A negative airway reversibility test result does not mean the forced expiratory volume in 1 second limit that can increase after bronchodilator treatment in chronic obstructive pulmonary disease.

Myoung Kyu Lee

The Graduate School
Yonsei University
Department of Medicine

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Myoung Kyu Lee

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This certifies that the master's thesis of Myoung Kyu Lee is approved.

[Signature]_____Thesis Supervisor : Won-Yeon Lee

[Signature]_____Kye Chul Shin : Thesis Committee Member #1

[Signature]_____Suk Joong Yong : Thesis Committee Member #2

The Graduate School

Yonsei University

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감사의 글

1996년 의예과를 시작으로 벌써 17년의 시간이 흘러갔습니다. 의사과정과 전문의가 되는 것이 목표였던 저에게 어느덧 호흡기내과 분과의 길과 대학원 과정까지 진학할 것은 생각지도 못한 일이었지만 많은 분들의 도움으로 여기까지 올 수 있었습니다. 특히 호흡기내과의 어른으로 권위보다는 항상 저희를 편안하게 지켜봐 주시고 격려해주시면서 가끔은 아랫사람보다 더 열심히 현장에서 환자를 보시는 신계철 교수님과 현재의 연세대학교 원주세브란스기독병원 호흡기내과가 발전할 수 있었던 발판을 마련해주시고 이끌어주시는 용석중 교수님께 깊은 감사를 드립니다. 또한 호흡기내과 과장으로써 버팀목이 되어 환자진료뿐만 아니라 수련의 과정 동안 든든한 조언과 현재의 논문을 진행할 수 있고, 완성할 수 있게끔 도움을 아끼지 않으셨던 리원연 교수님께 진심으로 감사의 말씀을 드립니다. 그리고 현재는 연수로 멀리 계시지만 레지던트뿐만 아니라 수련의 과정에서 진정한 전문의의 모습을 보여주시고 바탕이 되어 주신, 그리고 어쩌면 현재의 제가 있게 해주신 김상하 교수님께도 깊은 감사를 드립니다. 그 외에도 많은 분들이 도움을 주었지만 가족과 아이들의 희생과 부모님의 믿음과 격려에 깊은 감사를 드립니다.

이 논문과 그 동안의 경험을 통해 더 나은 연구와 논문을 쓸 수 있도록 노력하겠습니다. 다시 한 번 관심과 격려를 보내주신 모든 분들께 감사 드립니다.

차 례

그림 차례

표 차례

국문 요약

기도가역성검사에서 음성을 보이는 만성폐쇄성폐질환 환자에서 흡입기 치료 후 폐기능의 향상 정도 비교

배경: 만성폐쇄성폐질환은 기관지확장제에 충분히 가역적이지 않는 기도 폐쇄를 보이는 질환이다. 그러나 일부의 만성폐쇄성폐질환환자에서 기도가역성검사가 음성이더라도 기관지확장제의 충분한 사용 후 1초간노력성호기량이 의미있게 증가하는 것을 관찰할 수 있다. 따라서 우리는 COPD를 진단받고 3개월간 치료를 받은 환자에서 의미있는 폐기능의 향상을 보이는 환자의 특징을 알기 위해 본 연구를 진행하였다.

방법: 기도가역성검사에서 음성을 보인 만성폐쇄성폐질환 환자를 대상으로 3개월 이상 기관지확장제 치료를 유지한 환자를 대상으로 본 연구를 진행하였다. 환자들은 연령, 성별, 신체질량지수, 흡연, 사용중인 약제, 초기 및 기관지확장제 치료 후 폐기능 등의 결과를 확인하였다.

결과: 환자들의 평균연령은 66.0 ± 9.6 세였고 남자가 246 (76.3%)명이었다. 기도가역성검사는 모든 환자에서 음성이었다. 3개월 이상의 기관지확장제 사용 후 폐기능검사에서 1초간노력성호기량(L) 변화(delta FEV1(L))는 0.21 ± 0.29 L였고 1초간노력성호기량(%)변화(delta FEV1(%))는 9.6 ± 14.1 %였다. 기도가역성검사에서 기관지확장제후 1초간노력성호기량은 delta FEV1(%)이 12% 이상 증가한 군에서 그렇지 않은 군보다 유의한 증가를 보였다(8.1 ± 6.6 vs. 5.1 ± 5.3, $P < 0.001$). 현재흡연자도 delta FEV1(%)이 12%이상 증가한 군에서 유의하게 적었으며(7.9% vs. 29.2%, $P<0.001$), 기도가역성검사에서 1초후노력성호기량(%)이 12%이상 증가한 군도 delta FEV1(%)이 12%이상 증가한 군에서 유의하게 많았다(28.6% vs. 12.4%, $P<0.001$). 그리고 3개월

이상의 기관지확장제 치료 후 1초간노력성호기량(%)이 80%이상 증가한 군도 delta FEV1(%)이 12%이상 증가한 군에서 유의하게 많았다(46.8% vs. 16.3%, P<0.001). 그러나 기관지확장제후 1초간노력성호기량(%)과 delta FEV1(%)사이에 피어슨상관관계는 약한 상관관계를 보였다(r=0.232, P<0.001).

결론: 본 연구에서 우리는 만성폐쇄성폐질환환자에서 음성의 기도가역성검사 결과가 기관지확장제후 증가할 수 있는 1초간노력성호기량의 한계를 의미하는 것은 아니며, 기도가역성검사가 음성이더라도 기관지확장제후 1초간노력성호기량(%)이 증가하는 정도가 많을수록 delta FEV1(%)도 더 증가하는 것을 알 수 있었다.

핵심되는 말: 기도가역성검사, 만성폐쇄성폐질환, 1초간노력성호기량

A negative airway reversibility test result does not mean the forced expiratory volume in 1 second limit that can increase after bronchodilator treatment in chronic obstructive pulmonary disease.

Lee, Myoung Kyu

Department of Medicine

The Graduate School, Yonsei University

Directed by Professor Won-Yeon Lee

I. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation not fully normalized after an inhaled bronchodilator [1]. This means post bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) is lesser than 0.70 and FEV1 does not increase by 12% or 200 mL of the pre-test value [2]. However, some COPD patients increase their FEV1 by 12% and >200 mL, which guidelines define as

'reversible' [2, 3]. Thus, reversibility is a candidate CODP phenotype, and has been used by clinicians as a marker for patients more likely to respond to bronchodilators. And recently, reversibility has been linked to a specific COPD genotype [4]. And even though reversibility test is negative in COPD, some patients' FEV1 is significantly increased after inhaled bronchodilator therapy in follow-up pulmonary function test (PFT).

After more than two decades of intensive study and a long series of negative and positive publications on this issue, bronchoreversibility testing is still largely used in clinical practice and deemed to guide the clinician through the diagnostic and follow-up process [1, 3]. A positive response of FEV1 and/or FVC or vital capacity (VC) above 12% and 200 mL baseline value will lend support to bronchodilator therapy independently of the underlying disease. Even a 'negative' response, i.e. an increase in either FEV1 or FVC or VC below 12% and 200 mL baseline value may be often associated with reduction in dyspnea. In > 50% of the cases, this is consistent with significant improvement in airway function, as suggested by increments in partial flow and airway conductance, thus supporting the indication to continuous therapy even in negative reversibility patients [5].

And also, in the European Respiratory Journal, HAN et al. [6] document the presence of bronchoreversibility, even in COPD with moderate-to-severe emphysema. By reviewing data from 544 COPD patients with severe bilateral emphysema participating in the National Emphysema Treatment Trial, the authors observed that, despite that only a quarter of the patients exhibited a significant increase in the FEV1 on one or more occasions, two-thirds of the population exhibited impressive increments in FVC > 400ml. In other study, to the extent that an increase in FVC reflects clinical improvements in dyspnea at rest and during physical activity [7].
As recently suggested in two large clinical trials, Calverley et al. and Tashkin et al. s' data add further support to the notion that COPD is not a fully irreversible disease [8, 9].
As a result, we need to know the characteristics of the COPD patients who significantly increased lung function after bronchodilator therapy despite the negative airway reversibility test (ART). Thus, the authors reviewed that the COPD patients showed negative ART in initial pulmonary function test and analyzed the differences between the patients who showed significantly increased pulmonary function and who did not after three months follow-up spirometry.

II. Materials and Methods

Data source

This observational study involved a retrospective analysis of PFT records. We reviewed targeted total 328 patients who had been followed up for three months or more and who showed negative ART among 2,058 COPD patients aged ≥ 40 year-old and smoking history ≥ 10 pack-years (py) who diagnosed at respiratory center of a Yonsei University Wonju Christian Hospital from October 2009 to September 2010. COPD was defined as forced spirometry with a post bronchodilator FEV1<80% predicted and an FEV1/FVC<0.70. During COPD management, the patients were prescribed medications including inhaled corticosteroids, long-acting $beta_2$ agonists, long-acting muscarinic antagonists, theophylline, or leukotriene modifiers etc. respectively.

Study design

We checked from patients' data including: age (40 - 64 years or ≥ 65 years), sex, body mass index, smoking status (current or former) and amount (10 - 39 py or ≥ 40 py), current medications, initial PFT (pre and post-bronchodilator forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC, airway reversibility test (ART)) and follow-up PFT. Follow-up PFTs were checked only 3 months or more after initial treatment. And then we measured the changes of lung function including FEV1 (L), FEV1 (%), FVC (L) and FVC (%), respectively between two PFTs.

Procedures

Pulmonary function testing was conducted by experienced respiratory therapists/technicians using automated pulmonary function testing equipment(Vmax Encore 20c Spirometer CareFusion; SensorMedics, San Diego, CA) in keeping with current recommended standards [10-11].

Patients were required to withdraw from all short-acting and long acting bronchodilators for at least 4 and 12 hours, respectively. Reversibility testing was performed using salbutamol 200mcg by metered dose inhaler; post-dose measurements were performed 20 min after inhalation. To avoid bias from differences in baseline measurements, changes in FEV1 and various lung volumes were assessed and compared as percentages of predicted normal values (%predicted) [12,13].

Data analysis and statistical methods

SPSS 18.0 (SPSS Inc.; Chicago, IL, USA) were used for statistical analysis. The changes in spirometric values after bronchodilation were expressed as: (a) absolute change (mL); (b) percentage change from baseline; and (c) change in percentage predicted normal values. Continuous variables were expressed in the form of mean value ± standard deviation. A p value less than 0.05 was considered to be statistically significant.

A positive response of airway reversibility test (ART) was defined as an increase in the FEV1 of more than 200 mL and 12% predicted [14, 15]. And we also checked positive ART (mL) that was defined as an increase in the FEV1 of more than 200 mL and positive ART (%) that was defined as an increase in the FEV1 of more than 12%, respectively.

Chi-square tests were used for categorical data and unpaired t-tests were used to compare differences between initial and follow-up spirometry including FEV1, FVC, ART and body mass index (BMI) values. Delta FEV1

was defined as the differences between pre-bronchodilator FEV1 at follow-up and pre-bronchodilator FEV1 at initial pulmonary function test, and ‘significant increase of delta FEV1’ was defined as an increase of pre-bronchodilator FEV1 more than or equal to 200 mL or 12% between follow-up and initial spirometry. Regression analyses were used for evaluating the effect of follow-up FEV1 (%) changes (delta FEV1 (%)) or FVC (%) changes (delta FVC (%)) on ART (%) variables.

Ethics

This study was conducted under the approval by the Institutional Review Board of Yonsei University Wonju Christian hospital.

III. Results

Total subjects

Of the 328 subjects included in this analysis, 246 (76.3%) were male and 82 (23.7%) were female. The mean age was 66.0 ± 9.6 years. Mean body mass index was 23.0 ± 3.7 kg/m^2.

At total subjects, the mean post-bronchodilator FEV1/FVC (%predicted) was 50.2 ± 12.5 and post-bronchodilator FEV1 (%predicted) was 61.4 ± 17.0. Mean interval time was 253.1 ± 150.0 days (Table 1).

Airway reversibility test (ART) results showed negative in total subjects. But the subjects those FEV1 (%) increased more than or equal to 12% in ART were 62 (18.6%). After three month or more COPD treatment, we checked follow-up pulmonary function test. At follow-up study, the mean FEV1 (L) change (delta FEV1 (L)) was 0.21 ± 0.29, and mean FEV1 (%) change (delta FEV1 (%)) was 9.36 ± 14.1. Especially, the subjects those delta FEV1 (L) was more than or equal to 0.20 L were 152 (46.3%), and those delta FEV1 (%) was more than or equal to 12% were 126(38.4%) (Table 1).

Table 1. Characteristics of subjects

Characteristics	Subjects
Subjects, No.	328
Age at index date, mean ± SD, y	66.0 ± 9.6
40 - 64 y, %	37.2
≥ 65 y, %	62.8
Female sex, %	23.7
Height, cm	160.5 ± 7.6
Body mass index, kg/m^2	23.0 ± 3.7
Initial FEV1, L	1.34 ± 0.48
Initial FEV1, %predicted	57.2 ± 16.5

Initial FVC, L	2.79 ± 0.81
Initial FVC, %predicted	83.1 ± 18.2
Initial FEV1/FVC, %predicted	48.9 ± 12.1
Post-bronchodilator FEV1, L	1.43 ± 0.48
Post-bronchodilator FEV1, %predicted	61.4 ± 17.0
Post-bronchodilator FEV1/FVC, %predicted	50.2 ± 12.5
Airway reversibility test, L	0.09 ± 0.09
Airway reversibility test, %predicted	7.6 ± 7.8
Follow-up FEV1, L	1.57 ± 0.55
Follow-up FEV1, %predicted	67.1 ± 20.8
Follow-up FVC, L	3.02 ± 0.85
Follow-up FVC, %predicted	90.8 ± 19.1
Follow-up FEV1/FVC, %predicted	52.6 ± 12.8
FEV1 change (delta FEV1), L	0.21 ± 0.29
< 0.20	0.02 ± 0.12
≥ 0.20	0.44 ± 0.26
FEV1 change (delta FEV1), %	9.6 ± 14.1
< 12	1.2 ± 8.4
≥ 12	23.0 ± 10.6
Interval time, days	253.1 ± 150.0
Medication, %	
Inhaled corticosteroids	81.9
Long-acting $beta_2$ agonists	80.8
Long-acting muscarinic antagonists	70.8
Methylxanthine	68.0
Leukotriene modifier	31.5
Smoking status, %	
Former smoker	78.5
Current smoker	21.5
Smoking amounts, py	
10 - 39	54.3
≥ 40	45.7

Abbreviations: cm, centimeter, kg/m^2, kilogram/$meter^2$; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; L, liter; No., number; SD, standard deviation; py, pack*years; y, years

Pulmonary function differences according to delta FEV1 (%)

According to delta FEV1, we differentiated pulmonary function between less than 12% and more than or equal to 12%. Initial FEV1 (L) and FVC (L) was higher in delta FEV1 (<12%) group, but initial FEV1 (%) and FVC (%) was not different between two groups. And also post-bronchodilator FEV1 (%) was similar between two groups (P=0.769) (Table 2).

In Airway reversibility test, post-bronchodilator FEV1 (%) was more increased in delta FEV1 (≥12%) than the other group (8.1 ± 6.6 vs. 5.1 ± 5.3, P < 0.001). and also follow-up FEV1 (%), FVC (%), FEV1/FVC was significantly increased in delta FEV1 (≥12%) (Table 2).

Table 2. Pulmonary function test between delta FEV1 < 12% and delta FEV1 ≥ 12%

Characteristics	Delta FEV1 < 12%	Delta FEV1 ≥ 12%	P value
Age, y, mean ± SD	65.0 ± 10.1	67.5 ± 9.3	0.025
Body mass index, kg/m^2	22.7 ± 3.8	23.5 ± 3.3	0.054
Initial FEV1, L	1.40 ± 0.53	1.23 ± 0.38	0.001
Initial FEV1, %	58.2 ± 17.6	56.2 ± 15.0	0.267
Initial FVC, L	2.85 ± 0.81	2.63 ± 0.76	0.015
Initial FVC, %	83.1 ± 18.3	83.0 ± 18.1	0.951
Initial FEV1/FVC, %	49.9 ± 13.1	48.0 ± 10.7	0.138
Post-bronchodilator FEV1, L	1.47 ± 0.53	1.32 ± 0.38	0.003
Post-bronchodilator FEV1, %	61.1 ± 18.1	60.6 ± 15.5	0.769
Post-bronchodilator FEV1/FVC, %	51.1 ± 13.5	48.7 ± 11.2	0.088
Airway reversibility test, L	0.06 ± 0.07	0.09 ± 0.06	0.001
Airway reversibility test, %	5.1 ± 5.3	8.1 ± 6.6	< 0.001

Follow-up FEV1, L	1.46 ± 0.55	1.71 ± 0.52	< 0.001
Follow-up FEV1, %	59.4 ± 19.6	79.2 ± 17.5	< 0.001
Follow-up FVC, L	2.92 ± 0.82	3.11 ± 0.87	0.045
Follow-up FVC, %	85.1 ± 18.2	99.4 ± 16.4	< 0.001
Follow-up FEV1/FVC, %	50.9 ± 13.7	55.5 ± 11.7	0.002
Delta FEV1, L	0.05 ± 0.14	0.47 ± 0.28	< 0.001
Delta FEV1, %	1.2 ± 8.4	23.0 ± 10.6	< 0.001
Delta FVC, L	0.07 ± 0.32	0.48 ± 0.44	< 0.001
Delta FVC, %	2.0 ± 10.1	16.3 ± 13.1	< 0.001

Abbreviations: ART, airway reversibility test; kg/m^2, kilogram/$meter^2$; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; L, liter; No., number; SD, standard deviation; y, years

Univariate analysis of characteristics between delta FEV1 (<12%) and delta FEV1 (≥12%)

When we compared to characteristics of subjects between delta FEV1 (<12%) and delta FEV1 (≥12%), female was higher in delta FEV1 (≥12%) group (31.7% vs. 20.8%, P=0.026). Current smoker was significantly lower in delta FEV1 (≥12%) group (7.9% vs. 29.2%, P<0.001). And also the subjects with ART (%) positivity was higher in delta FEV1 (≥12%) group (28.6% vs. 12.4%, P<0.001).

And at follow-up spirometry, the subjects with increased FEV1 more than or equal to 80%predicted was significantly higher in delta FEV1 (≥12%) group (46.8% vs. 16.3% in delta FEV1 (<12%), P<0.001). When compared to COPD medications, delta FEV1 (≥12%) group more used inhaled corticosteroids than delta FEV1 (<12%), and there was statistically significant (87.3% vs. 78.7%, P=0.049) (Table 3).

Table 3. Differences of subjects between delta FEV1 < 12% and delta FEV1 ≥ 12%

Characteristics	Delta FEV1 < 12%	Delta FEV1 ≥ 12%	OR	95% CI	P value
Age at index date, ≥65 y, No (%)	119(58.9)	87(69.0)	1.556	0.972, 2.490	0.065
Female sex	42(20.8)	40(31.7)	1.772	1.068, 2.939	0.026
Current smoking	59(29.2)	10(7.9)	4.786	2.345, 9.770	< 0.001
Chest abnormality	59(29.2)	36(28.6)	1.031	0.631, 1.686	0.902
Initial FEV1 (≥50%)	134(66.3)	80(63.5)	1.133	0.711, 1.805	0.599
Initial FVC (≥80%)	122(60.4)	71(56.3)	1.181	0.752, 1.855	0.469
ART (%) positivity (≥12%)	25(12.4)	36(28.6)	2.832	0.602, 5.007	< 0.001
Inhaled corticosteroids	159(78.7)	110(87.3)	1.859	0.997, 3.468	0.049
Long-acting $beta_2$ agonists	156(77.2)	108(85.7)	1.769	0.973, 3.216	0.059
Long-acting muscarinic antagonists	145(71.8)	93(73.8)	1.108	0.671, 1.829	0.689
Methylxanthine	135(66.8)	86(68.3)	1.067	0.663, 1.717	0.377
Leukotriene antagonists	58(28.7)	42(33.3)	1.241	0.768, 2.006	0.789
Follow-up FEV1/FVC (≥0.70)	14(6.9)	14(11.1)	1.679	0.772, 3.650	0.188
Follow-up FEV1 (≥80%)	33(16.3)	59(46.8)	4.510	2.704, 7.521	< 0.001

Abbreviations: ART, airway reversibility test; CI, confidence interval; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; L, liter; No., number; OR, odds ratio

Multivariate analysis of characteristics between delta FEV1 (<12%) and delta FEV1 (≥12%)

In univariate analysis, female gender, current smoking, ART (%) positivity, and inhaled corticosteroids use showed to be statistically significant (Table 3). When we performed multivariate analysis by the factors shown to be significant by univariate analysis, current smoking (P<0.001) and ART (%) positivity (P=0.007) were associated with delta FEV1 (%). But female gender, inhaled corticosteroids use did not show significance with delta FEV1 (%) (Table 4).

Table 4. Multivariate analysis of subjects between delta FEV1 < 12% and delta FEV1 ≥ 12%

Characteristics	OR	95% CI	P value
Female sex	1.281	0.745, 2.201	0.370
Current smoking	4.152	2.010, 8.575	< 0.001
ART (%) positivity (≥12%)	2.287	1.260, 4.149	0.007
Inhaled corticosteroids	1.482	0.767, 2.862	0.241

Abbreviations: ART, airway reversibility test; CI, confidence interval; OR, odds ratio

Pearson’s correlation coefficient between post-bronchodilator FEV1 change (%) after ART and delta FEV1 (%), delta FVC (%)

We analyzed respectively Pearson’s correlation coefficient between post-bronchodilator FEV1 change (%) after ART and delta FEV1 (%), ART (%) and delta FVC (%). Between post-bronchodilator FEV1 change (%) and delta FEV1 (%), Pearson’s correlation coefficient (r) was 0.232 and showed mild significant correlation (P<0.001) (Fig. 1-A). And between post-bronchodilator FEV1 change (%) and delta FVC (%), Pearson’s correlation (r) was 0.170 and also showed mild significant correlation (P=0.002) too (Fig. 1-B).

Figure 1.

Fig. 1-A

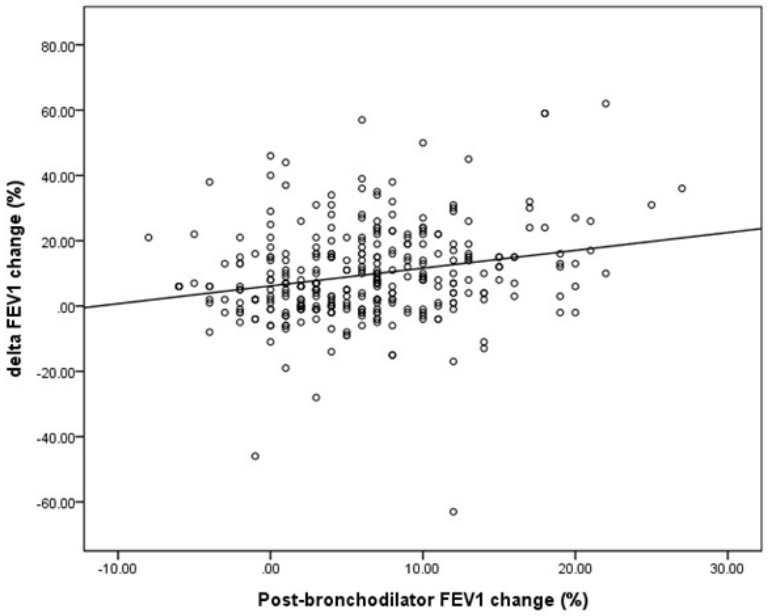
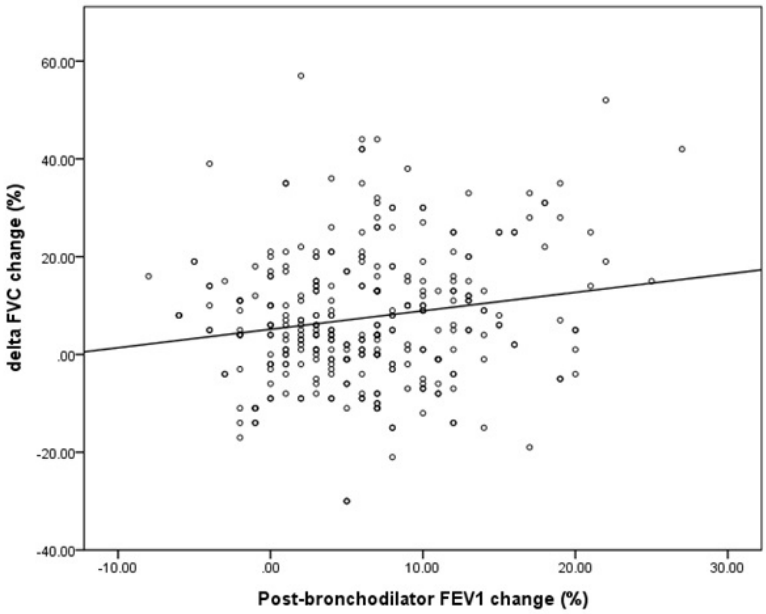


Fig. 1-B



Pearson's correlation coefficient performed between post-bronchodilator FEV1 change (%) and delta FEV1 (%), between post-bronchodilator FEV1 change (%) and delta FVC (%). Between post-bronchodilator FEV1 change (%) and delta FEV1 (%), it showed mild significant correlation (r=0.232, P<0.001) (Fig. 1-A). Between post-bronchodilator FEV1 change (%) and delta FVC (%), it also showed mild significant correlation (r=0.170, P=0.002) (Fig. 1-B).

Abbreviations: ART, airway reversibility test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; L, liter; r, Pearson's correlation coefficient

IV. Discussion

The main findings of this study were as followed: 1) negative airway reversibility test (ART) results did not mean the FEV1 limit that could increase after bronchodilator treatment in COPD patients; 2) Even if ART was negative, delta FEV1 (%) was more increased in follow-up spirometry as post-bronchodilator FEV1 change was higher in initial spirometry; 3) ART (%) positivity could predict the rate of FEV1 increase after bronchodilator treatment in some COPD patients.

Bronchodilators may result in a greater improvement in the FEV1 than the FVC, which increases the FEV1/FVC ratio [16]. Reversibility testing is performed in the diagnosis of obstructive diseases like asthma and COPD. Results of this test can be helpful in defining factors increasing or decreasing probability of disease. And we find in the literature the term 'not fully reversible airway obstruction' or equivalents like: 'partially reversible obstruction' and 'poorly reversible obstruction' [17, 18]. However, in clinical practice, we occasionally could find that FEV1 on follow-up pulmonary function test significantly increased after bronchodilator therapy in COPD patients even though airway reversibility test was negative.

In another study, Chhabra et al. reported that the diagnostic ability of acute bronchodilator responsiveness in separating bronchial asthma from COPD was limited [19]. And none of the different methods of measuring the response gave a clear-cut separation between the two diseases. Thus, these cut-offs leave a substantial scope for misdiagnosis. These results were the consequence of a substantial overlap in the response to bronchodilator between asthma and COPD and the fact that a fairly large proportion of subjects with asthma did not show acute bronchodilator responsiveness while a large proportion of COPD patients had a good reversibility[19].

Our results showed that at follow-up pulmonary function test after 3 months or more, FEV1 (L) was significantly increased more than or equal to 0.20L (delta FEV1 (L) $\geq$ 0.20L) in 46.3% COPD patients with negative ART and FEV1 (%) was increased more than or equal to 12% (delta FEV1 $\geq$ 12%) in 38.5% of COPD patients. And these results also showed that follow-up FVC (L) or FVC (%) was significantly increased in delta FEV1 $\geq$ 12% COPD patients, respectively ($P<0.001$). In this study, we could observe that many COPD patients with negative ART frequently showed much increased pulmonary function test after bronchodilator therapy. So

even though airway reversibility test is negative in COPD, Some patients may preserve airway reversibility for bronchodilator and would expect much improved pulmonary function.

Calverley et al. suggested that the current definitions of bronchodilator reversibility have significant limitations in established COPD and may be potentially misreading. And this study also referred that despite all being irreversible to salbutamol at the first visit in COPD patients, 38% of those classified by the European criteria changed their apparent responder status with time [20].

We could not rule out the possibility to combine bronchial asthma completely in many COPD patients with negative ART. But, we thought that there could have several features in these patients with more increasing follow-up FEV1 than ART results, so compared the differences between two groups of delta FEV1 ≥ 12% and <12% in follow-up spirometry.

Among the two groups, we could find that the age of the COPD patients with delta FEV1 ≥ 12% was more significantly higher rather than the patients with delta FEV1 < 12% (67.5 ± 9.3 vs. 65.0 ± 10.1, p=0.025). In recent studies, it is known that age is a very important variable when assessing obstructive lung diseases given the known changes in lung function that occur with increasing age, and increasing age may be a powerful factor contributing to the manifestation of overlap syndrome (21, 22). Especially, elderly patients with asthma display more features of fixed obstruction than their younger patients, and their asthma may manifest as chronic persistent airflow obstruction mimicking COPD (23, 24). And, elderly asthma patients with mimicking COPD may show more increased lung function when they have long term bronchodilator therapy. In our study, we could consider that it might be also included elderly asthma or overlap syndrome among the COPD patients with delta FEV1 ≥ 12%. But, the ratio of the patients with age ≥ 65 year-old was no significant difference between delta FEV1 ≥ 12% and delta FEV1 < 12% (69.0% vs. 58.9%, p=0.065).

And among two groups, we could also found that delta FEV1 was more significantly increased in COPD patients with former smoker or with increased ART (%) ≥ 12%. It is well known that cigarette smoking interacts with the inflammation and remodelling that occur in asthma and COPD (25). And also, smoking promotes neutrophilic inflammation in both asthma and COPD which results in increased steroid resistance (26, 27). As a result, we suggested that reduced inflammation and steroid resistance by stop smoking had a clear impact on

significantly increased lung function after bronchodilator therapy.

Meanwhile, there were more female patients in those with delta FEV1 ≥ 12%, but there was no statistical significance in multivariate analysis. And also our data showed that those patients with using inhaled corticosteroids were more in delta FEV1 ≥ 12%, but did not show statistical significance in multivariate analysis, and other bronchodilators including LABA, LAMA did not show clinical significance, either. Calverley et al. also suggested that COPD patients treated previously with inhaled corticosteroids did not differ in their bronchodilator responses from those not so treated [20]. So the kind of bronchodilator seemed to do not affect the outcome of delta FEV1.

In another study, many patients with COPD respond to a bronchodilator with an increase only in FVC rather than in FEV1 [28, 29]. The increase in FVC (also called a volume response) most likely results from dilatation of the more peripheral airways leading to reduced air trapping [30]. Kesten and Rubeck observed that change in FVC expressed as percent increase over baseline value was similar in asthmatics and patients with COPD [31].
However, our results did not show a more increase of FVC (%) in the COPD patients with delta FEV1 ≥ 12%. During the mean delta FEV1 (%) 23.0 ± 10.6 % increase, mean delta FVC (%) was only increased 16.3 ± 13.1 %, so it showed a greater increase of delta FEV1 (%) than delta FVC (%). It suggested that a significant increase of delta FEV1 (%) was a result of reversibility after bronchodilator therapy rather than indirect increase by delta FVC (%). And despite there was no difference of initial pre and post-bronchodilator FEV1 (%) between delta FEV ≥ 12% and <12% groups in initial pulmonary function test, 46.8% COPD patients with delta FEV1 ≥ 12% (vs. 16.3%) showed increased FEV1 (%) more than or equal to 80%. So we suggest that even though ART is negative in COPD patients, bronchodilator therapy can be significantly increased with FEV1 (%), and also suggest that negative result of ART does not necessarily mean ‘not fully reversible’.
So far, the predictive value of achieving bronchodilator responsiveness based on predefined thresholds as a marker distinguishing patients who will have long-term positive outcomes with pharmacotherapy in COPD has been a matter of debate. But, the 4-year data from the UPLIFT trial also demonstrate that acute bronchodilator responsiveness testing as measured in this study should not be used in predicting long term health outcomes and

response to tiotropium in patients with COPD[32].

When we compared post-bronchodilator FEV1 (%) change after ART in initial spirometry, post-bronchodilator FEV1 (%) was increased 8.1 ± 6.6 % in delta FEV1 ≥ 12%, but was only increased 5.1 ± 5.3% in delta FEV1 < 12%. As a result, post-bronchodilator FEV1 (%) change in ART tended to be more increased in delta FEV1 ≥ 12%, but a weak correlation was seen between two group (r=0.151, P=0.006). However, we could know that post-bronchodilator FEV1 (%) change was associated with delta FEV1 (%), so we may predict response of bronchodilator therapy in COPD patients if we check post-bronchodilator FEV1 (%) change after ART.

Limitations

This study has the limitation that it was a retrospective cohort study, so we could not fully removed confounding variables including combined asthma, atopy, or other underlying diseases. And in the first visit, some COPD patients had severe dyspnea symptom including acute exacerbation of COPD, so they could not perform appropriate pulmonary function test. It could be caused lower measured pulmonary function test in initial visit, as a result, some patients could be measured exaggerated delta FEV1 (%) in follow-up study.

But, despite of these limitations, we could know that COPD patients had more significantly increased pulmonary function including FEV1 (%) after bronchodilator therapy even though negative reversibility test. So, we could suggest that the negative result of ART did not necessarily mean ‘not fully reversible’ in COPD patient.

V. Conclusion

In this study, we suggest that negative airway reversibility test (ART) result did not mean the FEV1 limit that could increase after bronchodilator treatment in COPD patients, and even if ART was negative, delta FEV1 (%) was more increased in follow-up spirometry as post-bronchodilator FEV1 (%) change was higher in initial spirometry. However, we could not distinguish well the differences of those COPD patients with delta FEV1 (%) ≥ 12%, therefore more studies are needed to know the characteristics of those COPD patients.

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Abstract

A negative airway reversibility test result does not mean the forced expiratory volume in 1 second limit that can increase after bronchodilator treatment in chronic obstructive pulmonary disease.

Lee, Myoung Kyu

Department of Medicine

The Graduate School, Yonsei University

Directed by Professor Won-Yeon Lee

Background: Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation not fully normalized after an inhaled bronchodilator. But even though reversibility test is negative in COPD, some patients' Forced expiratory volume in 1 second (FEV1) is significantly increased after inhaled bronchodilator therapy in follow-up pulmonary function test (PFT). So, we analyzed the differences between the patients who showed significantly increased pulmonary function and who did not after three months follow-up spirometry.

Methods: We reviewed targeted total 328 COPD patients who had been followed up for three months or more

and who showed negative airway reversibility test (ART). And we checked age, sex, body mass index, smoking status, current medications, initial and follow-up PFTs etc.

Results: The patients had the mean age of 66.0 ± 9.6 years with 246 (76.3%) male. ART results showed negative in total subjects. At follow-up spirometry, the mean FEV1 (L) change (delta FEV1 (L)) was 0.21 ± 0.29, and mean FEV1 (%) change (delta FEV1 (%)) was 9.6 ± 14.1. In ART (%), post-bronchodilator FEV1 (%) was more increased in delta FEV1 (≥12%) than the other group (8.1 ± 6.6 vs. 5.1 ± 5.3, $P < 0.001$). Current smoker was significantly lower in delta FEV1 (≥12%) group (7.9% vs. 29.2%, $P<0.001$). And also the subjects with ART (%) positivity was higher in delta FEV1 (≥12%) group (28.6% vs. 12.4%, $P<0.001$). The patients with increased FEV1 more than or equal to 80%predicted was significantly higher in delta FEV1 (≥12%) group (46.8% vs. 16.3%, $P<0.001$). But, between post-bronchodilator FEV1 (%) after ART and delta FEV1 (%), Pearson's correlation showed mild significant correlation ($r=0.232$, $P<0.001$).

Conclusion: we suggest that negative ART result did not mean the FEV1 limit that could increase after bronchodilator treatment in COPD, and even if ART was negative, delta FEV1 (%) was more increased in follow-up spirometry as post-bronchodilator FEV1 (%) change was higher in initial spirometry.

Key words: Airway reversibility test, chronic obstructive pulmonary disease, forced expiratory volume in 1 second.