Nasal Mucociliary Clearance in Subjects With COPD After Smoking Cessation

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BACKGROUND: Exposure to cigarette smoke causes significant impairment in mucociliary clearance (MCC), which predisposes patients to secretion retention and recurrent airway infections that play a role in exacerbations of COPD. To determine whether smoking cessation may influence MCC and frequency of exacerbations, the following groups were evaluated: ex-smokers with COPD, smokers with COPD, current smokers with normal lung function, and nonsmokers with normal lung function. METHODS: Ninety-three subjects were divided into 4 groups: ex-smokers with COPD (n = 23, 62.4 ± 8.0 y, 13 males), smokers with COPD (n = 17, 58.2 ± 8.0 y, 6 males), current smokers (n = 27, 61.5 ± 6.4 y, 17 males), and nonsmokers (n = 26, 60.8 ± 11.3 y, 7 males). MCC was evaluated using the saccharin transit time (STT) test, and the frequency of exacerbations in the last year was assessed by questionnaire. The Kruskal-Wallis test followed by Dunn’s test were used to compare STT among groups, and the Goodman test was used to compare the frequency of exacerbations. RESULTS: STT of smokers with COPD (16.5 [11–28] min; median [interquartile range 25–75%]) and current smokers (15.9 [10–27] min) was longer compared with ex-smokers with COPD (9.7 [6–12] min) and nonsmokers (8 [6–16] min) (P < .001). There was no difference in STT values between smokers with COPD and current smokers, and these values in ex-smokers with COPD were similar to the control group (P > .05). The frequency of exacerbations was lower in ex-smokers with COPD compared with smokers with COPD. CONCLUSIONS: One year after smoking cessation, subjects with COPD had improved mucociliary clearance. Key words: chronic obstructive pulmonary disease; smoking; mucociliary clearance; disease exacerbation; smoking cessation; respiratory infections.

Introduction

Smoking cessation is the most effective intervention in stopping the progression of COPD, as well as increasing survival and reducing morbidity.1 Constant exposure to cigarette smoke and other noxious particles causes a chronic inflammatory response in the lungs, characterized by parenchymal tissue destruction and disruption of normal repair and defense mechanisms, leading to an increased risk of exacerbations.2,3

Inhaled cigarette smoke induces a significant decrease in mucociliary clearance (MCC), which is the main de-
Mucociliary Clearance in COPD After Smoking Cessation

Methods

Study Design and Subjects

This cross-sectional observational study was undertaken with 93 subjects, age 45–80 y. Subjects were divided into 4 groups: ex-smokers with COPD, who had ceased smoking for at least 1 y; smokers with COPD; current smokers with normal lung function; and age-matched nonsmokers with normal lung function. The sample was composed of subjects and staff from the Studies and Assistance Center in Physiotherapy and Rehabilitation and participants of the Anti-tobacco Orientation and Awareness program, both at the UNESP Universidade Estadual Paulista, São Paulo, Brazil.

Inclusion criteria for current smokers and nonsmokers included a normal lung function confirmed by spirometry. Individuals with COPD established by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and clinically stable (no exacerbations or infections in the last 3 mo) were included. Individuals with cystic fibrosis, bronchiectasis, immotile ciliary syndrome, a history of nasal or trauma surgery, or inflammation process in the upper airway (determined during the initial assessment) were excluded from the study.

All participants were informed about the objectives and procedures of the study, and they signed the consent form, according to the Declaration of Helsinki of the World Medical Association. The study was approved by the institution’s ethics and research committee (study 122/2010).

Lung Function and Exhaled CO Measurement

Spirometry was performed according to the guidelines of the American Thoracic Society/European Respiratory Society using a portable spirometer (Spirobank-MIR 3.6, Medical International Research, Rome, Italy). Reference values specific for the Brazilian population were used.

Exhaled CO levels were used as a biochemical marker for abstinence from smoking, and were correlated with self-reported smoking status. Exhaled CO was measured using a CO analyzer (Micro CO Meter, Cardinal Health, Basingstoke, United Kingdom). Subjects were instructed to perform a deep inspiration to total lung capacity, hold their breath for 20 s, and then exhale slowly through a mouthpiece. Two successive recordings were performed, and the highest value was used. The exhaled CO levels provide an acceptable degree of discrimination between smokers and nonsmokers and are considerably cheaper and simpler to obtain than the collection and testing of body fluids.
Saccharin Transit Time Test

The saccharin transit time (STT) test is a technique for measuring nasal MCC and has been widely reported in previous studies\(^{26}\) as being a simple, noninvasive, valid, and reproducible method to determine the MCC.\(^{27-32}\) Furthermore, the nasal cavity has respiratory epithelium similar to the rest of the respiratory tract\(^{33}\) and the literature has established that nasal mucociliary transport has a good correlation with tracheobronchial transport,\(^{30,34}\) which obviates the need for more invasive procedures.\(^{35}\)

Subjects were seated and positioned with 10 degrees of neck extension. Granulated sodium saccharin (250 \(\mu\)g) was placed, under visual control, 2 cm inside the right nostril. The time from particle placement until the first perception of a sweet taste in the mouth was recorded in minutes as measured by a digital chronometer (Kenko-1046, Kenko International, Hong Kong, China). Individuals were instructed to maintain their initial position and were not allowed to breathe deeply, talk, cough, sneeze or sniff. If the sensation did not occur within 60 min, the test was stopped and the subject’s ability to perceive the taste of saccharin was verified by placing it on the tongue. If the subject was able to taste the saccharin directly, the test procedures were repeated on another occasion.

Each subject was instructed to not smoke; to not use pharmacologic agents such as anesthetics, analgesics, anti-epileptics, tranquilizers, or antidepressants; and to avoid the use of alcohol and caffeine-based substances for at least 12 h before the test.

Exacerbation History

Exacerbations were defined as more than one of a complex of respiratory symptoms (increase or new onset): cough, sputum, sputum purulence, wheezing, or dyspnea lasting 3 d or more and requiring treatment with an antibiotic or a systemic corticosteroid.\(^{36}\) A history of exacerbations was obtained from the subject’s self-report of his/her condition in the last year. The possible answers were: “not at all, once, 2–4 times, and 5 or more.” In the proposed classification scheme, any exacerbation is worse than no exacerbations and more exacerbations are worse than fewer exacerbations.\(^{37}\)

Statistical Analyses

Statistical analysis was performed using GraphPad Prism 3.0 (GraphPad, San Diego, California). The normality of data distribution was verified with the Shapiro-Wilk test. Comparisons of sample characteristics, spirometry data, smoking history, exhaled CO, and STT test values among the 4 groups were performed using one-way analysis of variance followed by the Tukey honest significant difference test (FVC\(\%\) and FEV\(_1\)\(\%\)) or Kruskal-Wallis test followed by Dunn test (age, BMI, FEV\(_1\)/FVC, pack-years, exhaled CO, and STT) depending on the normality of data. The Goodman test was used to compare the frequency of exacerbations among subjects with COPD, and correlation analyses were performed using Spearman’s test. Differences were considered significant at \(P < .05\).

Results

Sample Characteristics

Ninety-three subjects were included, consisting of ex-smokers with COPD (moderate \(n = 10\) and severe \(n = 13\)), smokers with COPD (moderate \(n = 10\) and severe \(n = 7\)), current smokers with normal lung function (\(n = 27\)), and nonsmokers with normal lung function (\(n = 26\)). There was no difference in STT between subjects with moderate and severe COPD, so these subjects were allocated to the same group: ex-smokers with COPD (moderate COPD STT = 10.6 ± 3.6, and severe COPD STT = 10.2 ± 4.2, \(P = .80\)) and smokers with COPD (moderate COPD STT = 22.4 ± 11.3, and severe COPD STT = 18.4 ± 8.8, \(P = .74\)). Sample characteristics, spirometric values, smoking history, and exhaled CO data for all groups are presented in Table 1. All groups were matched regarding age. Spirometric values were lower in both groups with COPD compared with current smokers and nonsmokers; in this last group, the FEV\(_1\) (% predicted) was significantly higher than in smokers. Exhaled CO levels were higher in smokers with COPD and current smokers compared with the other groups.

Saccharin Transit Time Data

The STT of smokers with COPD (16.5 [11–28] min, median [interquartile range 25–75%]), and current smokers (15.9 [10–27] min) was longer compared with ex-smokers with COPD (10.2 [6–12] min) and nonsmokers (8 [6–16] min) \((P < .001)\). There was no difference in STT values between smokers with COPD and current smokers, and these values in ex-smokers with COPD were similar to those for the control group (Fig. 1).

Exacerbation History

Table 2 demonstrates the frequency of exacerbations in subjects with COPD, in the last year. The proportion of subjects who had 5 or more episodes of COPD exacerbations was higher in smokers (24%) compared with ex-smokers with COPD (7%) \((P < .05)\).
Correlation Analysis Between STT and Frequency of Exacerbation

There was a weak positive correlation between STT and frequency of exacerbations in both groups, smokers with COPD ($r = 0.23, P = .366$) and ex-smokers with COPD ($r = 0.41, P = .135$), with no statistical difference. The Spearman test was used.

Discussion

This study showed better nasal MCC in ex-smokers with COPD and lower frequency of exacerbations compared with those who continued to smoke.

A better MCC in ex-smokers with COPD, assessed by STT, is strongly related to smoking cessation, just as has been observed in previous studies, in which smokers with normal lung function presented an improvement in this mechanism 15 d after quitting.14 Our results corroborate a previous study,38 in which smokers with COPD also showed worse nasal MCC than ex-smokers with COPD, but these findings presented rhinosinusitis as a tobacco-related respiratory comorbidity.

In contrast, Koblizek et al39 reported nasal MCC impairment in ex-smokers with COPD compared with healthy...
individuals who never smoked. This may due to the short period of abstinence in these subjects (from 6 months) which may have been insufficient to promote improvement in this mechanism. Thus, it would be interesting for further research to monitor a longer period after smoking cessation to ascertain the actual moment of MCC changes, in addition to investigating MCC reversibility in COPD.

In our study, the severity of COPD did not influence the MCC, unlike a previous study, which found a higher degree of airway inflammation in smokers with COPD with more severe obstruction. Smokers with COPD and current smokers with normal lung function showed similar nasal MCC. Vachier et al. reported that both smokers with and without COPD presented an increase in infiltration of CD8 T lymphocytes, which plays a significant role in the pathogenesis of airway mucosal inflammation. These results indicate that MCC impairment is associated more with chronic exposure to cigarette smoke than to the disease itself. Yaghi et al. showed worse ciliary beat frequency in COPD compared with those without the disease; however, the groups were composed of smokers and ex-smokers. Given that MCC is strongly related to smoking, the constitution of these groups may have influenced this response, since, after smoking cessation, this mechanism may reverse and probably become faster in those who have not yet developed the disease.

MCC impairment in patients with COPD leads to secretion retention, airway obstruction, and recurrent airway infections, mainly in smokers. In addition, chronic exposure to cigarette smoke also leads to chronic inflammation and progressive emphysema, which contributes to the impaired lung and immune system homeostasis that plays a role in COPD exacerbations. It is known that exacerbations still occur in patients with COPD even after smoking cessation. In the present study, no correlations were found between STT and frequency of exacerbations in COPD groups; however, ex-smokers with COPD showed a low frequency of exacerbations compared with smokers with COPD, which supports the hypothesis that frequency of exacerbations may be influenced by the maintenance of smoking.

The exhaled CO level measurement is the accepted standard method for an immediate, noninvasive and effective detection of smoking status. This research, concurs with the observation by Chatkin et al. noting elevated exhaled CO levels in current smokers with normal lung function and smokers with COPD compared with non-smokers with normal lung function and ex-smokers with COPD. The exhaled CO levels may be useful in monitoring changes in heme oxygenase enzyme activity in vivo, which might reflect inflammation or oxidative stress level in patients with airway and systemic inflammation. The improvement in MCC with lower levels of exhaled CO observed in our study contributes to the understanding of lung responses after smoking cessation and highlights the importance of quitting smoking in subjects with chronic pulmonary disease. Our results highlight the importance of monitoring MCC changes for 1 year after smoking cessation in patients with COPD.

A limitation of the study was the small sample size despite the statistically significant differences noted in MCC among groups. Although not statistically significant, the reduction in the number of exacerbations in ex-smokers with COPD may be related to improvement of MCC in these individuals. Therefore, it is crucial to thoroughly investigate the mechanisms related to exacerbations in ex-smokers with COPD.

**Conclusions**

This study demonstrated that smoking cessation, even in people with COPD, leads to an improvement in mucociliary clearance within 1 year of smoking cessation.

**REFERENCES**


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