ORIGINAL ARTICLE

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Evaluation of Dynamic Hyperinflation with Negative Expiratory Pressure Method in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Objective: Chronic Obstructive Pulmonary disease (COPD) is a disease characterized by progressive airflow limitation, which is not fully reversible. Expiratory flow limitation (EFL) is the most common cause of dynamic hyperinflation (DH) and increased respiratory workload in COPD. In our study, the relationship between negative expiratory pressure (NEP) and all pulmonary function tests, especially inspiratory capacity (IC), was investigated in the examination of DH in COPD patients.

Methods: Thirty four COPD patients with a mean forced expiratory volume in one second (FEV1) of 38.9±12.7% and 15 healthy subjects were included in the study. Pulmonary function tests and NEP were performed in all COPD patients.

Results: In 16 COPD patients (47.1%), EFL was positive with NEP. When pulmonary function tests of EFL positive and EFL negative patients were compared, significant differences were found only in obstruction parameters such as FEV1 and forced expiratory flow 25-75, but no difference was found with lung volumes and diffusion test. However, there was a statistically significant correlation between IC and FVC (mL and % predicted), FEV1 (% predicted) and lung volumes (mL and % predicted) and FRC (mL) ($p<0.05$). There was a negative but statistically insignificant correlation between IC and presence of flow limitation ($p>0.05$).

Conclusion: We think that NEP application in COPD patients does not provide additional information about DH and that IC is the best predictor of DH.

Keywords: Chronic Obstructive Pulmonary disease, inspiratory capacity, negative expiratory pressure

INTRODUCTION

Chronic Obstructive Pulmonary disease (COPD) is an inflammatory disease caused by various harmful particles and gases, and is characterized by progressive airflow limitation that is not fully reversible. Airflow limitation in COPD develops as a result of small airway disease and parenchymal destruction. While chronic inflammation leads to remodeling and narrowing of the small airways, the decrease in elastic recoil as a result of parenchymal damage makes it difficult to maintain the patency of the airways during expiration (1). In patients with COPD, the delay in lung emptying due to decreased expiratory flow during spontaneous breathing prevents the lungs from passively reaching the functional residual capacity (FRC) level before the next inspiration. As a result, the end-expiratory lung volume exceeds the FRC level. Pulmonary volume increases in COPD due to reduced elastic recoil and airway resistance. This leads to a new equilibrium at a higher level than FRC at the end of the expiration. This phenomenon is called dynamic hyperinflation (DH) (2). In COPD, pulmonary function tests (PFT) are the most commonly used laboratory methods in the diagnosis, evaluation of disease progression and prognosis and severity of the disease, and monitoring the treatment response (3). Spirometric examination is mandatory to confirm the diagnosis of COPD. It has been reported that inspiratory capacity (IC) is guiding for demonstrating the presence of dynamic collapse in the respiratory tract in COPD (3). IC is the volume of gas that can be inspired following a normal, quiet expiration. It includes tidal volume (TV) and inspiratory reserve volume. It constitutes approximately 75% of vital capacity. In recent studies, it has been

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shown that IC is an important parameter in demonstrating the presence of DH in the respiratory tract in COPD (4,5). The most important change that can be detected in spirometry in COPD is expiratory flow limitation (EFL). Negative expiratory pressure (NEP) technique is one of the simplest ways to demonstrate EFL, which is the most important cause of DH. The NEP technique usually involves applying a negative pressure around -5 cm H_2O into the mouth during tidal expiration and comparing the resulting flow-volume (F-V) loop with the previously made control expiratory F-V loop. In COPD patients, NEP technique can be applied during mechanical ventilation, exercise, dyspneic and orthopneic state, before and after bronchodilatation, and in different positions. Maximal expiratory flow can be achieved even at rest in conditions with airflow limitations, such as COPD. In patients with COPD, it is seen that the volume of gas remaining in the lungs increases at the end of expiration, especially during exercise. As a result, the expiratory reserve volume increases, the inspiratory reserve volume decreases, and the IC decreases. This is due to the collapse of the peripheral airways and increased expiratory reserve volume due to increased dynamic collapse during exercise. Increase in TV during exercise can reach up to IC value in COPD patients. In addition, flow velocities during TV can reach the flow velocities at maximal expiration loop. The reflection of this in the F-V loop is that the TV curve plotted during the exercise coincides with the maximal expiration curve, thus EFL being positive. Presence of EFL in COPD patients leads to DH, increased respiratory work, impaired inspiratory muscle function and progressive dyspnea (4-7). In this study, we aimed to investigate the relationship between NEP and PFT and lung volumes in the examination of DH in patients with COPD.

METHODS

Thirty four stable patients with COPD at stage 2 and 3 (1) and 15 healthy subjects without smoking history and respiratory disease were included in the study. Patients with COPD were on inhaled long-acting beta-agonists, anticholinergic, inhaler steroid and oral theophylline with inhaled short-acting beta-agonists. Stable period was defined as not having an acute exacerbation of COPD until four weeks prior to enrollment. According to this definition, the presence of two of the three criteria, including worsening in dyspnea, increase in purulence or amount of sputum, makes the diagnosis of COPD exacerbation clinically. Patients with known pulmonary disease other than COPD and who had received oral corticosteroid treatment in the last two months were excluded from the study. The control group was selected from the patients who applied to the chest diseases outpatient clinic and did not have any pathology in their examinations. Informed consent form was obtained from all subjects at the beginning of the study. All patients in the COPD and control groups were evaluated by PFT (spirometer, lung volumes) in sitting position and EFL examination by NEP in the respiratory laboratory. The study was approved by Ethics Board of Department of Chest Disesase (1724-2004).

Pulmonary Function Tests

Spirometric examinations were performed in the respiratory laboratory using Sensor Medics Vmax Series 22. Forced spirometric tracing was obtained by prompting the patient to inspire to the level of total lung capacity, followed by rapid and forced ventilation. The curve was plotted at least three times while the nose was closed and the maximum FVC and forced expiratory volume in one second (FEV1) values of the three curves were used in our study. Total lung volume and residual volume measurements were made using Nitrogen Washout method (8).

Negative Expiratory Pressure

In our study, NEP method was used to detect EFL. The tools required for the application of this method are as follows:

- Pneumatograph
- Differential pressure transducer
- Negative pressure generating device
- Data collection system

A plastic mouthpiece is connected to the T tube and pneumotograph. One end of the T tube is open to the atmosphere. The other end is exposed to the negative pressure created by the venturi apparatus or vacuum generator by means of a valve (solenoid valve, Hans Rudolph valve). When the valve is opened, NEP is applied to the airway. Airway flow (V°) is measured by pneumotograph, while airway opening pressure is simultaneously measured by the side port of the mouthpiece. Volume (V) is obtained from numerical integration of flow signals in data acquisition systems. The F-V loop obtained by NEP is overlaid with the F-V loop obtained by the previous normal respiration. Data analysis is performed by visual evaluation of two F-V loops (9). In our study, a Micro NEP brand NEP device was used (Micro Medical Ltd. Kent, UK).

The results obtained from the NEP technique are interpreted in three ways:

- No flow limitation
- Flow limitation during one part of expiration

- Limited flow throughout expiration. Flow limitation of expiration is given as a percentage of control TV % (9).

As shown in Figure 1, if NEP application leads to increased flow through the entire control VT, flow is not limited (NEP example, left panel). On the contrary, if the F-V loop formed during expiration with NEP intersects with some or all of the control F-V loop, the patient has EFL (NEP example, middle and right panel) (Figure 1).

Statistical Analysis

SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, Illinois, USA) for Windows 10.0 was used for data analysis. The determination of the number of samples in our study was based on the studies in the literature in which the NEP method was examined in COPD cases. The post hoc power analysis at the end of the study revealed a 100% power for FVC with 95% confidence interval. Normality of the data was evaluated by Kolmogorov-Smirnov test. Mann-Whitney U test was used to compare the parameters. Pearson method was used for correlation analysis. The values were expressed as mean ± standard deviation, and non-normally distributed data were expressed as median and interquartile range 25-75. P<0.05 was considered statistically significant.

RESULTS

Demographic characteristics of the patients are shown in Table 1. Regarding mean ages of the groups, no statistically significant difference was found between patient and control groups (p>0.05).

Spirometric values of patient and control groups are presented in Table 2 and lung volumes are presented comparatively in Table 3. NEP technique was applied to all participants. EFL was not detected in any of the subjects in the control group. EFL was positive in 16 COPD patients (47.1%). When the EFL was expressed as a percentage of TV, the mean EFL value was 31.44±38%. The study group was divided into two groups as EFL positive and negative, and the variables between the two groups were examined. There was no statistically significant difference between the two groups in terms of age, amount of smoking and disease duration (p>0.05). Spirometry values of the group with positive and negative EFL are presented in Table 4, and a statistically significant difference was found between FEV1 (%) and forced expiratory flow (FEF) 25-75% (%) values. The comparison of lung volumes of the group with and without EFL is shown in Table 5 and no statistically significant difference was found between the two groups. Table 6 shows the correlation coefficients of IC values measured in the COPD group with age, disease duration, presence of EFL, PFT and lung volumes. As shown in the Table 6, significant correlations were found

Table 1. Demographic characteristics of patient and control groups

	COPD group	Control group
Number of cases (F, M)	34 (2F, 32M)	15 (2F, 13M)*
Age (years)	66.3±7.9	66.7±7.7**
Disease duration (years)	7.97±5	-
Smoking (pack/year)	57.6±29.7	-
Number of patients who stopped smoking	31	-
Smoking cessation period (years)	4.1±4.7	-

COPD: Chronic Obstructive Pulmonary disease, F: Female, M: Male
*p>0.05, **p>0.05

Table 2. Pulmonary function test results in patient and control groups

Pulmonary function tests	Patient group	Control group
FVC (mL)	2365±643	3975±629*
FVC (%)	72.1 (61.1-81.2)	102.3 (94.6-110.2)*Ŧ
FEV1 (mL)	1001±300	3258±551*
FEV1 (%)	38.9±12.7	104.3±13.3*
FEV1/FVC (%)	42.8±7.6	79.7±5.2*
FEF %25-75 (L/sn)	0.25 (0.11-0.47)	3.4 (2.46-4.8)*Ŧ
FIV1 (mL)	1800 (1212-2500)	3480 (2600-4300)*Ŧ

FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, FEF: Forced expiratory flow, FIV1: Forced inspiratory volume in one
*p<0.000, Ŧ: Mann-Whitney U test used
The data in parentheses are median and interquartile range 25-75

Table 3. Lung volumes of patient and control groups

Lung volumes	Patient group	Control group
TLC (mL)	6610±1896	6157±776
TLC (%)	109.5±26.3	97.5±10*
RV (mL)	3980 (2504-4904)	2261 (1724-2803)**Ŧ
RV (%)	169.1±50.9	102.3±13.6**
RV/TLC (%)	59.6±8.9	35.2±3.3**
VC (mL)	2604±747	3919±554**
VC (%)	74.4±21.9	96.8±10.7**
IC (mL)	1885±499	3023±723**
FRC (mL)	4699±1643	2951±539**
FRC (%)	140.5±42.6	94.6±14.8**
ERV (mL)	705 (312-1115)	702 (524-1064)Ŧ

TLC: Total lung capacity, RV: Residual volume, VC: Vital capacity, IC: Inspiratory capacity, FRC: Functional residual capacity, ERV: Expiratory reserve volume
The data in parentheses are median and interquartile range 25-75
*p<0.05, **p<0.000, Ŧ: Mann-Whitney U test used

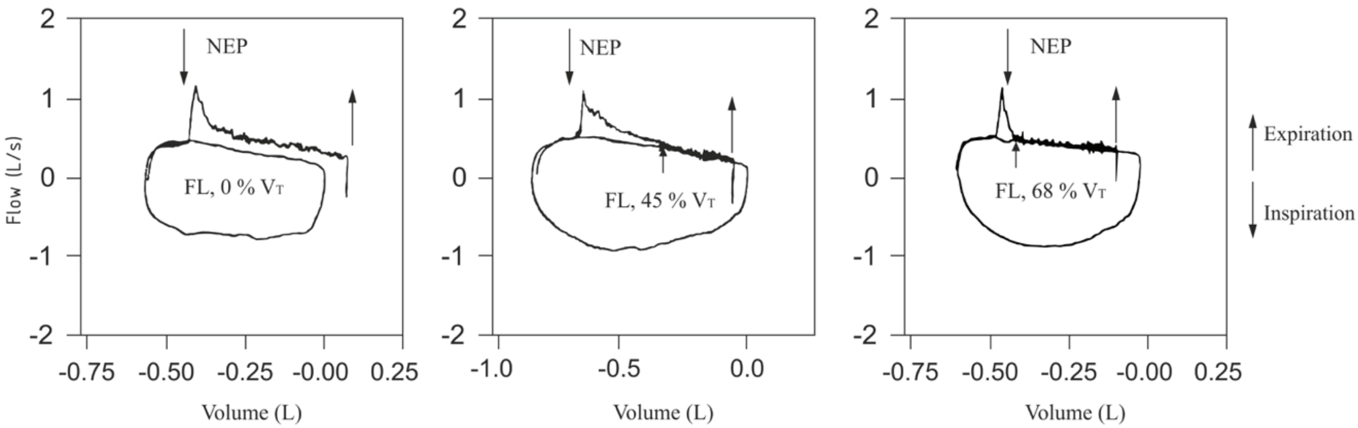

Figure 1. Negative expiratory pressure examples of cases with and without flow limitation (5)
NEP: Negative expiratory pressure

Table 4. Pulmonary function test values of the group with negative and positive expiratory flow limitation

Pulmonary function tests	EFL negative	EFL positive
FVC (mL)	2459.4±623.6	2260.6±6669.6
FVC (%)	76.7 (51.2-98.3)	68.2 (49.2-87.3)Ŧ
FEV1 (mL)	1080±326.5	913.7±248.3
FEV1 (%)	43.5±14.5	33.8±8*
FEV1/FVC (%)	44.6±8.8	40.9±5.5
FEF 25-75% (L/s)	0.37 (0.22-0.53)	0.29 (0.21-0.49)Ŧ
FEF 25-75% (%)	12.8 (7.3-16.4)	9.4 (6.4-13.4)*Ŧ

FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, FEF: Forced expiratory flow
The data in parentheses are median and interquartile range 25-75
*p<0.05, Ŧ: Mann-Whitney U test used

Table 5. Pulmonary function test values of the group with negative and positive expiratory flow limitation and positive group

Pulmonary volumes	EFL negative	EFL positive
TLC (mL)	6920±1605	6223±2219*
TLC (%)	116.3±20.4	101±31.1*
RV (mL)	4276 (3325-5135)	3620 (2704-4226)*Ŧ
RV (%)	180.3±39.6	155.1±61.2*
RV/TLC (%)	62±6.6	56.5±10.6*
FRC (mL)	4954±1385	4382±1935*
FRC (%)	148.4±33.4	130.6±51.7*
IC (mL)	1921±475	1843±543*

TLC: Total lung capacity, RV: Residual volume, IC: Inspiratory capacity, FRC: Functional residual capacity, EFL: Expiratory flow limitation
*p>0.05, Ŧ: Mann-Whitney U test used
The data in parentheses are median and interquartile range 25-75

between IC and PFT and lung volumes. However, a negative but not statistically significant correlation was found between IC and EFL.

Table 6. Parameters correlating with inspiratory capacity in Chronic Obstructive Pulmonary disease group

Parameters	Correlation coefficients (r)
Age (years)	0.242
Disease duration (years)	-0.373
Presence of expiratory flow limitation	-0.202
FVC (%)	0.592***
FEV1 (%)	0.519**
FEV1 /FVC (%)	0.047
PEF (%)	0.666***
TLC (%)	0.573**
VC (mL)	0.797***
VC (%)	0.599***
FRC (mL)	0.438*
RV (mL)	0.484*
RV (%)	0.429*

FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, PEF: Peak expiratory flow, VC: Vital capacity, TLC: Total lung capacity, RV: Residual volume
Pearson correlation analysis was used
*p<0.05, **p<0.01, ***p<0.001

DISCUSSION

The main pathophysiological point of COPD is the presence of EFL. The most important cause of EFL is DH and increased respiratory workload. It has been shown that IC is the best predictor for reflecting the presence of DH in the respiratory tract, especially in studies evaluating exercise intolerance. In recent years, the use of IC in place of FEV1 has also been recommended to evaluate the efficacy of bronchodilator therapy (10,11). One of the simplest ways to show EFL, which is the most important cause of DH, is the implementation of NEP. In our study, 16 (47.1%) of 34 patients with moderate and severe COPD had positive EFL in sitting position and 18 (52.9%) were EFL negative.

NEP application of two COPD cases with and without EFL is shown in Figure 2 and Figure 3. Koulouris et al. (12) applied NEP in 26 ambulatory COPD patients with a mean FEV1 of 60±22% and found EFL negative in seven patients (26.9%). Eltayara et al. (13) found that EFL was negative in 26 cases (22.2%) after the application of NEP in 117 patients with stable COPD, including 75 male and 42 female patients. In both studies, NEP was performed in the same patient in both sitting and supine positions. In both studies, no flow limitation was detected in both sitting and supine positions of the cases with negative EFL. In our study, since the application of NEP was performed only in the sitting position, the rate of negative EFL was found to be higher when compared with the literature. In two studies that examined the EFL by NEP only in the sitting position in the literature, the rates of positive EFL were found to be high as in our study. Positive EFL rate was 55.7% in the study conducted by Diaz et al. (14) and 61.1% in the study conducted by Tantucci et al. (15). In our study, when all PFT of the patients with positive and negative EFL were compared, only FEV1% predicted and FEF 25-75% predicted were found to be statistically significantly different ($p<0.05$). Studies in the literature have shown that FEV1% predicted is significantly lower in COPD patients with positive EFL (13,16).

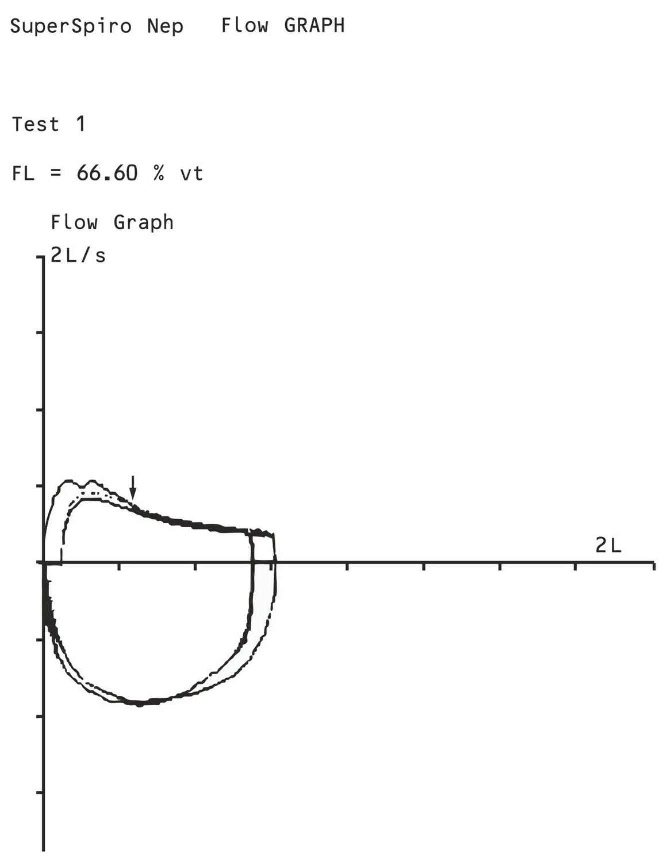

Figure 2. Negative expiratory pressure application of Chronic Obstructive Pulmonary disease patient with expiratory flow limitation

By examining the presence of EFL by using NEP method, information about DH can be obtained. In most of the studies on this subject, the presence of EFL in COPD patients was found to be significantly correlated with increased lung volumes. Koulouris et al. (16) found statistically significant difference in total lung capacity (TLC) %, RV%, RV/TLC, FRC% values, while Diaz et al. (17) found statistically significant difference in other parameters except TLC%. Boni et al. (18) found no significant difference in lung volumes between the groups with and without EFL, as in our study (14).

In recent studies, the importance of IC, which is a new parameter that correlates with dyspnea, has been emphasized in assessing the efficacy of pharmacological and surgical treatment in patients with COPD, identifying physiological changes during exercise (3). In our study, the relationship of IC with other lung volumes and NEP was evaluated in the evaluation of DH. There was a statistically significant correlation between IC and airway obstruction parameters such as FVC% predicted, FEV1% predicted and peak expiratory flow % predicted ($p>0.05$). Diaz et al. (17) Tantucci et al. (14) and Koulouris et al. (16) found a statistically significant negative correlation between IC and the presence

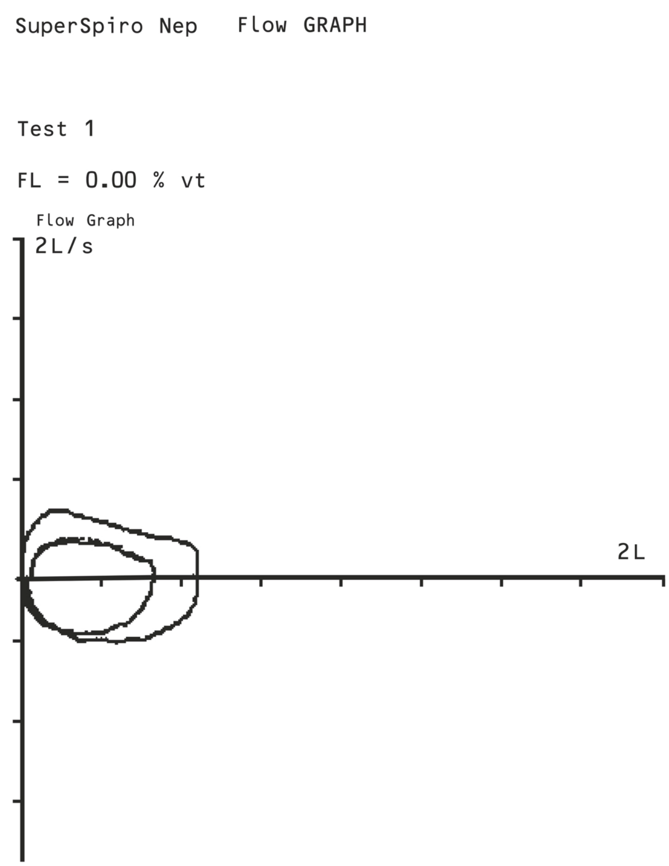

Figure 3. Negative expiratory pressure application of Chronic Obstructive Pulmonary disease patient without expiratory flow limitation

of EFL. In our study, a negative but not statistically significant correlation was found. The presence of the relationship between IC and EFL in COPD patients shows the importance of NEP method in the determination of DH. It reveals the widespread use of NEP, which is an inexpensive, practical and easy to use method for the detection of DH in COPD patients. In our study, TLC, FRC, VC and RV values in both mL and % predicted values were correlated with IC as in the study by Diaz et al. (17).

CONCLUSION

In conclusion, we demonstrated that the examination of EFL by NEP method in COPD patients did not provide additional information about DH. We can say that IC is the best predictor of DH.

Ethics

Ethics Committee Approval: The study was approved by Ethics Board of İstanbul University Cerrahpaşa Faculty of Medicine, Department of Chest Disesase (approval no: 1724-2004).

Informed Consent: Informed consent has been taken from all the patients.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Concept: H.İ., Design: H.İ., Data Collection or Processing: H.İ., Analysis or Interpretation: H.İ., Literature Search: H.İ., Writing: H.İ., G.U.

Conflict of Interest: No conflict of interest was declared by

the authors.

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