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위식도 역류질환이 있는 기관지확장증 환자에서 양성자 펌프 억제제의 효과

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Effect of Proton Pump Inhibitors in Bronchiectatic Patients with Gastroesophageal Reflux Disease

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Background/Aims: Bronchiectasis is aggravated by gastroesophageal reflux disease (GERD) owing to micro aspiration. Some researchers note the effect of antireflux surgery in bronchiectasis with GERD. However, few have investigated the effects of medical antireflux therapy. We investigated the effect of proton pump inhibitors (PPIs) in bronchiectasis with GERD.
Methods: From March 2003 to May 2015, the clinical records of patients who had bronchiectasis with GERD were reviewed. Patients underwent an initial pulmonary function test (PFT) and chest computed tomography when diagnosed with bronchiectasis. One group with typical GERD symptoms was treated with PPIs, while the other group was not. Both groups underwent PFTs within six months after completing PPI therapy. Population characteristics and associations were compared between the groups.
Results: Two hundred and fifty-seven patients (124 male, 133 female; mean age 67.6±10.0 years) were included. There were no significant differences between the groups in terms of forced vital capacity (FVC; p=0.239), forced expiratory volume in one second (FEV1; p=0.555), or FEV1/FVC (p=0.374) after PPI therapy. However, there were significant improvements in FVC (p=0.002) and FEV1 (p=0.006) in patients with high BMI in the PPI treatment group.
Conclusions: PPIs have no effect on the pulmonary function in patients with bronchiectasis and GERD. However, PPIs were noted to produce improvements in lung function in patients with bronchiectasis and high BMI. **(Korean J Gastroenterol 2016;68:10-15)**

Key Words: Bronchiectasis; Gastroesophageal reflux; Proton pump inhibitors

INTRODUCTION

Bronchiectasis is a chronic dilatation of the airways with thickening of the bronchial walls, which typically presents with chronic cough and sputum hypersecretion.[1] Studies from the USA estimate a prevalence of 4.2 per 100,000 people among those aged 18 to 34 years, which increases to 271.8 per 100,000 among people aged more than 75 years.[2] Several etiologies, ranging from idiopathic to congenital diseases, systemic diseases (e.g., autoimmune disease such as rheumatoid arthritis), and post-infective causes, have been implicated.[3]

The clinical presentation of bronchiectasis may be compli-

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cated by the coexistence of other conditions, including gastroesophageal reflux disease (GERD).[4,5] The prevalence of GERD in patients with bronchiectasis was approximately 40% according to Lee et al.[6] in 2014, compared to 18% in the control group. GERD has an inverse relationship with lung function tests in bronchiectatic patients.[4]

Bronchiectasis is aggravated by GERD due to vagally mediated reflex bronchoconstriction and pulmonary micro aspiration.[7] Research on the effect of antireflux surgery in bronchiectasis patients with GERD[8,9] finds that after surgery, respiratory symptoms and pulmonary function improves.[8,9] However, few studies have investigated the effects of antireflux medication. The purpose of this study was to determine the effect of proton pump inhibitors (PPIs) among the antireflux medical therapies in patients with bronchiectasis and GERD.

SUBJECTS AND METHODS

This retrospective study received institutional review board approval from Seoul National University Bundang Hospital (IRB No. B-1512-326-105), and informed patient consent was waived. We collected data from electronic medical records for patients who had bronchiectasis with GERD between March 2003 and May 2015. Heartburn, regurgitation, and chest soreness were considered suggestive of GERD. We also evaluated computed tomography scans of the chest in order to identify bronchiectasis.

Patients underwent initial pulmonary function tests in our institution when diagnosed with bronchiectasis. One group with typical GERD symptoms was treated with PPIs, while the other group was not. Both groups underwent pulmonary function testing within six months after finishing antireflux medical therapy. Several lung function parameters, specifically forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and FEV1/FVC, were analyzed. We excluded patients treated with PPIs for less than 21 days and those diagnosed with erosive gastritis or peptic ulcer on esophago-gastro-duodenoscopy. Twenty-seven patients who underwent antireflux medical therapy and 230 patients who did not undergo antireflux medical therapy were included.

Statistical analysis was performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). We compared the two groups by sex, drinking habits, smoking habits, and presence of diabetes mellitus, hypertension, pulmonary tuberculosis, chronic kidney disease, and GERD using the χ^2 test for to reduce confounding. Continuous variables are presented as means±SD. Continuous variables including age, BMI, and lung function were analyzed using the Mann-Whitney U test, as the data were not normally distributed. Correlations among age, BMI, severity of obesity, drinking, smoking, diabetes mellitus, hypertension, pulmonary tuberculosis history, chronic kidney disease, and lung function were analyzed using Spearman's rho. Null hypotheses of no difference were rejected if p-values were less than 0.05.

RESULTS

Two hundred and fifty-seven patients (124 male, 133 female; mean age: 67.6±10.0 years [24-92 years]) were enrolled in this study. The PPI treatment group comprised 27 individuals, including eight males with a mean±SD age of 71.6±8.5 years. The non-PPI treatment group comprised

Table 1. Baseline Characteristics of the Non-PPI Treatment Group and the PPI Treatment Group

	Non-PPI treatment group (n=230)	PPI treatment group (n=27)	p-value
Age (yr)	67.1±10.0	71.6±8.5	0.032
Sex, male/female	116/114	8/19	0.041
BMI (kg/m^2)	23.2±3.3	22.3±3.0	0.286
Drinking			0.171
Ex-drinker	5 (2.2)	1 (3.7)	
Current	38 (16.5)	4 (14.8)	
Smoking			0.815
Ex-smoker	10 (4.3)	3 (11.1)	
Current	30 (13.0)	5 (18.5)	
Diabetes mellitus	29 (12.6)	8 (29.6)	0.036
Hypertension	61 (26.5)	14 (51.9)	0.006
Pulmonary TB	55 (23.9)	15 (55.6)	0.000
CKD	3 (1.3)	2 (7.4)	0.087
GERD			0.162
NERD	151 (65.7)	20 (74.1)	
LA-A	23 (10.0)	1 (3.7)	
LA-B	8 (3.5)	3 (11.1)	
LA-C	0 (0)	1 (3.7)	
Pre-FVC (%)	91.6±16.2	87.1±16.9	0.257
Pre-FEV1 (%)	91.0±22.4	87.9±25.1	0.389
Pre-FEV1/FVC (%)	71.3±12.2	72.8±12.5	0.360

Values are presented as mean±SD or n (%).
PPI, proton pump inhibitor; TB, tuberculosis; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease; NERD, nonerosive reflux disease; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.

230 individuals, which included 116 males with a mean±SD age of 67.1±10.0 years. The baseline characteristics of the patients are summarized in Table 1.

The mean±SD pre-treatment FVCs (%) for the PPI treatment group was 87.1±16.9%, and for the non-PPI treatment group 91.6±16.2%. The mean±SD post-treatment FVCs (%) for the PPI treatment group was 84.5±20.7%, and non-PPI treatment group was 90.3±17.8%. The mean±SD difference between the pre-treatment FVC and the post- treatment FVC for the PPI treatment group was −2.6±13.0%, while for the non-PPI treatment group it was −1.3±11.0%. There were no statistically significant differences between the groups in terms of post-treatment FVC (p=0.239) or changes between pre-treatment and post- treatment FVC (p=0.975) (Table 2, Fig. 1).

The mean±SD pre-treatment FEV1s (%) for the PPI treatment group was 87.9±25.1%, and the non-PPI treatment group was 91.0±22.4%. The mean±SD post-treatment FEV1s (%) for the PPI treatment group was 87.9±28.0%, and the non-PPI treatment group 90.3±22.9%. The mean±SD differences of the pre-treatment FEV1 and post-treatment FEV1 for the PPI treatment group was 0±11.9% and the non-PPI treatment group were −0.7±11.2%. There were no statistically significant differences between the groups concerning post-treatment FEV1 (p=0.555) or changes between pre-treatment and post-treatment FEV1 (p=0.611) (Table 2, Fig. 1).

The mean±SD pre-treatment FEV1/FVCs (%) for the PPI treatment group was 72.8±12.5%, and for the non-PPI treatment group was 71.3±12.2%. The mean±SD post-treatment FEV1/FVCs (%) for the PPI treatment group was 74.5±15.8%, and non-PPI treatment group 72.1±14.8%. The mean±SD difference between pre-treatment FEV1/FVC and post-treatment FEV1/FVC for the PPI treatment group was 1.7±12.3%, and for the non-PPI treatment group was 0.9±9.7%. There were no statistically significant differences between the

Table 2. Comparison of Lung Function between Groups after PPI Treatment

	Non-PPI treatment group (n=230)	PPI treatment group (n=27)	p-value
Post-FVC (%)	90.3±17.8	84.5±20.7	0.239
Post-FEV1 (%)	90.3±22.9	87.9±28.0	0.555
Post-FEV1/FVC (%)	72.1±14.8	74.5±15.8	0.374
FVC diff. (%)	−1.3±11.0	−2.6±13.0	0.975
FEV1 diff. (%)	−0.7±11.2	0±11.9	0.611
FEV1/FVC diff. (%)	0.9±9.7	1.7±12.3	0.757

Values are presented as mean±SD.
PPI, proton pump inhibitor; diff., difference in lung function parameters before and after PPI treatment; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.

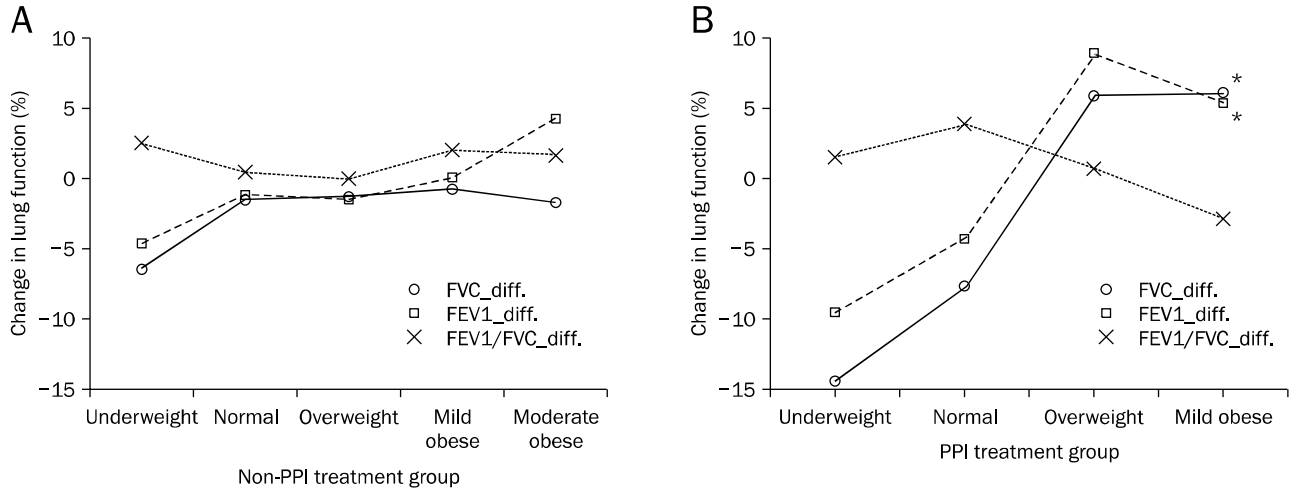

Fig. 1. Severity of obesity and lung function in patients with bronchiectasis and gastroesophageal reflux disease. (A) Differences in lung function between before and after antireflux treatment in the proton pump inhibitor (PPI) treatment group. (B) Differences in lung function between before and after antireflux treatment in the non-PPI treatment group. *p<0.05.
FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; diff., difference in lung function parameters before and after anti-reflux treatment.
Underweight: BMI <18.5; normal: BMI ≥18.5, <23; overweight: ≥23, <25; mildly obese: ≥25, <30; moderately obese: ≥30, <35; severely obese: BMI ≥35.

groups in terms of post-treatment FEV1/FVC (p=0.374) or changes between pre-treatment and post-treatment FEV1/FVC (p=0.757; Table 2).

We assessed the associations of factors such as age, BMI, and comorbid conditions, with the patients' pulmonary function parameters. In the PPI treatment group, FVC (r_s=0.564, p=0.002) and FEV1 (r_s=0.513, p=0.006) improved significantly from the pre-treatment values in patients with increased BMI. Improvements of changes in FVC (r_s=0.568, p=0.002) and FEV1 (r_s=0.501, p=0.008) in the PPI treatment group were significantly related to severity of obesity. This was not observed in the non-PPI treatment group. However, it was also noted that changes in FVC (r_s=−0.427, p=0.026) were significantly worse in patients in the PPI treatment group with a history of pulmonary tuberculosis (Table 3, Fig. 1).

Changes in FVC (R^2=0.348, p=0.001) and FEV1 (R^2=0.262, p=0.006) were significantly associated with increased BMI. Changes in FVC (R^2=0.282, p=0.004) and FEV1 (R^2=0.208, p=0.017) also significantly associated with the severity of obesity (Table 4).

DISCUSSION

The role of GERD in the pathogenesis of respiratory symptoms and diseases has been discussed. There is a high prevalence of reflux in asthma and chronic cough, which may be induced through different mechanisms, including micro aspiration and reflex bronchoconstriction.[7,10,11] Refluxed gastric material reaches the proximal esophagus and moves into

Table 3. Spearman Correlation between Lung Function Tests for the Two Groups

	Non-PPI treatment group (n=230)			PPI treatment group (n=27)		
	FVC diff.	FEV1 diff.	FEV1/FVC diff.	FVC diff.	FEV1 diff.	FEV1/FVC diff.
Age	0.100	0.002*	0.981	0.355	0.355	0.768
	(0.109)	(0.207)	(−0.002)	(0.185)	(0.185)	(−0.060)
BMI	0.525	0.822	0.388	0.002*	0.006*	0.209
	(0.045)	(0.016)	(−0.061)	(0.564)	(0.513)	(−0.250)
Severity of obesity	0.897	0.740	0.790	0.002*	0.008*	0.435
	(−0.009)	(−0.023)	(−0.019)	(0.568)	(0.501)	(−0.157)
Current drinker	0.626	0.495	0.352	0.343	0.862	0.075
	(−0.042)	(0.059)	(0.081)	(−0.194)	(0.036)	(0.355)
Current smoker	0.406	0.558	0.164	0.196	0.917	0.024*
	(−0.072)	(0.051)	(0.121)	(−0.257)	(−0.021)	(0.434)
Diabetes mellitus	0.611	0.341	0.654	0.698	0.569	0.227
	(0.034)	(0.063)	(0.030)	(−0.078)	(0.115)	(0.240)
Hypertension	0.355	0.510	0.510	0.670	0.887	0.869
	(0.061)	(0.044)	(0.044)	(−0.086)	(0.029)	(0.033)
Pulmonary TB	0.400	0.635	0.635	0.026*	0.058	0.444
	(0.056)	(−0.031)	(−0.031)	(−0.427)	(−0.369)	(0.154)
CKD	0.641	0.305	0.865	0.752	0.557	0.822
	(0.031)	(0.068)	(0.011)	(−0.064)	(−0.118)	(−0.046)

Values are presented as p-value (rho).
PPI, proton pump inhibitor; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; diff., difference in lung function parameters before and after PPI treatment; TB, tuberculosis; CKD, chronic kidney disease.
*$p < 0.05$.

Table 4. Linear Regression Analysis of Lung Function with BMI and with Severity of Obesity in the PPI Treatment Group

	FVC diff.			FEV1 diff.		
	B	R^2	p-value	B	R^2	p-value
BMI	2.522	0.348	0.001	2.004	0.262	0.006
Severity of obesity	7.729	0.282	0.004	6.075	0.208	0.017

PPI, proton pump inhibitor; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; diff., difference in lung function parameters before and after PPI treatment.

the hypopharynx with the potential to enter the trachea.[12] GERD may also cause bronchiectasis in the adult population.[4] In a study of four patients with severe bronchiectasis who completed dual-channel esophageal pH monitoring, the prevalence of distal reflux in 75% and proximal reflux in 50% suggests that patients with more severe bronchiectasis may be more likely to have GERD.[13]

Helicobacter pylori has been identified in tracheobronchial secretions, and a high seroprevalence is noted in patients with bronchiectasis.[14] *H. pylori* produces a wide range of toxins including urease, phospholipidases, alcohol dehydrogenase, hemolysin, platelet-activating factor, and mucolytic factor.[15] These toxins are harmful to the stomach and duodenum, and act by generation of an intense immune response, resulting in submucosal lymphocyte and neutrophil infiltration. They can likewise interact with other tissues.[16] Aspiration or inhalation of *H. pylori* exotoxins may contribute to chronic airway inflammation in patients with idiopathic bronchiectasis.[14] Longstanding respiratory disease related to GERD has negative effects on lung functions.[9,12]

Active antireflux interventions, such as laparoscopic fundoplication, Stretta radiofrequency, and crurorraphy, can prevent aggravation of chronic lung disease with bronchiectasis.[8,9] Several studies have noted improvements in lung function after these surgical procedures.[8,9]

Pasteur et al.[17] found GERD to be a cause in 4% of patients, based on gastrointestinal symptoms and symptomatic improvement after antireflux therapy. In the present study, we assessed the effect of PPIs among the antireflux medications on the lung function of patients with bronchiectasis. We compared the differences in lung function parameters before and after PPIs between the treatment and the control groups. There were no statistically significant differences in lung function tests between groups. However, we observed statistically significant improvements between the pre-PPI and the post-PPI FVC and between the pre-PPI and the post-PPI FEV1 based on BMI. Thus, although PPIs did not significantly change pulmonary function parameters in patients with bronchiectasis and GERD, there were statistically significant improvements in certain subgroups, specifically obese individuals. This is believed to result from obesity causing increased esophageal acid exposure time compared to the non-obese population.[18]

As antireflux surgery is an anatomical repair, it prevents the reflux of both acid and non-acid materials. PPIs, however, only prevent the reflux of acids. This may be why the lung parameters did not differ by PPI treatment.

This study has some limitations. First, this study is retrospective. The retrospective study design was non-randomized study. Furthermore, the PPI treatment duration varied from 22 days to 1,784 days in the PPI treatment group.

In conclusion, we were unable to reject the null hypothesis that PPIs have no effect on the pulmonary function in patients with bronchiectasis and GERD. We attribute this to the fact that unlike antireflux surgery, PPIs are unable to prevent non-acid materials from refluxing. However, PPIs do produce improvements in lung function in patients with bronchiectasis and higher BMI in accordance with the severity of obesity. This could be because obesity causes increased esophageal acid exposure time. Future studies are required with larger sample sizes and a randomized prospective design to determine the effects of antireflux medical therapy in obese patients with bronchiectasis and GERD.

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