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RESEARCH ARTICLE

NONINVASIVE METHODS FOR EARLY DETECTION OF AIRWAY INFLAMMATION RELATED TO CLEANING WORKERS OCCUPATIONAL ENVIRONMENT

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ABSTRACT

Background: There is consistent evidence that cleaning workers are at high risk of developing asthma. Predisposing factors are not fully understood and it is important to produce evidence that this risk is work-related. **Objective:** To assess whether the work environment induces pulmonary inflammation in asymptomatic cleaning workers and to determine the efficacy of noninvasive methods to detect early pulmonary inflammation. **Methods:** Sixty-seven workers were evaluated by comparing sputum cytology, fractional exhaled nitric oxide (FeNO) values and spirometry tests, performed during the work period and after vacations. **Results:** We observed a significant increase in FEV1 values after the vacation period (pre 2.90L ± 0.57L and post 2.94L ± 0.61L, $p < 0.05$), even though those values were within normal limits, in both periods. There was a reduction in the values of the FeNO measurements after vacations (pre 16.3 ± 9.7 and post 13.8 ± 7.8, $p < 0.05$) and a reduction of inflammatory cells count in the induced sputum (Eosinophils: pre 0.019 ± 0.05 and post 0.003 ± 0.01, $p < 0.05$ Lymphocytes: pre 0.16 ± 0.35 and post 0.01 ± 0.09, $p < 0.05$ Macrophages: pre 0.421 ± 0, 47 and post 0.235 ± 0.30, $p < 0.05$. **Conclusion:** We observed that the occupational environment to which the studied population was exposed caused inflammation in the airways without functional abnormalities. Noninvasive methods such as counting of cells after induced sputum and FeNO measures showed to be promising tools for the detection of pulmonary inflammation, although they still require standardization.

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INTRODUCTION

There is consistent evidence from epidemiological studies conducted at different sites that professional cleaners are at a high risk of developing asthma (Lipinska-Ojrzanowska *et al.*, 2014). They comprise a large workforce in many countries. In Brazil, it is estimated that 11 thousand companies provide cleaning services for homes, commercial buildings and industries, employing around a million cleaning professionals, which represents 1.5 million economically active population of the formal working sector (Zock, 2005). In the Metropolitan Region of São Paulo City, the prevalence of asthma among cleaners ranged from 3% to 40% according to the time accumulated in non-domestic professional cleaning work, with a risk ≥ 71% for those that have been working for 6.5 years or more when comparing to those that have been working for less than one year (Maçãira, 2007). Several epidemiological studies have shown that some workers are continually exposed to low levels of irritants in the workplace. However, few studies have shown some correlation between these low levels of exposure and development of asthma. The most persuasive evidence for irritant-induced asthma related to chronic exposure to moderate levels of irritants is provided by epidemiological studies with workers exposed to cleaning agents (Siracusa *et al.*, 2013). In the city of São Paulo, cleaning activity was the main occupation in terms of numbers of cases of occupational asthma among women, and cleaning products were the most cited agents in a study that evaluated occupational asthma in the period between 1995 and 2000 (Mendonca *et al.*, 2003). Currently, the diagnosis of work-related asthma is based mainly on the clinical history, the demonstration of functional changes through spirometry tests and non-specific and specific Broncho provocation tests, in

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addition to peak flow measurements in and off the workplace (Cartier, 2003). The monitoring and assessment of airway inflammation are important investigational tools of occupational asthma. Until recently, airway inflammation has been studied through invasive methods such as bronchial lavage and biopsy. The invasive nature of these investigations has limited their use in clinical practice. The use of noninvasive methods, such as the study of induced sputum and the determination of FeNO (fractional exhaled of Nitric Oxide), has been used for the study of inflammatory changes in asthma. Initially used in research, its clinical applications have been increasingly studied (Lemière, 2002). Currently, these methods have been used in research as markers of pulmonary inflammation also in occupational asthma. One of its potential uses is the possibility of early diagnosis of occupational asthma, considering that the inflammatory changes seem to occur before clinical symptoms and functional pulmonary alterations (Lemière *et al*., 2000). Thus, we hypothesized that frequent exposure, even at low doses of irritants, would represent a continuous aggression to the airway mucosa, causing an "overload" of the protective mechanisms, breaking the homeostasis of the airways that could lead to the development of asthma. This study aimed to investigate the functional and inflammatory response of the airways to exposures to inhaled substances present in the work environment, comparing the assessments before and after exposure.

MATERIALS AND METHODS

Study Design: This is a cross-sectional study considering two moments: before the worker leaves on vacation, and after a period of 30 days away from the workplace. Each worker was contacted at the workplace, two weeks prior to his/her vacation, when questionnaires, aeroallergens skin prick tests, spirometry tests and noninvasive measures were used to evaluate lung inflammation. During the holiday period the worker was instructed to record daily peak expiratory flow measures as well as to avoid exposure to household cleaners or other exposures to irritating substances and dust. The worker was re-evaluated, one day before returning to work, following the same sequence of tests.

Study Population: Two hundred and fourteen cleaning workers from a company that provides the outsourced service to a private University which has 6 units (campuses) located in the city of São Paulo, were invited to participate in the study. The products used for cleaning are strictly the same. Individuals with respiratory tract infections and asthmatic exacerbations at the time of the interview, or asthmatics receiving inhaled corticosteroids in the last 8 weeks were not eligible to take part of this study.

Questionnaires: Information on respiratory symptoms was collected using a translation of the Medical Research Council (MRC) questionnaire (Medical Research Council. Questionnaire on respiratory symptoms, 1976) and International Study of Asthma and Allergies in Childhood (ISAAC) asthma and rhinitis modules. The asthma module had previously been validated in Portuguese (Maçãira, 2005). Additionally, information about symptoms onset and cleaning-related airway symptoms were obtained. Information on the workers' employment histories and the characteristics of their current non-domestic cleaning work was obtained by means of a modified job-specific questionnaire that had been used within the European Community Respiratory Health Survey (ECRHS) (Ribeiro, 2007).

Skin Prick Tests

Skin prick tests were performed using a panel of ten allergens: *Dermatophagoides farinae* (100 BU/ml), *Dermatophagoi despteronyssinus* (100 BU/ml), *Blomiatropicalis* (not standardized), *Periplanetaamericana* (1%), *Blatellagermanica* (1%), cat epithelium (100 BU/ml), dog epithelium (100 BU/ml), pollen (100 BU/ml) and *Aspergillus fumigatus* (5%), Latex (Prickit – International Pharmaceutical Immunology do Brasil S. A. – IPI-ASAC). A positive response was defined as a mean wheal diameter 3 mm larger than negative control, read after 20 min (Bernstein, 1995).

Assessment of Pulmonary Inflammation - Fractional exhaled of Nitric Oxide (FeNO): The FeNO measurements were obtained by electrochemical reaction on a sensor of direct reading in the NIOX-MINO portable device and performed according to the recommendations of the ATS[13].

Assessment of Pulmonary Inflammation - Induced sputum: The subjects inhaled hypertonic solution for sputum sample collection according to the recommendations of the Working Groups concluded at the meeting of American Thoracic Society[14]. The vial containing the sputum was kept in a box with ice, and the material was processed up to 2 hours after sputum collection and cytology was performed according to a previously described technique[15].It was the last test to be performed, so as not to interfere in the result of spirometry.

Spirometry: For Pulmonary function tests it was used an electronic pneumotachograph (Kokopneumotachspirometer, PDS Medical Instruments, Louisville, USA), according to the recommendations of the American Thoracic Society (ATS) and the Brazilian Society of Pulmonology and Tisiology.

Ethical aspects: This study was approved by the Ethics Committee for Analysis of Research Projects of the institution where it was carried out. All participants signed an informed consent form before starting the study. At the end of the study, the final results and conclusions were shared with the Participating Company's Department of Occupational Medicine, obeying the secrecy rules of clinical research in Brazil.

RESULTS

Of the 214 workers who were invited to participate in the study, from June 1012 to June 2014, sixty-seven (31.3%) volunteers signed the informed consent and 62 (28.9%) volunteers completed the full evaluation, the majority being female. The age distribution of the studied population, presented an average of 40.2 years, with a standard deviation of 7.6 years (median = 40.5, minimum: 20 and maximum: 57).Table 1 summarizes the characteristics for each group of individuals. From the total sample (n = 67), 32.8% (n = 22) reported being smokers and 56.7% non-smokers. However, among non-smokers, 15.6% (n = 7) reported being former smokers. In total, 55.2% had rhinitis, 13.4% were considered as having work-related rhinitis and 19.4% as having work-aggravated rhinitis.

Table 1. Distribution of subjects according to age, gender, time of work, symptoms of asthma, atopic and smoking status

Characteristics	Casuistics (N=67) **N (%)**	Smokers (N=22) **N (%)**	Non smokers (N=45) **N (%)**	Atopics (N=38) **N (%)**	NonAtopics (N=38) **N (%)**
Age (mean ± SD)	40,2 ± 7,6	39,2 ± 8,0	40,7 ± 7,5	40,6 ±7,9	39,5 ± 7,2
Gender					
Male	11 (16,4)	06 (27,3)	05 (11,1)	04 (10,5)	07 (7,1)
Female	56 (83,6)	16 (72,7)	40 (88,9)	34 (88,1)	22 (75,9)
Time ofwork					
≤6years	37 (55,2)	12 (54,5)	25 (55,6)	19 (50)	18 (62,1)
>6years	30 (44,8)	10 (45,5)	20 (44,4)	19 (50)	11 (37,9)
Questionnaires	30 (55,2)	11 (50)	19 (42,2)	22 (57,9)	08 (27,5)
Asthma					
Work-related	06 (8,9)	03 (13,6)	03 (6,7)	03 (7,9)	03 (10,3)
Work-aggravated	04 (5,9)	0 (0)	04 (8,9)	03 (7,9)	01 (3,5)
ISAAC	15 (22,4)	05 (22,7)	10 (22,2)	10 (26,3)	05 (17,2)

Table 2. Reported symptoms and their relation to cleaning products and other agentes in the work environment

					Fatores	**de**	**Exposição**				
Reportedsymptoms	Dust	Hypochlorite	Remover	Multiusercleaner	Disinfectant	Stone cleaner	Latexgloves	Degreaser	PerfumedSpray	Detergent	Carpetcleaner
Drycough	06 (8,9)	17 (25,8)	02 (2,9)	0 (0)	01 (1,5)		0 (0)	02 (2,9)	01 (1,5)	01 (1,5)	0 (0)
Catarrhcough	01 (1,5)	05 (7,6)	01 (1,5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	01 (1,5)	0 (0)
Wheezing	02 (2,9)	04 (6,1)	02 (2,9)	0 (0)	0 (0)	0 (0)	0 (0)	01 (1,5)	1 (0)	01 (1,5)	0 (0)
Chesttightness	02 (2,9)	04 (6,2)	01 (1,5)	01 (1,5)	0 (0)	01 (1,5)	0 (0)	0 (0)	01 (1,5)	01 (1,5)	01 (1,5)
Dyspnea	05 (7,5)	09 (13,6)	0,2 (2,9)	0 (0)	01 (1,5)	01 (1,5)	0 (0)	01 (1,5)	01 (1,5)	01 (1,5)	0 (0)
Sneezing	18 (27,3)	14 (21,2)	02 (2,9)	0 (0)	0 (0)	01 (1,5)	0 (0)	0 (0)	02 (2,9)	0 (0)	0 (0)
Coryza	08 (12,1)	11 (16,7)	01 (1,5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nasal Obstruction	08 (12,1)	16 (24,2)	01 (1,5)	0 (0)	0 (0)	01 (1,5)	0 (0)	0 (0)	01 (1,5)	0 (0)	0 (0)
Nasal burning	07 (10,5)	22 (33,3)	02 (2,9)	01 (1,5)	0 (0)	02 (2,9)	0 (0)	0 (0)	0 (0)	01 (1,5)	0 (0)
Throatirritation	06 (8,9)	17 (25,8)	02 (2,9)	01 (1,5)	0 (0)	0 (0)	0 (0)	03 (4,5)	0 (0)	01 (1,5)	0 (0)
Eyeirritation	03 (4,5)	29 (43,9)	02 (2,9)	02 (2,9)	0 (0)	0 (0)	0 (0)	01 (1,5)	01 (1,5)	01 (1,5)	0 (0)
Skinirritation	0 (0)	11 (16,7)	01 (1,5)	0 (0)	0 (0)	02 (2,9)	05 (7,5)	0 (0)	0 (0)	01 (1,5)	0 (0)

Table 3. Evaluation of pulmonary function, exhaled nitric oxide andsputumcytologyofcleaningworkersbeforeandafterthevacationperiod.

			Casuistics (n = 67)			
	Predict	**Before**	**After**	**Diference**	**CI 95% (diference)**	**p**
PulmonaryFunction						
FEV1	2,8 ± 0,55	2,9 ± 0,57	2,9 ± 0,61	0,06 ± 0,21	0,0 – 0,1	0,034*
%FEV1	-	101,3 ± 21,8	101,7 ±29,2	-	-	-
EPF	6,7 ± 1,14	6,3 ±1,79	6,6 ±29,2	0,25 ± 0,90	0,0 – 0,5	*0,244 †*
FVC	3,3 ± 0,68	3,4 ± 0,67	3,5 ± 0,68	0,10 ± 0,19	0,0 – 0,1	*0,390 †*
FEV1/FVC	2,2 ± 10,6	0,85 ± 0,07	0,84 ± 0,07	-0,01 ± 0,05	-0,02 – 0,01	*0,576 †*
Nitric Oxide	-	16,3 ± 9,7	13,8 ± 7,8	2,5 ± 4,6	1,3 – 3,6	*0,030 †*
ExpiratoryFlow	-	366,1 ± 54,1	386,4 ± 62,9	24,1 ± 26,9	14,7 – 33,5	*0,134 †*
SputumCitology (x 10^6 cel/ml)						
Eosinophils	-	0,019 ± 0,05	0,003 ± 0,01	0,02 ± 0,05	0,0 – 0,03	*0,018 †*
Neutrophils	-	0,305 ± 0,50	0,117 ± 0,17	0,19 ± 0,47	0,07 – 0,31	*0,154 †*
Linfocites	-	0,168 ± 0,35	0,01 ± 0,09	0,16 ± 0,34	0,07 - 0,25	*0,000 †*
Macrofages	-	0,421 ± 0,47	0,235 ±0,30	0,19 ± 0,39	0,10 – 0,30	*0,002 †*
Gobletcells	-	0,002 ± 0,01	0,004 ± 0,02	-0,00 ± 0,02	-0,01 – 0,00	*0,353 †*
Cilliarycells	-	0,002 ± 0,01	0,002 ± 0,01	-0,00 ±0,00	-0,01 – 0,00	*0,657 †*

FEV1: Forced Expiratory volume in the first second; EPF: Expiratory Peak Flow; FVC: Forced Vital capacity; Mean ±SD; * T Student test;† Mann Whitney non parametric test.

Regarding the diagnosis of asthma based on the questionnaire responses, 14.9% (n = 10) workers were diagnosed as asthmatics. According to the report of onset of symptoms and reporting of symptoms in the work environment, 8.9% of the volunteers studied were considered as having work-related asthma and 5.9% with work-aggravated asthma. Concerning the symptoms associated to exposure in the work environment, 10.4% (n = 07) reported symptoms only in the lower airways, 32.8% in the upper airways only, and 28.4% in both. Eleven subjects reported skin irritation (16.4%) and, 11 (16.4%) denied any symptomrelated to the work environment. Seventy percent (70.2%; n = 47) reported symptoms in contact with hypochlorite and 31.3% (n = 21) reported symptoms when exposed to dust. Among the participants, the frequency of reporting of symptoms related to the use of other products used in the work was: remover (6%), multiuse cleaner (4.5%), disinfectant (1.5%), stone cleaner (6%), latex glove (6%), degreaser (6%), perfumed spray (4.5%), detergent (1.5%) and carpet cleaner (3%). Those data were summarized in Table 2, considering that each individual can present more than one symptom for each product. The effects resulting from the exposure of cleaning workers to substances from the working environment were assessed before and after the vacation period through lung function tests, measurement of the exhaled nitric oxide fraction and cytology of induced sputum.

For comparison and evaluation of improvement of the pulmonary function, the results of each individual's exams were collected in the Pre-vacation moment (exposure to the agents of the work environment) and Post-vacation (Interval without exposure to agents of the work environment). Only the FEV1 measurement obtained a symmetrical distribution and was compared by the Student's t-Test for paired samples, the other variables were analyzed by the Mann-Whitney test. Despite the values within normality, considering the predicted value, the present study observed a significant improvement in the pulmonary function of the volunteers studied when they were away from the workplace, with a significant increase in FEV1 ($p < 0.034$). The positive response to the bronchodilator in the Pre-vacation period was 4% (n = 02) and 2% (n = 01) in the post-vacation period. A reduction in FeNO values after the holiday period ($p = 0.030$) was observed. Differential cytology in induced sputum also showed significant reduction of eosinophils, lymphocytes and macrophages for the overall sample after the holiday interval (Table 3). Skin tests were positive for at least one allergen in 38 volunteers, and *Blomiatropicalis* was the most frequent sensitizing allergen, followed by *Dermatophagoi desfarinae* and *Dermatophagoi despteronyssinus*.

DISCUSSION

Assessing the airways inflammatory status of the studied population using the proposed noninvasive methods, we observed a significant reduction of eosinophils, lymphocytes and macrophages after the vacation period, as well as a reduction in the values of the FeNO measurement. Only 31.3% of the invited employees accepted to participate in this study and 28.9% completed the full evaluation. We believe that the methodology of induced sputum may have contributed to the greater number of withdrawals in the participation of this study. It is a laborious method for the researcher and uncomfortable for the research subject, according to volunteers. Some studies have confirmed the association between exposure to occupational agents and the presence of eosinophilic airway inflammation after exposure in individuals with occupational asthma. The addition of induced sputum to peak flow monitoring increases the specificity of this test when compared to specific bronchoprovocation (Lemiere *et al*., 1999). Eosinophils have been shown to increase in individuals with occupational asthma when they are in the work environment and decrease when removed from exposure, changes that are not observed in asthmatic patients without occupational asthma[16].However, the magnitude of eosinophil elevation that may be considered clinically significant is not yet clearly established. An increase in absolute eosinophil counts of 0.26×10^6/mL compared to baseline values achieved a sensitivity of 82% and specificity of 91.7% to predict a 20% drop in FEV_1 (Lemiere *et al*., 2001). It has already been shown that individuals who remain symptomatic after withdrawal from exposure have more sputum inflammation than individuals who become asymptomatic shortly after away from the workplace exposure (Maghni *et al*., 2004). On the other hand, inflammatory changes related to several occupational exposures have been demonstrated in asymptomatic individuals. Other studies have investigated changes in sputum cytology between periods of exposure and withdrawal from the working environment in healthy workers exposed to low molecular weight agents (Quirce *et al*., 2010). In our study, differential sputum cytology showed a significant reduction of eosinophils, lymphocytes and macrophages after the vacation period, which corroborates the hypothesis that the continuous exposure of asymptomatic cleaning workers to the occupational environment promotes inflammatory changes that precede clinical symptoms.

The measurement of the exhaled air condensate has been pointed out as a potential marker of lung injury caused by occupational exposure. Corradi *et al*. (2012) detected an increase in biochemical changes related to inflammation or oxidative stress in the group of asymptomatic cleaners compared to the control group[20]. Several studies have shown evidence of higher levels of exhaled nitric oxide in patients with respiratory diseases compared to the healthy population. The measurement of FeNO has been an additional tool for the diagnosis and management of asthma (Corradi *et al*., 2011). Although the role of measurement of exhaled NO levels has not yet been established, an increase in healthy individuals has been demonstrated through occupational exposure to both sensitizing agents (organic dusts) [22] and irritants (solvents) [23]. In a recent study with cleaning workers, Vizcaya D, *et al*. (2013), found an increase in exhaled NO levels among workers in the control group (without asthma), related to contact with some irritants in the workplace (Vizcaya *et al*., 2013). In the absence of consensus on the reference values to be used, Corradi M, *et al*. (2011), suggested, based on a meta-analysis study, the following reference values for occupational use: values above 25.8 ppb as a kind of borderline measure of normality, from which it would require attention. Already higher values (41.0 ppb), would be indicative of abnormalities (Corradi *et al*., 2011). The manufacturers of the Aerocrine brand NO meter (Aerocrine SV, Solna, Sweden), used in our study, propose that a value less than 25 ppb would be indicative of adequate control of eosinophilic inflammation in asthmatic patients. Other authors reported that some asthmatic patients maintain values persistently higher than 50 ppb, despite the treatment, emphasizing the importance of an individualized approach (Turner, 2008). In our study, this method proved to be useful to detect a decrease in lung inflammation after the holiday period. Interestingly, according

to the cutoff point mentioned above, the average of the FeNO values found before the holidays would be within normal limits. This can be explained by the fact that our volunteers are asymptomatic and it corroborates the hypothesis that the chronic exposure of cleaning workers to the work environment induces a pulmonary inflammation that precedes the symptoms. We did not find functional abnormalities, but we observed an increase in FEV1 after the holiday period. It is important to note that spirometry values in both pre- and post-vacation periods were normal. This was expected, since the study sample consisted of asymptomatic volunteers. Based on the answers to the questionnaires, our results reinforce previous studies in cleaning workers, in which this activity was associated with work-related asthma and other studies that related this profession to the risk of developing asthma[1]. However, our prevalence was slightly higher than that found in a previous study conducted in the city of São Paulo (11%) (Maçãira, 2007) and that found in another study that evaluated the prevalence of asthma among cleaners in 14 countries (14%) (Zock *et al*., 2002). However, the sensitivity of the use of questionnaires for the diagnosis of occupational asthma has been discussed (Malo *et al*., 1991). We have shown some suggestive evidence that the occupational environment to which non-domestic professional cleaning workers are exposed causes inflammation in the airways of asymptomatic workers. This inflammation can be measured by noninvasive methods such as cell counting after induced sputum and FeNo before changes appear in FEV1, although these methods still require standardization. It is important to produce evidence that this risk is related to work and not to social conditions or other competing factors, to know the underlying pathological abnormality, and to investigate possible agents. The accumulation of this knowledge will allow proposing measures to replace or control the use of the agents involved and prevent the occurrence of new cases unnecessarily. In addition, the use of new non-invasive techniques may facilitate the treatment, and early diagnosis of cases.

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Conflict of interest: The authors have no conflict of interest to disclosure.

Key Points

- There was a significant reduction of inflammatory cells after the vacation period, in the airways of asymptomatic cleaning workers, as well as, a reduction in FeNO values suggesting that the exposure to the occupational environment could promote inflammatory changes that precede clinical symptoms.
- No functional lung abnormalities, could be observed, since we assessed asymptomatic individuals, but there was an increase in FEV_1 values after the holiday period
- Noninvasive methods such as counting of cells after induced sputum and FeNO measures showed to be promising tools for the detection of pulmonary inflammation, although they still require standardization.

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