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ORIGINAL ARTICLE

Cough ability measurements and recurrent respiratory symptoms in individuals with Ataxia Telangiectasia

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Abstract

Objectives: Ataxia-Telangiectasia (A-T) individuals often present with respiratory muscle weakness, causing recurrent respiratory system infections, asthma-like symptoms, and chronic cough life-threatening events. The cough flow volume maneuver may reveal powerless airflow needed for efficient cough. The study aims to explore cough ability in relation to the flow/volume maneuver. *Methods*: Data collected retrospectively from clinical charts of 35 A-T patients (age 12.7 ± 4.9 years) included forced expiratory and cough flow/volume maneuvers performed on the same day. Analysis compared among the maneuvers matching indices, numbers of cough-spikes, flow rate decay, and the reference data of similar ages. Adjusted to age, BMI, and number of hospitalizations prior to the tests, values were correlated with the cough indices. *Results*: Cough peak-flow (C-PF) was propagated within 90 ± 20 ms compared with peak expiratory flow (PEF > 200 ms). C-PF measured values were higher than expiratory peak-flow measured values (3.27 ± 1.53 L/s versus 3.02 ± 1.52 L/s, respectively, but C-PF (%predicted) values were significantly lower than expiratory peak-flow (%predicted) (46 ± 15 versus 68 ± 20 %predicted, respectively, $p < 0.002$). The number of spikes/maneuver was low when compared with reference (2.0 ± 0.8 versus 6–12 spikes) and cough vital-capacity was lower than expiratory vital capacity (0.95 ± 0.43 versus 1.03 ± 0.47; $p < 0.01$). Inefficient C-PF was more prevalent in patients suffering from recurrent respiratory illness. The length of wheelchair confinement duration mostly influenced the C-VC level. *Conclusions*: The cough flow–volume curve can be applied as a method to follow cough ability in patients with A-T who showed a significantly reduced cough capacity. Further studies are needed to establish if the findings may aid decisions regarding cough assistance.

Keywords

Ataxia Telangiectasia, cough, pneumonia, spirometry

History

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Introduction

Ataxia Telangiectasia (A-T) is a rare, neurodegenerative, inherited disease that leads to severe disability and high morbidity and mortality in the second decade of life [1]. A-T patients often present with improper swallowing, frequent choking [2,3], and immune system abnormalities. Individuals with ataxia-telangiectasia (A-T) often present with respiratory weakness causing life-threatening recurrent respiratory system infections and persistent coughing [4,5].

Cough has a protective role in the normal functioning of the respiratory system. The sequence of events leading to an effective cough requires (a) inhaling a variable amount of air; (b) closure of the glottis, generating sufficient intra-thoracic pressure to cause dynamic compression of the airways; (c) contraction of the respiratory muscles; and (d) opening of the glottis. When the glottis is opened the air is forcibly released, leading to maximal forceful flow (cough peak flow [C-PF]) that is higher than voluntary expiratory peak flow (PEF). Secondary cough spikes with flows lower than the C-PF can be detected when a subject performs a full cough flow volume maneuver [6–8]. We suspect that these cough mechanisms are impaired in patients with A-T due to their progression of neurological disease, muscle weakness, and recurrent respiratory infections, but these impairments have never been studied.

Both expiratory flow and cough flow/volume maneuver share similar measures [9]. The inspiratory capacities are similar while the flows needed for an efficient cough are greater than those expected during forced expiration. The decay of cough flow-rate and expiratory flow-rate depends on the configuration of the flow-limiting segment. Differences between the rates of flow decays may stem from the differences in pressure levels imposed on the airway between voluntary expiration and during cough [6]. Differences between the maneuvers have been studied in healthy children, asthmatic children, and children with muscular

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dystrophy [10–12]. Thus, the cough flow/volume maneuver may help to reveal if adequate airflow is present for efficient cough.

This study aims to explore the relationship between cough ability, clinical symptoms, and the flow/volume maneuver.

Subjects and methods

Subjects

Retrospective data were collected from patients with A-T who are being followed and treated at the National A-T Center at Safra Children's Hospital, Sheba Medical Center, Israel. The study was approved by the Institute Review Board (IRB number: 8549-11-SMC). Criteria for the diagnosis of A-T were based on the clinical symptoms and laboratory findings.

All our patients presented with signs of motor coordination abnormalities and ataxic gait as the first symptom. The majority of patients had increased α-fetoprotein levels (range 75–418 kU/L, which is more than three times the upper limit of normal). Among the found mutations were 103C>T, 7240del, 368delA, 2789del2, C-T1339, C-1514T/C-1547T, and chromosomal break. Details were sought regarding length of wheelchair confinement and recurrent respiratory illness of asthma-like symptoms, i.e. recurrent wheezing, cough, and episodic shortness of breath, and positive response to bronchodilators [13].

Inclusion criteria

All A-T patients who visited the pulmonary function laboratory and performed both cough and forced vital capacity maneuver from age 5 years and onwards were reviewed.

Exclusion criteria

Pulmonary function test data were performed during (or within 2 weeks after) a respiratory exacerbation and hospitalization.

Methods

Data from clinical charts records and best yearly lung function were reviewed retrospectively. Each patient visited our AT national clinic at 3–4 times a year for follow-up and more if disease exacerbation occurs. Study data were collected between the years 2010 and 2011. Both cough and forced expiratory flow/volume maneuvers were performed as a routine procedure at the A-T center. The cough flow/volume maneuvers were performed ∼5 min after the expiratory maneuver (or when the patient was ready).

Forced expiratory flow/volume maneuver

Forced expiratory maneuvers were measured with the ZAN100 spirometer (n-Spire Health Inc., Longmont, CO) as described previously [13–15]. Measurements were primarily performed in the sitting position because most patients were confined to a wheelchair or when possible in the standing position, with the patient wearing a nose clip. We used mouthpieces and filters that could be held tightly around the lips, in order to prevent leaks. A nurse stood behind the patient and assisted in maintaining the head in a neutral position. Patient height was approximated by measuring arm span in those confined to a wheelchair. The guiding principles of quality control were those recommended by the ATS/ERS, adapted to A-T [15,16]. Each patient performed several (up to six) maneuvers separated by short breaks. Incentives of two targets (peak-flow and vital capacity) were used to encourage cooperation with the test. The curve with the highest forced expiratory vital capacity (FVC) + FEV1 (or FEV0.5 when FEV1 was absent) of all chosen curves were stored for further analysis. Response to bronchodilators is tested regularly. A response is considered positive if improvement of 12% in FEV0.5 was observed.

Cough flow/volume maneuver

The test position was similar to that in the forced expiratory maneuver. The subjects were instructed to inspire fully to total lung capacity (TLC) and then cough as forcefully as possible and continue coughing sequentially into the pneumotachograph without intervening inspirations between the individual coughing efforts [17]. Children were encouraged to produce as many cough-spikes as possible in sequence. The maneuvers were performed 2–3 times with several minutes of rest in between. The best and second best curves according to C-PF + C-VC were stored for analysis.

Analysis of the curves

The best chosen maneuvers (cough and forced expiration) were superimposed at total lung capacity point. The following indices were compared: inspiratory capacity, time rise to peak flows, peak flows, the ratio between C-PF and forced expiratory peak flow (PEF), vital capacities, and expiration time. An efficient cough was related to the initiation of at least six spikes having a flow above 160 L/min (2.67 L/s) [7].

Statistics

Reproducibility of C-PFs was calculated as the differences (%) between best and second best cough maneuver for each of the cough indices. Spirometry indices were compared with the common reference indices values [18] for children. Predicted C-PF values were retrieved from equations for C-PF of a healthy children population [11]. Matching indices between cough and forced expiration of the same patient were compared by paired *t*-tests. Significant differences between predicted values and disease were tested by Wilcoxon matched paired *t*-tests. Normality distribution was tested by the Kolmogorov–Smirnov test for cough VC, C-PF and age (progress of disease), BMI, and duration of being confined to the wheelchair (years), as well as the presence of asthma-like symptoms confirmed by a positive response to bronchodilators [14].

Correlations were sought between FEV0.5 %predicted and C-VC and C-PF. Correlation between the cough efficiency and the following parameters was also sought: age (progress of disease), BMI, duration of wheelchair confinement (years), and asthma-like symptoms.

Continuous variables were presented as mean (SD); categorical variables were presented as number of patients and as the percentage in each group. A two-tailed

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$p < 0.05$ was considered statistically significant. All analyses were performed with SPSS software (ver. 21.0; SPSS Inc., Chicago, IL).

Results

Thirty-five of 38 individuals with A-T who were able to perform technically proper cough maneuvers, 24 performed the tests at the sitting position, and 11 in the standing position.

Their anthropometric data and clinical features are presented in Table 1. Despite coordination difficulties, most patients cooperated with the tests and claimed to be providing their best efforts. The approximated testing duration was 15 ± 5 min/patient depending on the patient's physical condition and the rest periods between tests. Typical cough maneuvers superimposed over forced expiratory maneuvers are presented in Figure 1. The difference between best and second best C-PFs (reproducibility) was $8.0 \pm 8.4\%$.

Table 1. Anthropometric and clinical data.

Parameter		Comments
N	35	
Age (years)	12.7 ± 4.7	
Arm-span (cm)	138 ± 22	
Wt (kg)	29.6 ± 13.1	
BMI[a]	14.9 ± 2.8	
BMI (centile)	13.4 ± 17.1	
Age at diagnosis (years)	4.6 ± 3.9	
Clinical conditions	Number of patients in the group	
Confined to wheel chair	24	Age of confining to wheelchair 8.6 ± 2.6 (years)
Recurrent pneumonia	17	
FTT[b]	24	≤15 centile
Recurrent respiratory symptoms treated for asthma	13	
Swallowing dysfunction	22	
IVIG[c] treatment	20	Mean age 7.7 ± 4.5

[a]BMI, body mass index.
[b]FTT, failure to thrive.
[c]IVIG, intravenous immuno-globulin.

Measured and %predicted values for each maneuver are presented in Table 2. Inspiratory capacities prior to the efforts were similar in both maneuvers. Time rise to C-PF was within the healthy range (<100 ms), but significantly shorter than time rise to peak expiratory flow (PEF). C-PF (%predicted) values were significantly lower than PEF %predicted, although similar in absolute values. All patients could perform a C-PF but only 17 patients (48%) could produce a C-PF > 2.67 L/s. C-PF/PEF ratio was lower than reference in 80% of our patients (1.06 ± 0.24 versus 1.38 ± 0.22, $p < 0.0001$ for the whole group).

Secondary spikes number included only 2.0 ± 0.8 spikes per cough-maneuver (expected > 6 spikes; $p < 0.0001$). A second-spike was achieved by 17 patients. A third-spike was initiated by 11 patients and four patients produced 4-spikes; of them only 3-patients produced an efficient four spikes. Cough duration per maneuver was significantly shorter than that of forced expiratory maneuver, resulting in a significantly reduced C-VC compared with FVC.

The correlations between FEV0.5 (%predicted) and C-PF and C-VC (%predicted) are presented in Figure 2. Both C-VC and C-PF %predicted were highly correlated with FEV0.5 %predicted values. C-PF efficiency did not correlate with FEV0.5 %predicted values.

Inefficient C-PF was more prevalent among patients having recurrent respiratory symptoms and a response to bronchodilators (asthma-like symptoms; $n = 13$) and/or recurrent pneumonia (seven of 13; 54%) than in other patients (eight of 22 patients; 36%).

The effect of wheelchair confinement duration ($n = 24$) on C-VC is presented in Figure 3. C-VC grew lower as the duration of wheelchair confinement increased. After being confined to a wheelchair for longer than 2 years C-VC deteriorated significantly compared with patients who were walking (37 ± 15 %predicted versus 51 ± 17 %predicted;

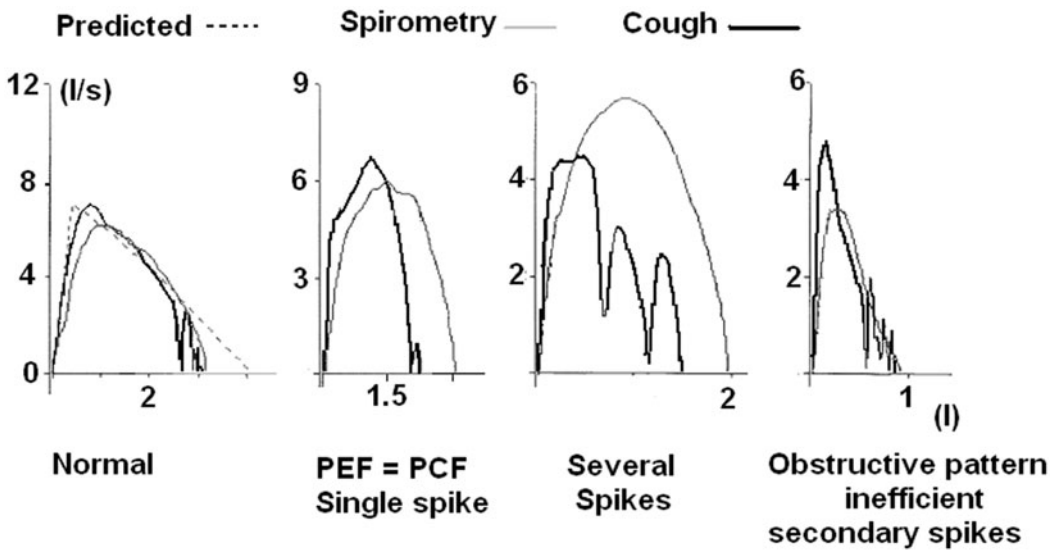


Figure 1. Typical superimposed cough maneuvers over forced expiratory maneuvers.

Table 2. Measured and %predicted values for each maneuver.

Parameter	Cough maneuver		Forced expiratory maneuver		p Value for %Predicted
	Actual	%Predicted	Actual	%Predicted	
IC (L)	0.85 ± 0.47	36 ± 15	0.86 ± 0.42	38 ± 14	NS
VC (L)	0.89 ± 0.47	40 ± 17	1.06 ± 0.62	46 ± 18	0.0012
FEV1 (L)			0.98 ± 0.64	49 ± 20	
FEV0.5 (L)			0.92 ± 0.52	60 ± 23	
Peak flow (L/s)	3.27 ± 1.53	46 ± 15	3.02 ± 1.52	68 ± 20	0.0001
Time rise to peak flow (ms)					
Median	90		250		0.0001
Range	60–180		90–800		
Expiratory time (s)					
Median	1.4		4.0		0.0001
Range	1.2–1.6		3.5–4.8		
Secondary spikes					
Spike-2 (L/s) ($n = 27$)	1.48 ± 0.97				
Spike 3 (L/s) ($n = 11$)	1.20 ± 0.73				
Spike 4 (L/s) ($n = 4$)	0.55 ± 0.29				

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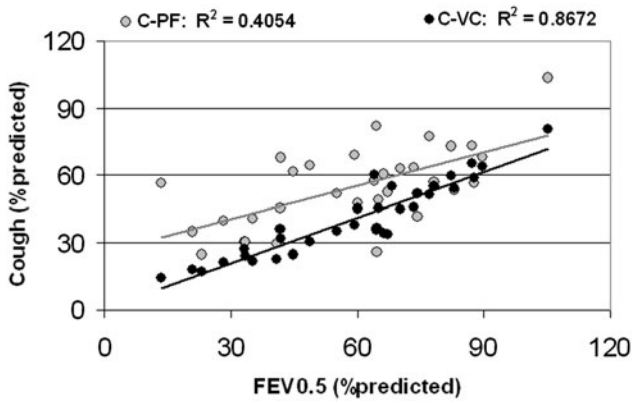


Figure 2. The correlations between FEV0.5 (%predicted) and C-PF and C-VC (%predicted).

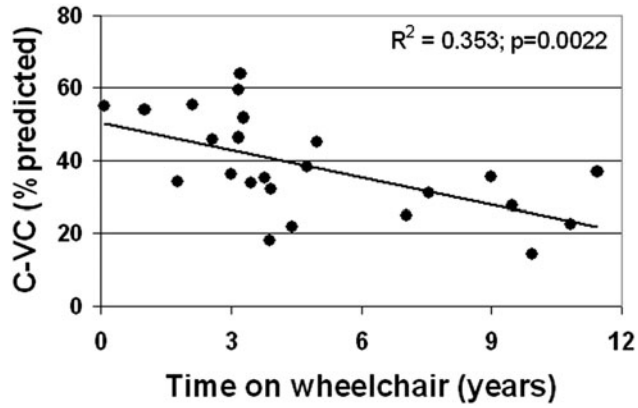


Figure 3. The effect of wheelchair confinement duration ($n = 24$) on C-VC.

$p = 0.0292$) but no correlation could be established. C-PF efficiency did not correlate with P-CF/PEF ratios, with age or with BMI (centile), with wheelchair confinement duration.

Discussion

The study explores the cough characteristics by cough flow/volume maneuver and in relation to forced vital capacity maneuver in a group of A-T patients. The cough flow volume curve method was accepted by most patients despite difficulties in coordination, and the results were reasonably reproducible. Our main new findings indicate that the only index that was similar in both maneuvers was the inspiratory capacity prior to the effort; additionally, time rise to C-PF was within the normal range unlike time rise to PEF, which was longer than demanded.

Many of our A-T patients had inefficient cough as demonstrated by low C-PF rates and a limited number of efficient secondary cough-spikes (regardless of FEV0.5 %predicted values) and short duration of cough flow decay leading to low C-VC. Inefficient C-PF was more prevalent in patients suffering from chronic respiratory symptoms. The length of wheelchair confinement duration mostly influenced the C-VC level. All these findings may lead to recurrent respiratory infections, which were indeed found in most of our patients.

Cough inspiratory volume inhaled prior to the cough may be as little as tidal volume or as great as inspiratory vital capacity [19,20]. Yet, a low volume inhaled prior to coughing may substantially influence the effectiveness of the cough force [21,22]. We found that our A-T patients' C-IC reached 85% of their C-VC, which is considered a normal ratio. Still, this C-IC absolute volume may be too low to initiate an effective cough. Our findings are in agreement with lower-than-predicted C-IC found in patients with neuromuscular disease who have inspiratory and expiratory muscle weakness, making it difficult to draw a deep breath [21,22].

We found that the time rise to C-PF was within the expected healthy expiratory muscle recruitment time of ~100 ms; in our previous study, we found that the time rise to PEF was slower (>250 ms) [13]. The longer time rise to PEF may be the result of progressive loss of muscular coordination secondary to progression of neurological disease. Our findings suggest that the cough reflex is preserved and enables the expiratory muscles to react quickly.

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We found that the C-PF and PEF measured values were similar, but C-PF was significantly more reduced compared to healthy children. These findings agree with the lower than healthy inspiratory and expiratory mouth pressures that were found in A-T patients [4]. Ineffective cough was also reported in patients with neuromuscular disorders having weak expiratory muscles that cannot produce an effective cough [23–26].

We found that most patients had a low C-PF/PEF ratio compared with healthy subjects who have considerably higher C-PF [11,26]. Considerable differences between C-PF/PEF ratios were previously suggested as an objective measure of central nervous system involvement and its evolution in several neuromuscular diseases [27]. Braun et al. [28] and Kang et al. [29] suggested that this part of the cough depends on inspiratory and expiratory muscle strength. Expiratory muscle weakness may influence cough efficiency, adversely affecting expiratory pressures and thereby the expiratory flows needed for an effective cough [30,31]. Thus, the inability to produce an effective cough increases the risk of developing atelectasis and pneumonia. Yet this index could not be related in our study to severity of the disease.

Cough-initiated C-VCs were significantly lower than FVC. Abnormal lung injury repair, inflammation, and recurrent respiratory infections may contribute to decreased cough vital capacity [4]. Still, reduction in C-VC correlated with the duration of wheelchair confinement. A weakening of respiratory muscles due to prolonged reduction in vital capacity has long been known [29,30].

C-PFs and secondary spikes flow-rates were lower than those found to provide effective airway clearance in adult patients with stable neuromuscular disease who still have bulbar function [11]. Additionally, most patients had a limited number of spikes; only three patients had three efficient spikes, whereas one would expect at least six efficient spikes [6–8]. Secondary spikes are transient supramaximal flow during a cough maneuver. Inability to produce secondary spikes was formerly related to inspiratory muscle weakness and to ventilatory failure [21–33]. Our study indicates that secondary spikes may better reflect inefficient cough than C-PF/PEF ratio.

Study limitations

We used C-PF reference values previously published [11]. The reference group included 649 children (341 females) tested by the MIR spirometer (MIR Medical International Research S.r.l. – via del Maggiolino 125, 00155 Roma, Italy), which is a Turbine-based pneumotachograph. There was no significant difference between MIR spirometer and ZAN nSpire spirometer (n-Spire Health Inc., Longmont, CO) in the flow-volume curve values [34,35]. This number of healthy children was considered sufficient for our purposes. The healthy population was similar in growth charts and age to that of our study population. As in other studies, a single, highly experienced pulmonary function test technician performed the lung function tests in our study. We, therefore, assume that our chosen reference is representative and should not alter our findings and conclusions.

There are no global standardizations for the cough flow volume curve maneuver. Standardizations of cough maneuver and global reference values for children could have strengthened (or weakened) our findings.

We did not measure muscle strength or did we perform EMGs in our patients. Such measurements could have better revealed weakness of the respiratory muscles and strengthened the connection between C-PF values and weakness of the respiratory muscles. However, they are not routinely performed in our laboratory setup.

The cough ability in A-T patients seems to be similar to results reported on the other neuromuscular diseases, which makes our results not unique to A-T; however, the use of the cough-flow volume curve is rare and in this context may be valuable for other neuromuscular diseases.

The authors found the reduced cough capacity was related to recurrent respiratory symptoms, and a positive response to bronchodilators and/or recurrent pneumonia in the children with Ataxia-Telangiectasia. The severe impairment of cough ability may be the cause of recurrent respiratory symptoms and/or pneumonia or the results of recurrent pneumonia in these patients. Since it is a retrospective study, we do not know which is true.

We see a drawback in our measuring of cough flow/volume maneuver after spirometry. It would have been better to use a random order. Still, the cough flow volume maneuver is an exhausting process for the patients, and we therefore decided on the order described above. In that respect, one could argue that the findings are related to fatigue originating in the repetition of spirometry tests before cough maneuver. We propose that in case of such fatigue, the correlations with the forced expiratory maneuvers would have been weaker.

Conclusions

The cough flow/volume maneuver reveals that many A-T patients may have inefficient C-PFs, pronounced limited number of spikes with low flow rates, and fast cough flow decay. These impairments are influenced by recurrent respiratory symptoms and by the duration of wheelchair confinement. The cough maneuver explores impairments in cough mechanics that appear regardless of FEV0.5 %predicted values. The use of the cough flow volume maneuver may, therefore, be justified and may be clinically important in AT, but further standardization is required in order to recommend its use.

Declaration of interest

None of the authors have any conflict of interest to declare or do any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. The study was supported by the J. Baum Foundation of Israel Lung Association, Tel-Aviv Israel.

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