The Journal of Physical Therapy Science

Case Study

Disordered voluntary cough as freezing phenomenon in parkinsonism

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Abstract. [Purpose] In patients with parkinsonism, the precise mechanism of impaired voluntary cough remains poorly understood. This study used the flow–volume curve to clarify whether disordered voluntary cough reflects the freezing phenomenon. [Subjects and Methods] Case 1 was a 58-year-old female who had been suffering from progressive supranuclear palsy-pure akinesia with gait freezing. Case 2 was a 59-year-old female who had advanced juvenile parkinsonism. The subjects were asked to take a deep inspiration to the total lung capacity and then cough more than five times through the face mask into the spirometer without intervening inspirations between the coughing efforts. [Results] Hesitation in cough initiation (case 2), decreased peak cough flow (case 1), and rounding of the first spike (cases 1 and 2) were observed. In addition, movements of the spike wave at a lower lung volume became progressively smaller and faster (cases 1 and 2). [Conclusion] These clinical manifestations in our patients are similar to those observed in the freezing phenomenon. However, to date, the concept of cough freezing has been underrecognized in clinical practice. From the present study, it could be hypothesized that the freezing phenomenon can occur in voluntary cough as well as in gait, speech, and writing.
Key words: Cough, Freezing phenomenon, Parkinsonism

INTRODUCTION

In patients with parkinsonism, aspiration pneumonia is the major cause of death. Voluntary cough is an important airway protection behavior. It has been reported that the assessment of peak voluntary cough flow is useful for identifying the risk for aspiration[1]. Although it has been postulated that impaired voluntary cough may be due to bradykinesia affecting the abdominal muscles, chest wall rigidity, reduced central neural drive, and/or poor laryngeal coordination[2], the precise mechanism remains poorly understood. In addition, in contrast to paralytic disease, manually assisted coughing with manual hyperinflation[3] is often ineffective for airway clearance.

Cough produces intrathoracic pressure, resulting in dynamic compression of the airways. The decrease in the cross-sectional area increases the airflow velocity at the compressed site, thereby causing a shearing force on the airway walls. This increases cough effectiveness. Dynamic compression occurs at the trachea and main-stem bronchi at a high lung volume above the functional residual capacity and moves more distally as the lung volume decreases[4]. Thus, coughing at a high lung volume is effective for clearing material from the larger airway.

In order to remove material from the smaller airways, cough must be produced at lower lung volumes. Therefore, effective airway clearance is accomplished by sequential cough, consisting of multiple voluntary coughs produced at a time in a single inhalation[4].

In the flow–volume curve, sequential coughs of normal subjects show multiple spike waves due to a transient increase

in expiratory flow resulting from rapid glottis opening (Fig. 1)[5]. Irregular and grossly distorted cough flow–volume curves have been observed in case of bulbar amyotrophic lateral sclerosis (ALS)[5]. However, there is no such report in case of parkinsonism.

The clinical features in patients with parkinsonism are characterized by (1) initiation failure and (2) a gradual reduction in the amplitude with a high frequency elicited by alternating repetitive movement[6]. Therefore, in order to investigate the manifestation of impaired cough, we hypothesized that the assessment of sequential cough by the flow–volume curve may be useful. The purpose of this study was to clarify the characteristics of sequential cough in patients with parkinsonism using the flow–volume curve.

SUBJECTS AND METHODS

Two cases are reported in this study. Case 1 was a 58-year-old female who was diagnosed with progressive supranuclear palsy (PSP)-pure akinesia with gait freezing (PAGF)[7] 5 years previously. She had writing disorder (fast micrographia), speech disturbance (rapid hypophonia), and freezing of gait (FOG). She had no reported rigidity and tremor. Her voice was breathy. She explained that she had difficulty in removing secretions. Pulmonary function test data are provided in Table 1. The spirometry findings showed a pattern consistent with upper airway obstruction (UAO) because of decreased peak expiratory flow (PEF), increased ratio of forced expiratory volume in one second ($FEV_{1.0}$) per PEF ($FEV_{1.0}$/PEF), and saw-tooth pattern[8].

In normal healthy subjects, $FEV_{1.0}$/PEF ratio shows less than 8.5 ml/l/min. Patients with UAO have a lower PEF than subjects without UAO. However, $FEV_{1.0}$ is less sensitive to changes in PEF, leading to a nearly normal $FEV_{1.0}$. This results in an increased $FEV_{1.0}$/PEF ratio. Saw-tooth pattern in flow-volume curve means the oscillatory movements of upper airway structures[8].

Case 2 was a 59-year-old female with a 34-year history of juvenile parkinsonism. Although wearing off phenomenon was well controlled by a combination of L-DOPA and a dopamine agonist and an increase in the frequency/dose of L-DOPA, postural stability and freezing of gait (FOG) had been resistant to L-DOPA. She also reported speech freezing, such as hesitation in speech, repeating the syllables of a word (pallialia), and hastened speech (tachyphemia). The times of administration of L-DOPA were 6:00 AM, 8:30 AM, 0:00 PM, 3:00 PM, 6:00 PM, and 8:00 PM. The maximal clinical efficacy occurred between 30 and 120 min after oral intake. At this best "on" state of the medication cycle, she reported normal pulmonary function. Further, 10 min after the administration of L-DOPA, at the onset of its action, UAO was observed (Table 1). This temporal relationship of respiratory disturbance with the administration of L-DOPA may be due to diaphasic dyskinesia[9, 10].

Ethical approval was obtained from the Bukkyo University's Research Ethics and Governance Panel. The subjects were informed about the details of the study, agreed to participate in the study, and provided written informed consent.

Sequential cough was measured using a spirometer (Fukuda, Japan). A face mask covering the nose and mouth was connected to the measurement devices. Cough was measured three times per session, and the maximum value of three measurements of peak flow was recorded. Measurements were performed with the subjects in a seated position. The subjects were asked to take a deep inspiration to the total lung capacity and then cough more than five times through the face mask into the spirometer without intervening inspirations between the coughing efforts[5]. We qualitatively assessed the cough spike patterns using the flow–volume curve. We also digitized the graphic data using the free software Graphcel (T.KOBO). Numeric data were thereby obtained. In case 2, the temporal changes in cough impairment in relation to the administration of L-DOPA were assessed.

RESULTS

Results of the numeric data are provided in Table 2. In case 1, rounding of the first spike, decreased peak cough flow, and progressively smaller-faster spike wave movements at a lower lung volume were observed (Fig. 2).

The cough pattern obtained from case 2 at 2:00 PM (approximately 120 min after the administration of L-DOPA) showed a near normal series of cough spike waves superimposed on the maximal expiratory flow–volume curve (Fig. 3A). At 3:15 PM (15 min after the administration of L-DOPA), hesitation in cough initiation, rounding of the first spike, and severely reduced second spike wave flow were observed. In addition, movements of the spike wave at a lower lung volume became progressively smaller and faster (Fig. 3B). At 3:25 PM to 3:30 PM (25–30 min after the oral administration of L-DOPA), this smaller–faster cough spike pattern gradually improved, reaching a nearly best "on" state in the medication cycle. However, rounding of the first spike still remained (Fig. 3C and 3D).

DISCUSSION

Hesitation in cough initiation and rounding (slower rising) of the first spike may be the same phenomenon as difficulty in initiating movement (akinesia)[11], e.g., gait initiation failure (start hesitation) or hesitance in speech. In the compressive phase which is the time from the end of the inspiratory phase to the beginning of the expiratory phase of cough, there is an adduction of the glottis with the onset of expiratory muscle contraction in order to increase the positive intrathoracic pressure. It has
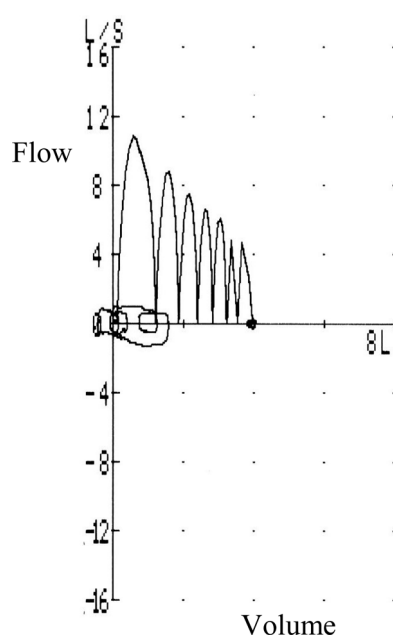
Fig. 1. Flow–volume curve obtained by sequential coughing in a normal healthy subject

Multiple spike waves due to transient increase in expiratory flow resulting from rapid glottis opening

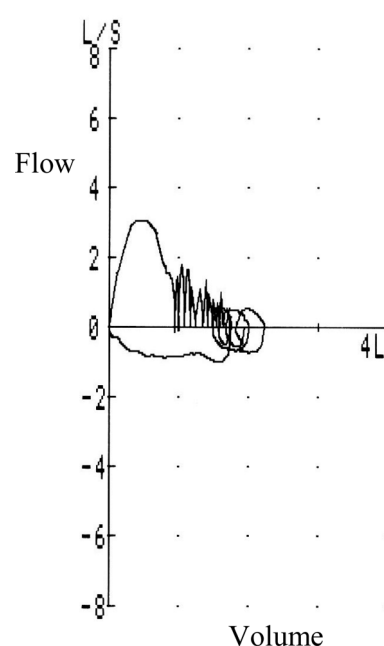Spiral curve: quiet breathing before expiratory effort

Fig. 2. Flow–volume curve during sequential coughing in case 1 Decreased peak cough flow, rounding of first spike wave, and progressively smaller–faster spike wave movements at lower lung volume

Spiral curve: quiet breathing before expiratory effort

Table 1. Pulmonary function test

	Minute after intake of L-DOPA	PEF (L/sec)	FEV1.0 (L)	FEV0.5 (L)	FVC (L)	FEV1.0/PEF (ml/L/min)	FEV1.0/ FEV0.5
Case 1		3.35	1.78	1.35	2.14	8.86	1.32
Case 2	110 min	5.83	1.92	1.64	2.56	5.49	1.17
	10 min	3.67	2.35	1.68	2.88	10.7	1.40

PEF: peak expiratory flow; $FEV_{1.0}$: forced expiratory volume in one second; $FEV_{0.5}$: forced expiratory volume in 0.5 second; FVC: forced vital capacity
110 min after intake of L-DOPA 1:50PM
10 min after intake of L-DOPA 3:10PM

Table 2. Results of numeric data in sequential coughing

|	Case 1	Case 2			
		A	B	C	D
Peak spike (L/s)	3.08	5.94	5.99	5.63	5.74
Second spike (L/s)	1.22	3.29	0.64	2.47	3.15
Third spike (L/s)	1.66	2.03	0.70	1.50	1.92
Volume at first spike (L)	0.35	0.40	0.89	0.80	0.72
Volume at second spike (L)	0.95	1.18	2.19	1.77	1.49
Volume at third spike (L)	1.02	1.47	2.34	2.04	1.81
First spike flow / Second spike flow	2.52	1.81	9.36	2.28	1.82
Distance between first and second spike (L)	0.60	0.78	1.30	0.97	0.77
Distance between second and third spike (L)	0.07	0.29	0.15	0.27	0.32
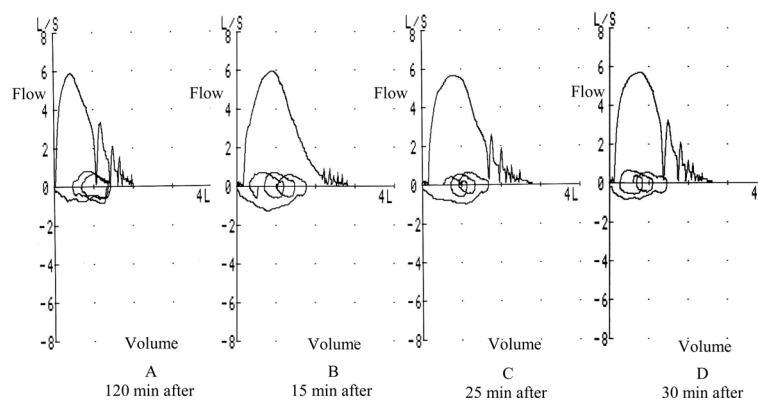
Fig. 3.   Temporal changes in sequential coughing after the administration of L-DOPA in case 2
A (2:00PM): A near normal series of cough spike waves superimposed on the maximal expiratory flow volume curve
B (3:15PM): Hesitation in cough initiation, rounding of first spike wave, reduced second spike wave flow, and progressive smaller-faster movements of cough spike wave
C, D (3:25PM, 3:30PM): Gradual improvement in smaller-faster cough spike pattern
Spiral curve: quiet breathing before expiratory effort

been reported that the longer compressive phase may be compensation for reduced motor drive to the expiratory muscles[12]. Therefore, hesitation in cough initiation may be, in part, due to prolonged glottis closing before the expulsive phase. In addition, it is speculated that impaired precise timing of onset of vocal fold abduction. These may result from a disorder of the motor set, which refers to the preparation of motor cortical neurons in a state of readiness for movement[13]; thus, it is possible to reflect decreased activation of the supplementary motor area (SMA) which play crucial roles for initiating movement as a result of impaired functional connectivity between the basal ganglia (BG) and SMA due to increase in the inhibitory output of the BG[11].

At the initiation of the expiration phase in normal healthy subjects, the glottis opens abruptly, resulting in spike waves due to a transient increase in expiratory flow. Previous study using laryngeal video endoscopy indicated the associations between expiratory phase rise time and post-compression (expulsion phase) vocal fold abduction angular velocity[14].

Thus, the rounding of the first spike wave indicates a disorder of transient increase in expiratory flow. This slower rising of the first spike (delay in reaching the first peak cough flow) may reflect the inadequate velocity of laryngeal abduction and/or abdominal muscle contraction and consequent decreased cough acceleration. Cough impairments including the rounding of the first spike wave in case 2 developed at the onset of L-DOPA action. This temporal reversible change associated with the administration of L-DOPA indicates that it may be due to bradykinesia and not due to a less expulsive effort. It has been reported that UAO in parkinsonism may be more related to bradykinesia than to rigidity[9]. Rigidity is more likely to cause restrictive respiratory impairment than UAO. Our patients did not report rigidity and severe loss of FVC, but they reported UAO. Thus, in our patients, UAO due to bradykinesia may be associated with cough initiation failure.

It has been suggested previously the associations between PCF and maximum vocal fold abduction angle during expulsion phases[14]. Diminished peak cough flow in case 1, in which there was adequate FVC of more than 1.5 L, may be due to the following factors[2]: (1) restricted glottal opening extent by prolonged excessive contraction of the intrinsic laryngeal adductor muscles or poor activation of abductors during the expulsive phase and/or (2) less coordination of the glottal opening and concurrent expiratory muscle contraction.

On the other hand, it is difficult to explain the progressively smaller-faster cough spike wave by UAO alone. Sequential movements require the automatic implementation of movement amplitude and frequency. Repetitive movements rely on BG–cortical interaction[13]. The BG maintains cortically selected movement plan (motor set) in the SMA and provides internal cues to the SMA in a timely manner[15]. The freezing phenomenon has been reported to occur in alternating repetitive movement. In patients with the freezing phenomenon, movements become progressively smaller (the sequence effect) and faster (hastening) with ongoing performance, eventually leading to convergence. The high-frequency components and gradual reduction in amplitude are often observed in gait, speech, and writing[5]. The sequence effect can result from a progressive delay in the timing of phasic motor cues from the internal globus pallidus of BG to SMA and the premotor cortex[13].

Sequential cough is associated with repetitive rapid glottal opening and closing. Repetitive cough movements may result in a progressively decreased amplitude and increased frequency of vocal fold abduction. It has been reported that the first cough peak flow is ranges between 1.6 and 2.1 times the second cough peak flow[16]. A remarkable loss of cough spike amplitude at a lower lung volume in our patients may indicate the difficulty in airway clearance from the lower airways.

These clinical manifestations in our patients are similar to those observed in the freezing phenomenon. However, to date, the concept of cough freezing has been underrecognized in clinical practice. From the present study, it could be hypothesized

that the freezing phenomenon can occur in voluntary cough as well as in gait, speech, and writing. Thus, disordered voluntary cough should be, at least in part, considered to reflect the freezing phenomenon.

PSP-pure akinesia gait freezing is characterized by no sustained response to L-DOPA[7]. Abnormal cough pattern of Case 2 developed at onset of action of L-DOPA. In addition, it has been reported that sequence effect does not respond to medication[15]. Therefore, in our patients, it is difficult to control the cough freezing by L-DOPA.

Although the measurement of peak cough flow is a popular and standard method for cough assessment, our results suggests that in parkinsonism, it may be necessary to pay attention to not only the peak cough flow but also cough wave transformation on the flow–volume curve. Characteristic features of sequential cough measurement using the flow–volume curve may be, as a new hallmark, useful for the early detection of risk factors for aspiration pneumonia in clinical practice.

Further studies involving more patients with parkinsonism are required to clarify whether characteristic cough patterns are based on similar pathologies of FOG and speech freezing. Therefore, the following should be investigated: (1) whether there is a significant difference in cough patterns between groups classified by the presence of FOG and speech freezing and (2) the influence of the loss of FVC and UAO on cough patterns.

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