parkinson's disease (PD) patients is currently unclear. The aim of the present study was to compare the spatial distribution pattern of electromyographic activity during sustained isometric contraction in PD patients during on- and off-medication periods using multi-channel surface electromyography (SEMG). Ten female PD patients were recruited for the present study. All patients performed a sustained isometric knee extension at 10% maximum voluntary contraction task for 60 s. To evaluate alterations in the spatial SEMG potential distribution, the coefficient of variation (CV) of force, normalized root mean square (RMS), modified entropy, CV of the RMS, and correlation coefficients were calculated at during contraction task. The off-medication period exhibited more fluctuation during the contraction task than those in the on-medication period. The off-medication period exhibited less change in modified entropy, the CV of RMS, the correlation coefficient and patterns of spatial SEMG distribution. These data demonstrated that the heterogeneity and changes in the activation pattern are smaller in the off-medication period than in those in the on-medication period. These findings might indicate that levodopa enhanced the activation of muscle action potentials during force production.

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders next to Alzheimer disease, with a prevalence of 180.3 per 100,000 individuals in Japan (Yamawaki et al., 2009). Parkinsonism describes a syndrome characterized by rigidity, resting tremor, and postural reflex disturbance, of which PD is the main cause (Samii et al., 2004). In general, pharmacological treatment is the first choice for treating these symptoms in PD patients. Effective medication therapeutics for PD patients have been established and are commonly used worldwide (Fahn et al., 2004, Lewitt, 2008). As an effect of such medications in PD patients, several studies have reported that the neuromuscular activation of agonist muscles was reduced by medication withdrawal (Brown et al., 1997, Corcos et al., 1996, Folland et al., 2011). However, the effect of medication on muscle activation properties (e.g., motor unit (MU) recruitment and activation heterogeneity) in PD patients is unclear.

Recently, neuromuscular functions, such as the MU recruitment strategy or functional compartmentalization within a muscle, have been assessed in the spatial distribution pattern of muscle activation using a multi-channel surface electromyography (SEMG) technique (Holtermann et al., 2008, Merletti et al., 2008). Previous studies using this technique have demonstrated that the spatial SEMG potential distribution pattern within a muscle is altered by contractions or fatigue level (Farina et al., 2008, Holtermann and Roeleveld, 2006). This phenomenon has been explained by spatial inhomogeneity in the location of different types of muscle fibers (Chanaud and Macpherson, 1991) and the clustering of muscle fibers innervated by one MU in a limited area (Lexell and Downham, 1991). Previous studies have also demonstrated that changes in the spatial distribution of multi-channel SEMG can be explained by the physiological phenomenon of MU recruitment, which suggests that the spatial distribution of multi-channel SEMG can be used to study changes in MU recruitment (Holtermann et al., 2005, Holtermann et al., 2009). While this technique is an indirect assessment of MU behavior, multi-channel SEMG can non-invasively investigate MU activation in a large muscle area during force

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production in PD patients. Using multi-channel SEMG, we observed reduced activation of the vastus lateralis (VL) muscle and greater force fluctuations in PD patients than in healthy subjects (Nishikawa et al., 2017b). Previous studies have reported that abnormal and irregular MU activation in PD patients by the disinhibition of reticulospinal pathways, which was induced by degeneration of the substantia nigra pars compacta (Chronister et al., 1988, Delwaide et al., 1991). Based on these findings, the recruitment of new MUs is difficult due to the loss of dopaminergic neurons in PD patients. Levodopa was developed as a treatment to restore striatal dopamine levels. Therefore, we considered that PD patients exhibited levodopa-induced changes in MUs activation.

Here, we describe the changes in the spatial SEMG potential distribution pattern in PD patients before and after medication (levodopa intake) and show the effects of medication on a sustained isometric contraction task. We hypothesized that compared with the off-medication period, PD patients would exhibit (1) decreased force fluctuations during an isometric sustained contraction task and (2) greater changes in the multi-channel SEMG amplitude distribution over time during the on-medication period.

2. Materials and methods

2.1. Subjects

Ten female PD patients were enrolled in the present study (Table 1). Our previous study showed that compared with healthy young males, healthy females exhibited greater differences in the spatial distribution pattern of a sustained isometric contraction (Nishikawa et al., 2017a). Therefore, we included only female subjects in the current study. The exclusion criteria were the following: injury to the lower extremities, diagnosis of another neuromuscular disease (e.g., progressive supranuclear palsy, frontotemporal dementia, Alzheimer's disease and dystonia), or a history of cardiovascular disease, chronic obstructive pulmonary disease, and diabetes mellitus. All procedures were performed in accordance with the Declaration of Helsinki and were approved by Hiroshima University's Committee on Ethics in Research (approval number No. E-53-1). All subjects signed an informed consent form and consented to the publication of this article. Muscle strength and multi-channel SEMG measurements were performed in all patients when on and off (withdrawal) levodopa. For the off-medication measurements, all participants were requested to refrain from taking levodopa (did not change the intake of other medicines) for a period of 12 h (Brown et al., 1997).

2.2. Experimental design

All subjects performed MVCs during isometric knee extension. Isometric knee extension was performed using a Biodex system (Biodex System 3, Biodex Medical Systems, Shirley, New York, USA) (Watanabe et al., 2012b). The contraction task was performed at a target force of 10% MVC (Folland et al., 2011, Nishikawa et al., 2017a, Watanabe et al., 2012b). The subject was required to match the target force as displayed on the monitor and was verbally encouraged to sustain the force for 60 s. The contraction was terminated when the subject deviated from the target force by −4% MVC force for > 2 s, despite strong verbal encouragement (Nishikawa et al., 2017a). The Unified Parkinson's Disease Rating Scale (UPDRS) was used to assess physical function. The UPDRS characterizes impairments and functional ability using a rating scale from 0 to 4. A same neurologist performed the UPDRS assessments.

Table 1
Characteristics of Parkinson's disease patients.

Variables	Female Parkinson's disease patients (n = 10)
Age, years	64.7 ± 6.1
Height, cm	154.3 ± 5.8
Weight, kg	57.3 ± 4.9
Disease duration, years	8.5 ± 2.2
UPDRS part III	7.0 (2–20)
Daily dose of levodopa, mg/day	300 (100–450)

Data are presented as the mean ± SD or median (min–max).
UPDRS, Unified Parkinson's Disease Rating Scale.

2.3. SEMG recording

Multi-channel SEMG signals were detected from the VL muscle using a semi-disposable grid of 64 electrodes (ELSCH064RS3, OT Bioelettronica, Torino, Italy) according to the same procedure used in previous studies (Nishikawa et al., 2017a, Watanabe et al., 2012b). The VL muscle of each PD patient was measured on the more affected side. The grid consisted of 13 columns and 5 rows of electrodes (diameter, 1 mm; inter-electrode distance, 8 mm in each direction), with one missing electrode in the upper left corner. The subject's hair was removed, the skin was cleaned with alcohol, and the electrode was attached to the skin with a bi-adhesive sheet (KITAD064, OT Bioelettronica) after applying conductive paste (Elefix Z-181BE, NIHON KOHDEN, Tokyo, Japan) corresponding to the placement of the electrodes. The center of the electrode grid was attached at the center of the line between the superior lateral edge of the patella and the greater trochanter protuberance. The columns of the electrode grid were placed parallel to the longitudinal axis of the VL muscle. The site of the missing electrode was placed proximal to the VL muscle. A reference electrode was attached at the anterior superior iliac spine. All procedures were performed by the same investigator.

Monopolar multi-channel SEMG signals were amplified by a factor of 1000, sampled at 2048 Hz per channel and converted to digital data using a 12-bit analog-to-digital converter (EMG-USB2+, OT Bioelettronica). The recorded monopolar multi-channel SEMG signals were off-line bandpass filtered (10–500 Hz) and transferred to software for analysis (MATLAB 2016a, Math Works GK, MA, USA). Bipolar multi-channel SEMG signals (n = 59) along the columns were divided from the 64 electrodes. To calculate the root mean square (RMS) of multi-channel SEMG signals, signals were sampled over 0.5 s, from 0.5 s before the given time to the given time at 15–60 s of contraction time. We normalized the RMS estimates to the values obtained at the 15-s contraction time. Furthermore, we calculated that coefficient of variation (CV) of force (standard deviation (SD)/mean x 100, CV force) at the same time-instants as the SEMG variables (Nishikawa et al., 2017b).

To characterize the heterogeneity in the spatial multi-channel SEMG potential distribution at each contraction time, we determined the modified entropy, the CV of RMS, and the correlation coefficients. The correlation coefficients were computed between the RMS distribution at the 15-s contraction time and the RMS distribution obtained for each contraction time (i.e., 1-s epoch). The modified entropy of the spatial distribution of the EMG amplitude was calculated for 59 RMS values (in space) of single differential signals computed over a 1-s epoch taken at contraction time during the isometric sustained contraction. According to methods published by Farina et al. (2008) in a previous study, modified entropy was defined as the entropy of the signal power as follows:

$$E = -\sum_{i=1}^{59} p(i)^2 \log_2 p(i)^2,$$

where $p(i)$ is the square of the RMS value of channel i divided by the sum of the squares of all 59 RMS values at the given contraction time. Therefore, $p(i)^2$ represents the normalized power of each channel. The value is $E = 0$ when all of the $p(i)$ are zero except one and is maximal and equal to $\log_2 59 = 5.884$ when the $p(i)$ values are identical and equal to 1/59 (all channels have the same energy). The CV of RMS was defined as the quotient of the SD of the 59 RMS measurements and the