EFFECT OF *IN VIVO* OXYGEN THERAPY ON MUCOCILIARY CLEARANCE

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Abstract

Background: Nasal mucociliary clearance is an important defense mechanism of the respiratory system. This study aimed to investigate *in vivo* the short-term effects of non-humidified oxygen therapy on nasal mucociliary clearance time in healthy individuals.

Method: Twenty-one healthy non-smokers (14 male and seven female) with no history of nasopharyngeal symptoms or disease were enrolled in this study (Table 1). All individuals received three hours of standard nasal cannula oxygen therapy without humidification, at 2 L/min and 4 L/min. Nasal mucociliary clearance using *in vivo* saccharin transit time (STT) was measured as described by Rutland and Cole. The time in minutes at which the subject reported a sweet taste after saccharin application on the inferior turbinate of the nasal cavity under direct visualization was recorded using a stopwatch. Nasopharyngeal symptoms were also assessed. A one-way ANOVA was run followed by *post-hoc* Tukey analysis. A P value of 0.005 was considered significant.

Results: The nasal mucociliary clearance was significantly decreased after three hours of oxygen therapy at 4 L/min compared to the baseline (15.46 ± 2.89 vs. 18.86 ± 4.03 minutes; ANOVA P = 0.003), as shown in Figure 1. None of the individuals had any nasopharyngeal symptoms before the application of oxygen therapy.

Seven out of the 21 individuals (33%) experienced at least one nasal symptom after 2 L/min of oxygen via nasal cannula, and 14 out of 19 (74%) individuals experienced at least one nasal symptom after 4 L/min of oxygen via nasal cannula. There was a general increase in the number of all symptoms during the oxygen therapy treatment, and the most common nasal symptom at both flow/liters was dryness of the nose. The higher the oxygen flow, the more symptoms were noticed.

Conclusion: Our results show that three hours oxygen therapy slows the nasal mucociliary clearance time and is associated with several upper airways symptoms.

Keywords: oxygen therapy; mucociliary clearance; nasal cannula; nasopharyngeal symptoms; flow/liters; healthy individuals.

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Introduction

The nose and the upper respiratory tract are the first barriers for inhaled dust particles, microbes and other substances. Nasal mucociliary clearance (MCC) is a vital defense mechanism of the upper respiratory tract,[1] and any harmed mucociliary clearance may cause mucus retention, increased chance of nasopharyngeal or respiratory symptoms, and airway inflammation. In the respiratory tract, the combination of the ciliary and mucus functions plays a significant role in the mechanism of efficient mucociliary clearance.[2] MCC refers to the respiratory system where different types of pathogens, allergens, debris and toxins are captured and further moved out with the help of ciliary mechanism.[3] The cilia continuously beat in synchrony to perform efficient clearance. However, when the cilia beat becomes asynchronous, the MCC mechanism may become ineffective.[4] In primary ciliary dyskinesia, asynchronous movements were reported.[5] During the process of inspiratory breathing, air travels through the nose, pharynx, larynx and trachea. Due to the efficient ability of the nose and upper airway system to humidify and warm the inspired gas, the inspired gas is humidified and warmed up to the level of body temperature and efficiently saturated with water vapor on the way down towards the alveoli. The upper airways, and in particular the nose, are also found to work as excellent radiators: during the process of normal breathing, even with the presence of cold and dry air, they are able to maintain proper temperature in the oropharyngeal space.[6] Supplemental oxygen therapy, however, is not commonly humidified when given at lower flow rates. Bubble humidifiers are used occasionally for humidifying medical gases delivered to patients with spontaneous breathing, but the absolute humidity of the emergent gas remains low.[7] However, non-humidified air may cause ciliary dysfunction and changes in mucus properties that lead to MCC impairment.[8]

We conducted this study to understand the behavior of nasal mucociliary clearance time with *in vivo* use of oxygen therapy in healthy individuals.

Method

Upon recruitment, the purpose of the study was explained, and written informed consent was obtained from the participants. The Institutional Review Board of the Prince Sultan Military College of Health Sciences approved the study (approval number: IRB-2017-18-09).

Study population:

A total of 21 healthy non-smokers (14 male and seven female participants) with no history of nasopharyngeal symptoms or disease were enrolled in this study.

The exclusion criteria were ongoing respiratory exacerbation, uncontrolled asthma, rhinitis, nasal surgeries, nasal and chest allergies, smokers, and individuals taking nasal medications. Also, participants with obstructed nostrils and rhinorrhea were excluded.

Study procedure

All study participants received three hours of standard nasal cannula oxygen therapy without humidification, at 2 L/min (n = 21) and 4 L/min (n = 19). Nasal mucociliary clearance (NMC) with the help of *in vivo* saccharin transit time (STT) was measured as described by Rutland and Cole.[9]

This is the standard technique for measurement of NMC. Before the initiation of the procedure, all individuals were especially instructed to spend at least 60 minutes in a normal environment, which was devoid of any dust particles and breeze with relative humidity.

Protocol

A saccharin particle of 1 mm in diameter was placed in the inferior nasal turbinate at the medial surface, at least 1 mm behind the anterior end of the turbinate. The individual was positioned and adjusted in such a manner that the head was flexed at 10 degrees. All individuals were instructed to not sneeze, sniff, cough, drink or eat during the test period. The individuals were instructed to record the taste of the saccharin as soon as it was noted. The time between placing the saccharin particle in the nose and the initial perception of the sweet taste was recorded down in minutes. If taste was not perceived after 60 minutes, the test was terminated. The time in minutes at which the subject reported a sweet taste after the saccharin application on the inferior turbinate of the nasal cavity under direct visualization was recorded using a stopwatch. Nasopharyngeal symptoms were also assessed during the oxygen delivery.

Statistical analysis

A power analysis considering a difference of 2 min in mucociliary clearance to be clinically significant and a standard deviation of 3 min in the average mucociliary clearance (pilot data) as well as a Type I error of 5% and Type II error of 20% (i.e., power of 80%), at least 18 subjects are needed for the study.

The data were analyzed using GraphPad Prism 8 software (GraphPad Software Inc., La Jolla, CA, USA). The Kolmogorov-Smirnov test of normality was applied. A one-way ANOVA was run to examine the dose-response differences between oxygen therapy treatments, followed by *post-hoc* Tukey's multiple comparison tests. Frequency was used to compare nasopharyngeal symptoms at baseline and after 2 and 4 L/min of oxygen therapy. A P value <0.05 was considered statistically significant.

Results

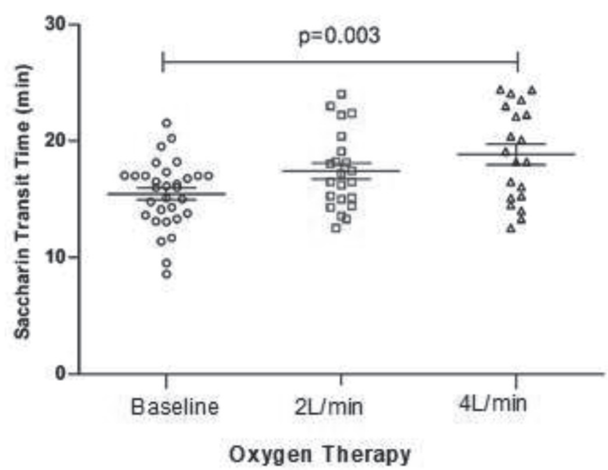
The characteristics of the healthy volunteers enrolled in the study are reported in Table 1.

A total of 21 healthy volunteers participated in the experiment (21 participants at 2 L/min and 19 participants at 4 L/min as 2 subjects dropped from the 4 L/min group. The nasal mucociliary clearance rate was found to be considerably decreased after the period of three hours of oxygen therapy at 4 L/min, when compared to the baseline (15.46 ± 2.89 vs. 18.86 ± 4.03 minutes; ANOVA P = 0.003), as shown in Figure 1.

Table 1
Baseline information of subjects enrolled in the study

Details of subjects studied	2 L/m (n =21)		4 L/m (n =19)	
	Mean	SD	Mean	SD
Age, years	24.5	3.9	24.6	3.8
Weight, kg	63.2	8.8	63.8	9
Height, cm	166	10.8	167	11.2
Smoking history	Never-smoking		Never-smoking	
Nasal symptoms	None		None	
Medications	None		None	

Fig. 1
Oxygen therapy causes a flow-dependent alteration in nasal mucociliary clearance. Lines represent mean and standard error. Significant differences illustrated using ANOVA with post-hoc analysis



The nasopharyngeal symptoms before and after oxygen therapy are presented in Table 2. None of the individuals had airway symptoms before the oxygen therapy. None of the individuals experienced sneezing at 2 L/min. However, 2 out of 19 (10.5%) individuals were found to be affected at 4 L/min. Itchy nose was noted in 4 out of 21 (19%) individuals at 2 L/min and in 9 out of 19 (47.4%) individuals at 4 L/min. Seven of the individuals (33%) experienced at least one nasal symptom (nasal dryness) after receiving 2 L/min oxygen via nasal cannula, and 14 out of 19 (74%) individuals experienced nasal dryness after the 4 L/min therapy. Dry mouth and blocked ears were reported at 4 L/min in 6 out of 19 (31.6%) and 1 out of 19 (5%) participants respectively, while 1 (5%) individual reported dry mouth and throat at 2 L/min. There was a general increase in the number of all the nasopharyngeal symptoms during oxygen therapy and the most common nasal symptoms at both flow/liters was dryness of the nose, as shown in Table 2.

Discussion

This study indicates that dose-response oxygen therapy via nasal cannula slows the mucociliary clearance and results in the development of nasopharyngeal symptoms. The development of these symptoms is related to the increase in the oxygen therapy application.

Breathing dry air is also known to reduce nasal mucociliary clearance.[10] This study reported that dry oxygen gas elicited complaints from the patients, including itchy nose, dryness of the nose, mouth and throat, as well as other nasal symptoms. Unconditioned introduction of medical gases increases airway resistance in order to protect the respiratory system from cold or dry inspired air by reducing the air flow in the upper and tracheobronchial airways. Fontnari and his team reported similar changes in airway resistance induced by inhalation of dry cold air or moist air in normal subjects.[11] Similar findings were also noted by Salah and his team, who studied nasal mucociliary transport in healthy individuals and found that mucociliary transport is slower when breathing dry air.[10]

Breathing dry gas may lead to excessive loss of water by the nasal mucosa,[12] which may further lead to the reduction of the nasal mucociliary clearance rate through changes in the rheological properties of the mucus in the nasal cavity and/or reduction of ciliary pulses.[10] Commonly the conventional oxygen devices are found to be associated with mask discomfort, oral dryness, nasal dryness, nasal and eye trauma, eye irritation and gastric distention.[13] Our study reported similar symptoms but further described the consequences of such symptoms on mucociliary clearance and possible pro-inflammatory activity. Future studies will need to investigate the pro-inflammatory response to different gas flows at higher rates.

A study conducted by Rubin et al.[14] showed an increase in mucociliary clearance observed in asymptomatic smokers mediated through the changes in the physical properties of the mucus. This effect was likely in recognition of loss from acute epithelial damage. Togias et al.[15] demonstrated that inhalation of cold dry air acts as a physical stimulation to the airways, causing a local release of pro-inflammatory mediators probably due to osmolarity changes of the extracellular fluid. Multiple inflammatory mediators were found to be responsible for the increase in the ciliary beating frequency.[16]

Studies of the percentage of tracheobronchial deposition as a function of radio-aerosol inhalation (no medication) showed a reduced deposition from the last inhalation increased.[17] These findings are similar to our findings, where it suggested that as the airway becomes dry, the subjects find it increasingly more

Table 2

Total nasopharyngeal symptoms with oxygen therapy application to health-subjects in vivo

Nasal Cannula (oxygen therapy)	**Nasopharyngeal symptoms**				
	Sneezing	**Itchy nose**	**Dryness in nose**	**Dry mouth/ throat**	**Blocked ears**
Baseline (no treatment)	0	0	0	0	0
2 L/m (n = 21)	0 (0%)	4 (19%)	7 (33%)	1 (5%)	0 (0%)
4 L/m (n = 19)	2 (10.5%)	9 (47.4%)	14 (74%)	6 (31.6%)	1 (5%)

∗ Data are expressed as number (%) of subjects.

uncomfortable to clear secretions of the airway. It is commonly presumed that contact with an inspired humidified gas warmed to body temperature will cause less mucociliary desiccation and thus maintain mucociliary clearance when compared to other methods of oxygen delivery.

Our study demonstrated that the dose-response of oxygen application was associated with the functional consequences of reduced nasal clearance and with more significant nasopharyngeal symptoms when compared to lower air gas. Studies have shown that nasal CPAP resulted in reduced mucociliary clearance and induced airway inflammation.[18] These studies showed that more than 50% of the individuals experienced at least one nasopharyngeal symptom after the initial CPAP application. In our study, there is a similarity in the prevalence of nasopharyngeal symptoms which was increased with a higher dose-response of oxygen therapy. Our results add to the literature by revealing a direct effect of the airflow, rather than a consequence of mechanical or pressure stretch. It is unlikely that the nasal epithelium is able to contain stretch mechanisms, given the confines of the nasal cavity within the bony structures of the skull.

This study has limitations. These data consist of a small sample size and represent a preliminary data set for a large study to assess the mucociliary clearance and inflammation associated with different oxygen modalities. However, this study presents only one type of oxygen modality. The study did not compare humidification and other oxygen modalities to the current study design.

Conclusions

The results demonstrated that three hours of oxygen therapy slows the nasal mucociliary clearance time and is associated with a number of upper airways symptoms. These preliminary results also suggest that pre-hydration is beneficial for maintaining better nasal mucociliary clearance during application of oxygen therapy even with lower liter of oxygen flow. Strategies to counter the initial side effects of any medical dry gas treatments and to improve treatment retention may target the epithelial lining of the respiratory airway system.

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