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The effects of levodopa on tongue strength and endurance in patients with Parkinson's disease

Miet De Letter[1], Patrick Santens[2] and John Van Borsel[1]

[1]Department of Oto-Rhino-Laryngology, [2]Department of Neurology, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium

Abstract

The aim of this study is to investigate the effects of levodopa on measures of strength and endurance of tongue muscle contraction in patients with Parkinson's disease (PD). Ten patients with idiopathic PD were included. All patients were studied in practically defined on- and off-phases. They were asked to perform isometric tongue protrusions, which were registered by means of a calibrated tocograph. Results of on- and off-conditions were compared using non-parametric tests.

Maximum force and contraction duration did not differ significantly between both conditions, but the integrated measurement of both (area under curve) was significantly larger in the on-state. The force decay slope was significantly lower in the on-state. No correlations were found with disease severity, disease stage or age.

These findings fit the known pathophysiological effects on patterns of isometric muscle contraction in PD. It remains to be demonstrated if the effects of levodopa on tongue strength and endurance correlate with alterations in speech intelligibility, articulation and respiration.

Introduction

Dysarthria is commonly encountered in patients with Parkinson's disease (PD). Although its etiology is probably multifactorial, reduced strength of the tongue musculature has been mentioned as one of the principal factors involved (Solomon N. P. *et al.*, 1995). Indeed, single-case reports as well as group studies of isometric tongue protrusion have shown significantly decreased tongue strength and endurance in PD patients, studied during a medication on-phase, when compared to normal controls (Dworkin J. P. *et al.*, 1995). Studies of lip force in PD patients yielded similar results (Netsell R. *et al.*, 1975). In PD as well as in normal controls, strength and endurance of the tongue muscles were found to be inferior to those of the hand musculature (Solomon N. P. *et al.*, 2000). There is no general consensus on the reduction of isometric force of upper and lower limbs in PD.

To the best of our knowledge, no attempts have been made to study the effects of levodopa on tongue strength and endurance. Moreover, both parameters have always been measured separately in previous reports. Therefore our aim was to study simultaneously differences in both tongue strength and endurance between the on- and the off-state in PD patients. The effects of levodopa on these parameters may be implicated in its effects on speech intelligibility and articulatory precision.

Patients and methods

Subjects

Ten patients (5 men, 5 women) with clinically diagnosed idiopathic PD were included in this study. Mean age was 68 years (range 63-80 years). Severity of the disease as scored by the Hoehn and Yahr stages ranged from 2 to 3 in the on-condition and from 4 to 5 in the off-condition. Unified Parkinson's disease rating scale motor scores (UPDRS part III) were obtained in the on- and off-states. Mean score in the off-state was 42.9 (range 30-61), in the on-state 14.1 (range 9-19). All patients were tested during an in-hospital stay for adjustments to their medication scheme.

None of the patients had psychiatric or cognitive dysfunction that could interfere with the measurements. Treatment with medication that could interfere with muscular function, such as myorelaxants or high doses of sedatives was also considered an exclusion criterion. None of the patients included had clinical or neuro-imaging signs suggestive of significant comorbid neurological disease. None of them was treated by means of deep brain stimulation.

Apparatus

The apparatus for measurement of tongue strength consisted of a Hewlett Packard 8030A cardiotocograph and tocotransducer (Hewlett Packard, Palo Alto, California, USA) connected to a conventional personal computer, running PCS-32 (Velleman, Gavere, Belgium) and Microsoft Excel. Patients were required to protrude the tongue against a button with a diameter of 2 cm located in the middle of a flat surface of 7 × 7 cm. This flat surface was held firmly against the lips while the patient protruded the tongue against the button. The tocograph was carefully calibrated before this study. As the output of PCS-32 is given in units of Volts/time, volts were converted to kgf using the equation of 1 Volt = 0,0787 kgf.

Procedure

All patients were examined during the morning in both on- and off-conditions, as to avoid effects of fatigue as much as possible. The order of testing was the same in all patients. Anti-parkinson medication was stopped for at least 12 hours to induce a practically defined off-condition. UPDRS and Hoehn and Yahr scores were obtained. Next, the patients were seated in a comfortable upright position and instructions were given on how to use the apparatus. Two minutes of practice were allowed. Then the patient was asked to protrude the tongue against the button as firmly and as long as possible. The starting sign was a verbal command of the examiner. No visual or auditory feedback on the performance was given to the patient. The measurement was ended when the patient stopped pushing or after a maximum of 60 seconds if the the isometric contraction had been sustained that long.

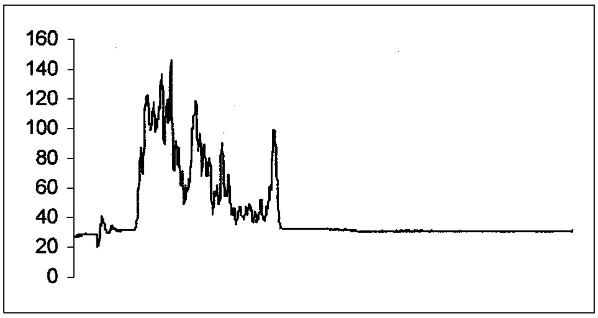
After that the regular morning dose of antiparkinson medication was given. One hour later, during a practically defined on-condition, the entire procedure was repeated.

UPDRS, and Hoehn and Yahr scores were obtained by the same neurologist (PS) in all patients. Measurement of tongue strength was done by the same examiner (MDL) in all patients.

Data analysis

For all twenty obtained curves, maximum force and contraction duration could be determined directly from the measurements. The area under the curve (AUC) was calculated in MS Excel. The force decay slope was determined by applying linear regression to data starting at the time point where maximum force had been reached. Statistical procedures were performed SPSS 9.0 (SPSS Inc, Heverlee, Belgium). Results of on vs. off measurements were compared using Wilcoxon's signed-ranks test. Correlations between clinical or demographic data and measurements were calculated using Spearman's rank correlation test. P-values of < 0.05 were considered statistically significant for all measurements.

To detect rhythmic compounds in the force-time curves fast-fourier transformations were applied to all 20 obtained curves. This procedure was performed in MATLAB 5 (MathWorks, Natick, Mass, USA).



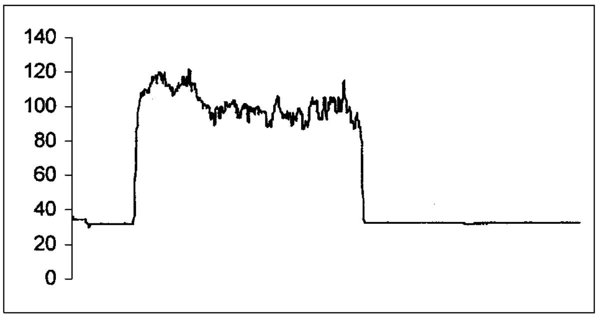


FIG. 1. — Example of tongue protrusion force measurement in offand on-condition (upper and lower curve respectively).

Results

In all patients measurements could be performed in optimal conditions. An example of obtained curves is shown in fig. 1.

The results of maximum tongue force, duration of contraction, slope of force decay and AUC in both conditions are shown in fig. 2. Maximum force and duration were not significantly different between both conditions ($p = 0.445$ and 0.139 respectively).

Significant differences between on and off-measurements were found for AUC ($p = 0.021$) and for force decay slope ($p = 0.047$). This means that in the on-condition the integrated measurement of force and endurance was significantly larger than in the off-state. Moreover, the effects on force decay slopes suggest that during the on-condition patients have increased ability to sustain maximum force. No significant correlations were found between any of our measurements and age, disease stage or severity. Fast-fourier transformation revealed the presence of rhythmic compounds with a 6 Hz-frequency during isometric contraction in the off-condition in two patients (Nrs. 2 and 4).

Discussion

The aim of this study was to investigate the effects of levodopa on strength and endurance of tongue muscle contraction in patients with PD. Both parameters were simultaneously studied in this protocol. We failed to demonstrate effects on maximal force and endurance of contraction sepa-

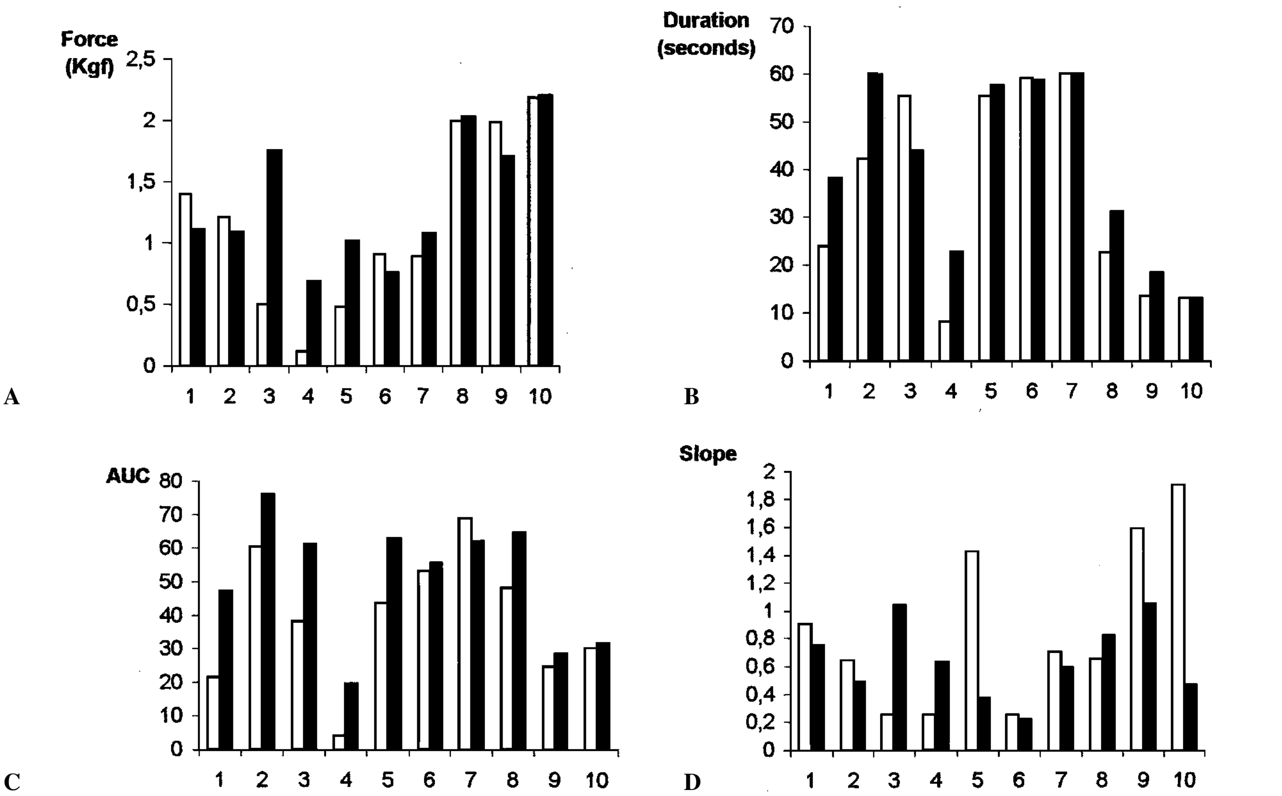


FIG. 2. — Results of on-and off-condition measurements : A: Maximum force ; B : Contraction duration ; C : Area under curve ; D : Force decay slope.

Legend : Results of off-condition are displayed in white, results of non-condition in gray.

rately. However, the integrated measurement of tongue force and endurance, as expressed by the AUC, was found to be significantly larger during the on-state when compared to the off-state. Moreover, the slope of force decay was significantly smaller in the on-state, which means that contraction is more sustained in the on-state. The increase of AUC may be a consequence of this smaller decay slope as well as of a tendency to increased strength and endurance, which in themselves are not statistically larger in the on-state.

Whatever the explanation may be, our results suggest that levodopa is able to revert some pathophysiological mechanisms that lead to decreased performance in isometric contractions of tongue musculature during the off-state.

Several factors may be involved in this decreased performance during off-phases. In earlier reports a "sense of effort" is often mentioned as possibly contributing to decreased performance. This implies a subjective combined sense of force, time, effort, independent from peripheral sensations. Muscle weakness correlates with an increased "sense of effort" and may therefore be a secondary, as well as a primary factor contributing to decreased performance (McCloskey D. I. *et al.*, 1983 ; Gandevia SC, 1988). Bigland-Richie *et al.* studied the influence of "sense of effort" in PD patients by comparing endurance of a voluntary muscle contraction with the endurance during a tetanic contraction by direct electrical stimulation of a peripheral nerve (Bigland-Richie B. *et al.*, 1983). Patients were able to sustain tetanic muscle contractions significantly longer, which, in the opinion of the authors, implies that "sense of effort" is a determining factor in endurance of muscle contractions in PD.

In patients 1, 2, 4 and 8 there was increase of duration of contraction in the on-phase as compared to the off-state. These four patients indicated that they feared not to be able to perform the task in the off-condition. Therefore it is not impossible that motivational factors may have influenced our results. However, Brown *et al.*, in their pharmacological study of muscle force in PD patients, found the effects of motivational differences insignificant (Brown P. *et al.*, 1997).

From a physiological point of view, decreased muscle strength in PD is considered to be the consequence of an inability to recruit motor units sufficiently fast to start and sustain muscle contraction (Grimby L. *et al.*, 1981). Salenius *et al.* examined the coherence of electromyographic activity in wrist extensors and the electro-magneto-encephalographic signals of the hand region in the primary motor cortex (Salenius S. *et al.*, 2002). PD patients the off-state demonstrated significantly decreased coherence in the higher frequency regions (15-30 and 35-60 Hz) and increased coherence in lower frequency ranges (5-12 Hz). The hypothesis is that this leads to difficulties with fusion of motor unit activities, which causes the problems of bradykinesia, muscle weakness and underscaling, necessitating multiple bursts of muscle contraction to reach a target (Berardelli A. *et al.*, 2001). Moreover, this increased coherence in lower frequency ranges and the resulting problems with fusion of motor units may lead to rythmic interruptions in ongoing contractions, resembling a tremor with a frequency that is independent from resting tremor frequency. Salenius *et al.* demonstrated a reversal of this pathophysiological mechanism by administration of levodopa, and concluded that the basal ganglia have important effects on the temporal organisation of cortical motor activity. We suspect that this mechanism also explains our findings of increase of integrated force and endurance in tongue muscles in our study. Fourier analysis of the data obtained in all our patients in both conditions only showed rythmic components in 2 patients during the off-state, with a frequency of 6 Hz. Whether these correspond to the mechanisms explained above, remains to be proven.

Bradykinesia often improves when movements are guided by external cues, such as visual or auditory targets or rhythms. This is explained by different motor networks for internally and externally guided movements. The former are mediated more by medial motor cortical regions, while the latter are more dependent on lateral motor cortical activities (Berardelli A. *et al.*, 2001). It was therefore important to exclude visual or auditory feedback on motor performance in this study. However, Solomon *et al.* showed that tongue force, even with visual and auditory feedback, was lower in on-state PD patients than in controls (Solomon N. P. *et al.*, 1995). This implies that even the combination of feedback and levodopa is not able to fully revert the pathophysiological mechanisms involved in the decrease of muscle force.

Contrary to Solomon *et al.* we could not find any correlation of any of our parameters with disease severity, age or stage (Solomon N. P. *et al.*, 1995). Therefore, our results suggest that once the basal ganglia output is disturbed, the severity of the deficits has little effect on tongue muscle strength and endurance. In conclusion, our results suggest that levodopa, has a significant effect on the integrated measurement of tongue strength and endurance. Further experiments should study the correlations of these findings with alterations in speech intelligibility and articulation.

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P. Santens,
Department of Neurology,
Ghent University Hospital,
De Pintelaan 185,
B-9000 Ghent (Belgium)
E-mail : patrick.santens@rug.ac.be.