

ORIGINAL

Effect of exposure to an Asian dust storm on fractional exhaled nitric oxide in adult asthma patients in Western Japan

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Abstract : Background : Epidemiological investigations indicate that an Asian dust storm (ADS) can aggravate respiratory disorders. However, the effects of ADS on airway inflammation remain unclear. The aim of this study was to investigate the association of exposure to ADS with airway inflammation. **Methods :** The subjects were 33 adult patients with asthma who measured daily peak flow expiratory (PEF) from March to May 2012. Fractional exhaled nitric oxide (FeNO) was measured before and after ADS. **Results :** The FeNO values were 13.8 ± 13.7 ppb before the ADS and 20.3 ± 19.0 ppb after the ADS, with no significant difference. There was also no significant association of PEF with ADS exposure. However, the increase of FeNO after ADS exposure was proportional to the decrease of PEF ($R = -0.78$, $P < 0.0001$). **Conclusion :** These results suggest that airway inflammation aggravated by ADS exposure may induce a decrease in pulmonary function in some adult patients with asthma. *J. Med. Invest.* 62 : 233-237, August, 2015

Keywords : Asthma, airway inflammation, Asian dust storm, fractional exhaled nitric oxide, peak flow expiratory

INTRODUCTION

The large-scale and long-range transport of sand dust from the deserts of Mongolia, northern China, and Kazakhstan in East Asia is referred to as an Asian dust storm (ADS). ADS can occasionally be large enough to spread around the globe (1). In Japan, the highest frequency of ADSs occurs from March to May. Recent studies have shown an association of ADS exposure with an increased risk of exacerbation of asthma (2, 3). Our previous telephone surveys also showed that ADS can aggravate respiratory symptoms and pulmonary function in adult patients with asthma (4, 5). In animal models, ADS airborne particles can increase pulmonary inflammation and infiltration (6, 7), but it remains unclear how exposure to an ADS influences airway inflammation in humans.

Kharitonov *et al.* first reported that measurement of fractional exhaled nitric oxide (FeNO) was clinically useful for detection and management of cytokine-mediated airway inflammation as a non-invasive marker in patients with asthma (8). There is now good evidence for a strong relationship of FeNO value with airway inflammation in asthma, and FeNO measurement has become a practical tool for diagnosis and management of asthma (9).

In this study, daily peak flow expiratory (PEF) and FeNO were measured before and after ADS in adult patients with asthma. The relationship of exposure to the ADS with airway inflammation was investigated based on the FeNO value, and the association of PEF with FeNO after ADS exposure was examined. As far as we are aware, this is the first study of the effect of ADS on airway inflammation in patients with asthma using measurement of FeNO.

MATERIALS AND METHODS

Patients

A longitudinal study was conducted with measurement of FeNO before and after an ADS and monitoring of daily morning PEF in adult patients with asthma from March to May 2012. The subjects were 33 outpatients aged > 18 years old with asthma who were recruited into the study from December 2010 to January 2011. At this time the subjects had moderate asthma based on National Heart, Lung, and Blood Institute criteria (10) and a score on the Japanese version of the Asthma Control Test (ACT-J) of ≥ 20 (11). The patients were residents in Yonago City, Japan, and outpatients at Tottori University Hospital. Based on Global Initiative for Asthma (GINA) criteria, asthma was defined as positive if a case met (1) and (2) or (3) of the following criteria : (1) a history of intermittent wheezing ; (2) airway hyperresponsiveness to methacholine ; and (3) reversible airflow limitation (12% and 200 ml variability in FEV₁) (12). The study was approved by the institutional ethics committee (Ethics Committee of Tottori University, Approval Number 1656) and all patients gave written informed consent.

Definition of the period of ADS exposure and monitoring of air pollutants

The period of ADS exposure was determined using information from the Japan Meteorological Agency based on the criterion of visibility < 10 km due to dust arising from the deserts of East Asia, as determined by meteorological satellites. The concentration of suspended particulate matter (SPM) was confirmed based on monitoring at many locations in Japan by the Japanese Ministry of the Environment. In this study, we used data for SPM in Yonago City. LIDAR data for sand dust particles and air pollution aerosols were provided by Matsue observatory, which is located 25 km from Yonago City, because the Yonago observatory does not have a LIDAR system.

Recording of daily morning PEF and FeNO

From February to May 2012, all patients recorded their daily morning PEF using a peak flow meter (Mini-Wright, Harlow,

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England, American Thoracic Society scale). February was used as the practice period. PEF was measured three times within 30 min of getting up in the morning and before inhalation of corticosteroids or β_2 -agonists or taking oral drugs. Patients recorded the best value from three attempts. The minimum morning PEF (% recent best) was determined based on the lowest daily morning prebronchodilator PEF (13). The recent best value is defined as the best PEF from March to May 2012 in each patient. Lowest PEF values were also determined for the post-ADS (April 23 to 29) and pre-ADS (April 15 to 21) periods.

FeNO was measured using NObreath (Bedfont Scientific, Maidstone, Kent, UK) following American Thoracic Society/European Respiratory Society recommendations (14). ADS days are predictable based on the LIDAR system. Patients were requested by telephone to visit Tottori University Hospital for measuring FeNO before and after an ADS in Yonago City. FeNO was measured once from April 15 to 21 and once from April 24 to April 26, and these values were defined as the pre-ADS and post-ADS values, respectively.

Statistical analysis

Results are shown as the mean \pm standard deviation (SD). SPSS Statistics software (Japanese ver. 16.0 for Windows; IBM Japan, Tokyo, Japan) was used for statistical analysis. Differences in PEF and FeNO between the post-ADS and pre-ADS periods were analyzed by *t*-test. The association between PEF and FeNO was evaluated by linear regression analysis. Significance was defined as $p < 0.05$ in all analyses.

RESULTS

Patient characteristics

All 33 registered patients recorded daily respiratory symptoms and PEF for > 98% of the study period (March to May). Their characteristics are shown in Table 1. A treatment step according to the Japanese guidelines for adult asthma of March 2012 was used (15).

Table 1. Characteristics of the patients

Item	Value
Number	33
Gender (Male/Female)	15/18
Age (Years)	62.5 \pm 16.4
Smoking status (Number)	
Never	21
Former	12
Current	0
Pulmonary function	
FVC (L)	3.04 \pm 0.66
FEV ₁ (L)	2.26 \pm 0.61
%FEV ₁ (%)	103.3 \pm 22.2
Treatment step (Number)	
Step 2	8
Step 3	25

Data are shown as a number or mean \pm SD
FVC; forced vital capacity, FEV₁; forced expiratory volume in 1 second, %FEV₁; percentage of predicted FEV₁

Sand dust particles and SPM

Daily levels of sand dust particles and SPM from March 1 to

May 31 2012 are shown in Figure 1. Two ADS days were identified based on information from the Japan Meteorological Agency: April 23, and April 24. Daily levels of sand dust particles were not calculated on 16 days of the study period (March 1, 2, 3 to 6, 17, 18, 23, and 24; April 3, 4, 11, and 20; and May 2, and 3).

PEF and FeNO

The minimum morning PEF values were 93.9 \pm 4.5% in the pre-ADS period and 91.5 \pm 9.1% in the post-ADS period, with no significant difference between the periods (Fig. 2). The respective FeNO values were 13.8 \pm 13.7 parts per billion (ppb) pre-ADS and 20.3 \pm 19.0 post-ADS, also without a significant difference (Fig. 3). After exposure to an ADS, there was a significant negative relationship between the change in PEF and the change in FeNO ($R = -0.78$, $P < 0.0001$; Fig. 4); that is, the increase of FeNO was proportional to the decrease of PEF.

DISCUSSION

The effect of exposure to ADS on airway inflammation in adult patients with asthma was investigated in this study. Of 33 patients, 25 had increased FeNO value after the ADS compared to before the ADS. There was no significant association of exposure to the ADS with the FeNO value, but the increase in FeNO after ADS exposure induced a significant decrease in pulmonary function, which suggests that airway inflammation induced by exposure to ADS can aggravate pulmonary function in some adult patients with asthma.

There have been several studies of the association of FeNO with exposure to particulate matter (16), with some showing a significant association with an increase in FeNO, whereas others have not found a significant relationship between exposure to air pollutants and FeNO. Variation in the composition of particulate matter may be a reason for these different results (17). Onishi *et al.* suggested that ADS events can be classified into three types based on LIDAR data: Type 1 events with high counts of air pollution aerosols; Type 2 events with high counts of mineral dust particles, compared to air pollution aerosols; and Type 3 events with very low counts of air pollution aerosols (18). Thus, the compositions of ADS particles can also vary. During this study, the only ADS days were April 23 and 24. Therefore, we were only able to measure post-ADS FeNO once, and further investigation of the association of ADS exposure with FeNO will need several more measurements of FeNO before and after an ADS.

Exposure to particulate matter has been widely shown to increase the number of neutrophils and the concentration of pro-inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)- α , and myeloperoxidase in the airway (19, 20). However, an increase in FeNO may more strongly reflect airway eosinophilic inflammation compared to neutrophilic inflammation (21). Neutrophils migrate to the lungs during acute inflammation induced by exposure to particulate matter in patients with asthma (22). The concentration of IL-8 in bronchoalveolar lavage fluid (BALF) and IL-8 mRNA expression in bronchial biopsy tissue from healthy subjects are also increased by particulate matter (23), and IL-8 is a key cytokine in exacerbation of airway inflammation by exposure to particulate matter. In contrast, although many studies have shown that particulate matter, including ADS particles, is able to aggravate eosinophilic airway inflammation in animal models (24, 25), as far as we know, there has been few studies to investigate this association in humans using induced sputum, bronchial biopsy, BALF, or urinary leukotriene. In the current study, we only measured FeNO to investigate the effect of ADS on airway inflammation, but ADS particles may augment neutrophilic airway inflammation and other pro-inflammatory cytokines, rather than eosinophilic airway inflammation.

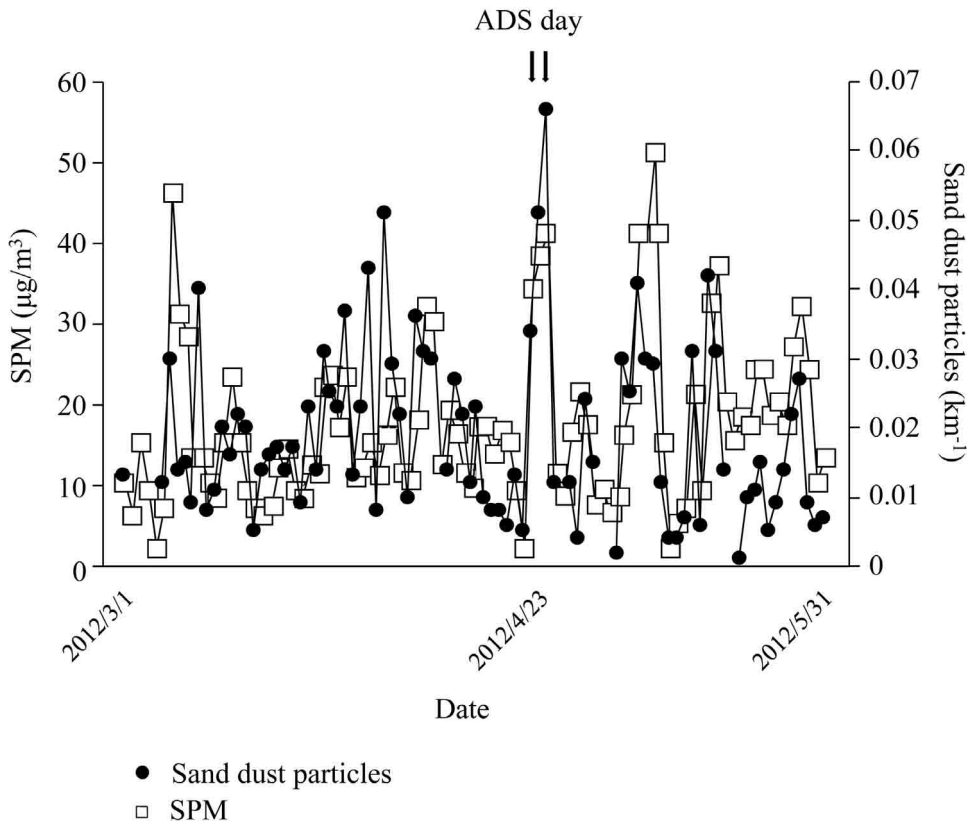


Figure 1. Daily levels of sand dust particles (closed circles) and SPM (open squares). Arrows indicate the ADS day. Data for sand dust particles are missing from March 2 to 5 and April 2, 3, 11 and 21 due to a LIDAR failure.

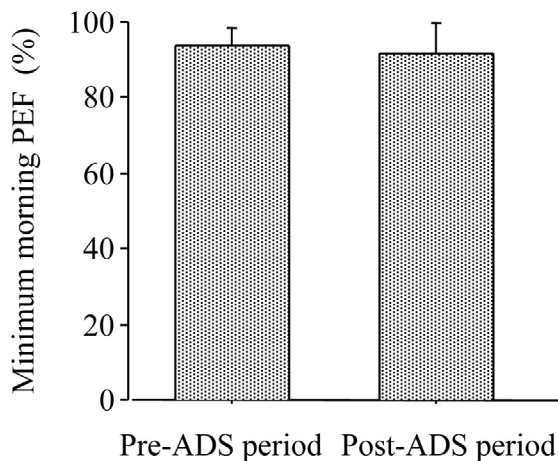


Figure 2. Minimum morning PEF (% recent best) in the pre-ADS (April 15 to 21) and post-ADS (April 23 to 29) periods. The recent best value is defined as the best PEF from March to May 2012 in each patient.

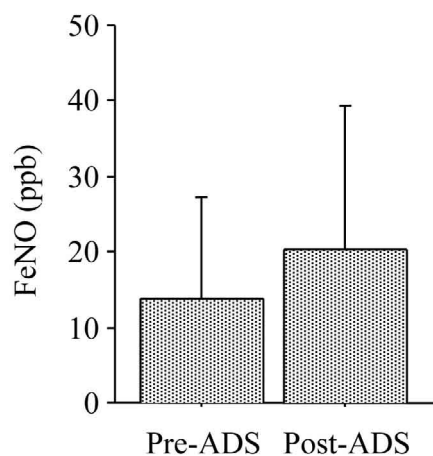


Figure 3. FeNO values before and after the ADS. FeNO measured 7 days before the ADS days was defined as the pre-ADS value. FeNO measured from April 24 to April 26 was defined as the post-ADS value.

In this study, an increase in FeNO value after exposure to ADS was significantly associated with a decrease in pulmonary function. This result suggests that ADS exposure can induce an increase of airway inflammation and a decrease of pulmonary function. We have not found a significant association of exposure to an ADS with pulmonary function in previous studies (4, 5). However, 11% to 22% of adult patients with asthma noted worsening lower respiratory tract symptoms on ADS days, and also had decreased

pulmonary function (4, 5). There are several clinical phenotypes in asthma (26) and the effects of ADS on asthma may differ in each patient, with only a minority of patients experiencing exacerbation due to exposure to ADS. When comparing patients with and without an increase of FeNO value after an ADS, no significant difference was seen in age, gender, treatment step, pulmonary function, or ACT score.

Pharmacotherapy to suppress airway inflammation can decrease

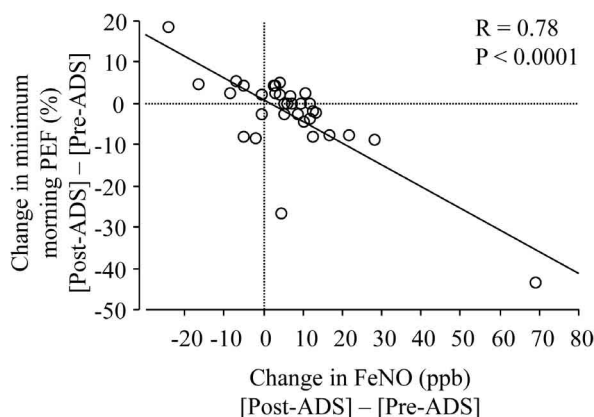


Figure 4. Relationship between the change in FeNO and the change in minimum morning PEF from before to after exposure to the ADS.

FeNO value and increase PEF value. In this study, none of the patients had emergency or unscheduled hospital visit, or needed a step up of treatment from pre-ADS period to April 24, which was the first ADS day. Therefore, pharmacotherapy did not affect FeNO value, but might have affected PEF value. On post-ADS measurement, two patients, who had more than 20% decrease of PEF value, needed an intravenous drip infusion of steroids. After post-ADS measurement, four patients needed to increase inhaled corticosteroid and/or long-acting β_2 -agonist. We may underestimate the effect of exposure to ADS on PEF value. We may underestimate the effect of exposure to ADS on PEF.

There may be an increased risk of hospitalization caused by an ADS in children with asthma (2, 3) and the influence of an ADS may differ between adult and pediatric asthma in Japan. Additionally, in studies of associations of ADS with hospitalization, the state of asthma control has been unclear; thus, ADS exposure may be a risk for hospitalization for patients with poorly controlled asthma, but not for those with well controlled asthma. The patients in the current study were well controlled by medication and had an ACT-J score ≥ 20 . The effect of exposure to ADS on asthma may be mild when the asthma is controlled well, and this may explain why we did not find associations of exposure to ADS with pulmonary function and airway inflammation in the current study.

There are several limitations in the study. First, we did not evaluate the extent of exposure to the ADS in each individual. However, patients recorded their time spent outdoors, and all patients spent more than one hour outdoors on ADS days, although the time outside varied among individuals. Controlled exposure studies are required to avoid this limitation. Second, the measurement time varied in this study, and recent reports have shown that patients with asthma have diurnal variation in FeNO, and that this is a predictor of the risk of future exacerbation (27). Thus, the measurement time may require standardization in a future study. Similarly, the day of measurement of FeNO was not the same in all patients. Our previous study demonstrated that the effects of exposure to ADS on PEF value were delayed by two days (28). The decrease of PEF value was highest on ADS day. Therefore, we may underestimate the effect of exposure to ADS on FeNO in patients measured on April 25 and 26 compared to those on April 24. Third, in order to investigate the effect of ADS on airway inflammation, we were unable to estimate other biomarkers such as the number of eosinophil in induced sputum and blood, C-reactive protein, and serum immunoglobulin E. Further study is needed to investigate these effects. Finally, we were unable to adjust our findings for other air pollutants such as ozone, sulfur dioxide, and nitrogen dioxide, exposure to all of which can also affect the FeNO value (16).

CONCLUSION

We were unable to find an association of exposure to ADS with airway inflammation based on measurement of FeNO in adult patients with asthma. However, an increase of FeNO after exposure to ADS induced a significant decrease of pulmonary function. This suggests that exposure to ADS may aggravate airway inflammation in some adult patients with asthma.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding publication of this paper.

AUTHORS' CONTRIBUTIONS

MW conceived of the study and ME, JK and HS participated in the design, MW and JK enrolled patients and acquired clinical data, MW and JK performed the statistical analysis. MW and ES drafted the manuscript. All authors read and approved the final manuscript.

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