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Technical Information

Effects of Sulfur Dioxide on Fractional Exhaled Nitric Oxide Concentration in the Child Residents of Miyakejima Island

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ABSTRACT The island of Miyakejima in Japan is subject to ongoing emissions of volcanic gases, including high concentrations of sulfur dioxide (SO_2). Annual health checkups on the island, therefore, include the examination of respiratory system parameters. Here, we aimed to investigate the relationship between SO_2 exposure and fractional exhaled nitric oxide (FeNO) concentration among children who received health checkups from 2008 to 2014. The subjects were 83 and 31 second-year junior high school students aged 13–14 years who resided on Miyakejima island and an SO_2-free reference island, respectively. SO_2 concentration in the air was measured at 6 fixed-point monitoring stations. FeNO was examined according to the American Thoracic Society guideline and European Respiratory Society recommendations for standardized procedures. Average concentrations of SO_2 on Miyakejima over a period of 3 months prior to each health checkup from 2008 to 2014 were 22.2, 20.6, 8.9, 10.5, 10.7, 4.4 and 8.0 ppb, respectively. Among the Miyakejima students, geometric mean (GM) FeNO concentrations measured at each health checkup from 2008 to 2014 were 28.2, 18.2, 23.6, 35.5, 36.9, 28.1, and 32.1 ppb. The GM FeNO concentration measured from all Miyakejima students across the study period was 28.3 ppb. No clear dose-response relationship was observed. The GM FeNO concentration among the students from the reference island was 27.7 ppb in 2017. No significant difference was observed between the two populations, even when the data was stratified by sex and sensitivity. There was no clear significant difference in GM of FeNO concentration between Miyakejima and control students, when the average concentration of SO_2 over a period of 3 months was 22 ppb or less.

KEY WORDS Volcanic gas, Sulfur dioxide, Fractional exhaled nitric oxide concentration, Junior high school students

1. INTRODUCTION

Miyakejima Island is a volcanic island 8 km in diameter located 180 km south-southwest of Tokyo. In the last 500 years, Mt. Oyama, the island's highest peak, has erupted approximately every twenty years. The most recent eruption began in June 2000, and due to continuous eruptions and emissions of lethal/unsafe levels of volcanic gas, the Miyake village government decided to evacuate all citizens from the island in September 2000. At the time of the evacuation, the amount of sulfur dioxide (SO_2) discharged, the main toxic component of volcanic gas, was ca. 50,000 tons/day. Volcanic activity gradually decreased, and has since ceased.

As Tokyo Metropolitan Government and the Cabinet Office of Japan (2003) reported that the volcanic gases from Mt. Oyama contain not only SO_2 but also hydrogen sulfide, hydrogen chloride, carbon dioxide, and suspended particulate matter (SPM). The concentrations of gases other than sulfur dioxide, however, are lower than reference values. For example, hydrogen sulfide was at the threshold limit value of 1 ppm recommended by the American Conference of Industrial Hygienists in 2010. Moreover, while it is highly likely that hydrogen chloride and SPM were also discharged, measured concentrations have been negligible. Therefore, volcanic gases other than SO_2 are unlikely to be the cause of health effects.

In September 2002, the Tokyo Metropolitan Government and the Cabinet Office of the Japanese Government organized a Scientific Committee for Assessment of Health Risk and Volcanic Activity on Miyakejima Island (Miyakejima gas kenntoukai) (2003) to discuss requirements for canceling the evacuation order and allowing residents to return to the island. The committee concluded that, although both an acute and chronic health risk due to volcanic gas inhalation remained, residents could return to the island as long as they understood these health risks and voluntarily returned with self-responsibility. The committee also advised the village government to continuously monitor SO_2 concentrations all around the island and to conduct health checkups to detect the early effects of SO_2.

After residents returned to the island, the village government conducted annual health checkupkes under the Ordinance of Security for Safety and Health against Volcanic Gas promulgated by the Miya Village Government. These findings enabled analysis of the effects of SO_2 at 10 years post eruption on the respiratory systems of child residents of Miyakejima as a prospective cohort study. Beginning in 2008, health checkups on the island incorporated measurement of the fractional exhaled nitric oxide (FeNO) concentration. The present study aimed to investigate the relationship between SO_2 exposure and FeNO by comparing FeNO levels from Miyakejima students and students from a reference island in Japan where SO_2 concentrations are far below the Japanese Environmental Standards (*JEStd*).

2. SUBJECTS AND METHODS

The village government of Miyakejima Island conducts annual health checkups under the Ordinance of Security for Safety and Health against Volcanic Gas promulgated by the Miyake Village Government. According to Japanese ethical guidelines on epidemiological studies, informed consent does not need to be obtained from human subjects of investigations conducted based on legal regulations. Therefore, we did not obtain informed consent from the participants on Miyakejima Island. However, we did obtain written consent from subjects from the reference island based on approval by the Ethics Committee of the School of Medicine of Keio University (approval number: 20100306).

2.1 Assessment of SO_2 Concentrations

Following the 2000 eruption, the Miyakejima Village Government initiated continuous monitoring of SO_2 levels using SO_2 monitors (100-AH, Rikenkeiki, Tokyo, Japan, APSA-360, Horiba, Kyoto, Japan and a UV fluorescence method conducted by the Air Quality Bureau of the Tokyo Metropolitan Government) 6 fixed-point monitoring stations in inhabited areas on the island's orbital road. SO_2 averages are reported every 5 minutes. Average SO_2 concentrations (ppb) over the 3- and 12-month periods prior to the health checkups were arithmetic means of the 6 monitoring stations. The Air Quality Standard for SO_2 in Japan specifies that the daily average of 1-h SO_2 concentrations should be 0.04 ppm or below, and that the 1-h SO_2 concentration should be 0.1 ppm or below. No measurement at any monitoring station on Miyakejima Island has yet achieved this standard. Miyakejima is an island centered around the erupted Mt. Oyama and many of its inhabitants live along an orbital road. Therefore, all residents are exposed to SO_2 in volcanic gas.

A reference island in the western part of Japan where air pollutants, including SO_2, are probably far below JEStds, in 2016.

2.2 Study Population

Eligibility criteria: Subjects were second-year junior high school students aged 13–14 years. The study was conducted on Miyakejima Island from 2008–2014. On the reference island, we conducted in 2016. We have FeNO observation and analyses for all participant (Fig. 1). The criteria for hypersusceptibility in this study were

(1) a current or a past history of asthma; and/or (2) symptoms of whistling and wheezing.

2.3 Medical Examination

According to ATS/ERS recommendations (2005), the FeNO concentration was measured using the nitric oxide gas analyzer NIOX MINO (Aeocrine Co.). Given that a nitrate-rich diet and contamination due to nasal inflammation increases FeNO levels, a questionnaire was also conducted on these factors when measuring FeNO.

2.4 Statistical Analysis

Average values and *prevalence* values between students from Miyake and the reference island were compared by analysis of variance and the chi-squared test. All statistical analyses were performed using SPSS version 24.0 (IBM Co.; Armonk, NY, USA).

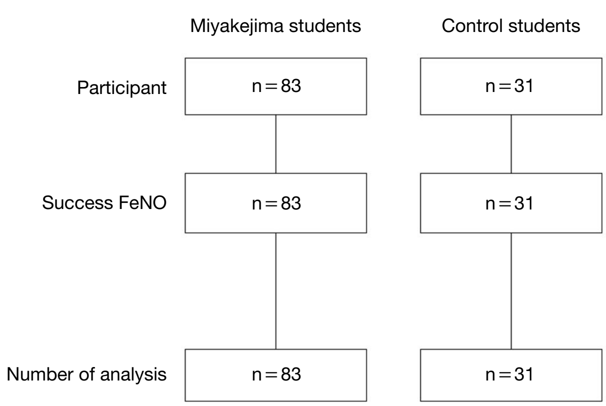

Fig. 1. The flow chart of participant and analysis.

3. RESULTS

3.1 Characteristics

Table 1 presents the characteristics of the participants and the concentration of SO_2 measured in each year of the study. The total number of students from Miyake and the reference island was 83 and 31 (male and female, 49 and 34, and 24 and 7, respectively). Average height was 161.2 cm and 158.7 cm, respectively. The prevalence of hypersusceptibility from Miyake and the reference island was 20.5% and 19.4% ($p=0.89$), respectively.

Average concentrations of SO_2 from the monitoring stations over a period of 3 months prior to each health checkup were 22.2, 20.6, 8.9, 10.5, 10.7, 4.4 and 8.0 ppb from 2008 to 2014. Likewise, average concentrations of SO_2 from the monitoring stations over a period of 12 months prior to each health checkup were 17.6, 17.6, 9.6, 7.3, 8.4, 4.2 and 5.0 ppb.

3.2 Medical Examinations

Table 2 shows the geometric mean (GM) of FeNO concentration of students in Miyake Island and the reference island. The annual GM of FeNO concentration among Miyake Island students was 28.2, 18.2, 23.6, 35.5, 36.9, 28.1, and 32.1 ppb from 2008 to 2014. The GM of FeNO concentration of all Miyakejima students was 28.3 ppb. In contrast, the GM of FeNO concentration

Table 1. Characteristics of the study population and concentration of SO_2.

	Miyakejima Island							Control Island
	2008	2009	2010	2011	2012	2013	2014	
Gender (male/female), n	9/5	9/2	4/7	4/3	9/4	5/8	8/6	24/7
Height (cm)	160.5	166.5	159.4	162.3	161.5	158.5	161.1	158.7
Hypersusceptibility	6	1	2	1	2	1	4	6
Concentration of SO_2[#]								
Last twelve months								
Mean (ppb)	17.59	17.56	9.55	7.34	8.35	4.19	4.97	*
Frequency $\geq$0.1 ppm in hourly measurements (%)	3.94	4.90	2.55	2.12	2.78	1.23	1.27	*
Last three months								
Mean (ppb)	22.2	20.6	8.92	10.5	10.7	4.38	8.01	–
Concentration of SPM				<13				*
Concentration of NO_2				–				*
Difference in mean temperature (°C)	0	0.5	0.1	−5.7	−0.9	2.6	−2.9	1.6
Mean air pressure change (hPa)	−1.5	−0.5	0.3	11	6.6	7.6	2.3	0.8

[#]5-min average concentration of SO_2. We calculated the total average value of the six monitoring stations.
*under the standard. There is no monitoring site in Control Island. From the Southwest Islands area and Okinawan data, we estimated that SO_2, SPM and NO_2 were lower than JEStd in Control Island.

Table 2. Geometric mean and Geometric standard deviation of FeNO among control and each health check-up.

		Control	Miyakejima students from 2008 to 2014	2008	2009	2010	2011	2012	2013	2014
n		31	83	14	11	11	7	13	13	14
GM	(ppb)	27.7	28.3	28.2	18.2	23.6	35.5	36.9	28.1	32.1
GSD	(ppb)	3.06	2.28	2.46	2.58	1.79	2.24	2.08	2.48	2.28
Female										
GM		25.51	23.12	24.30	30.74	20.42	22.68	31.34	19.74	23.88
GSD		2.90	2.15	2.87	2.76	1.97	1.96	2.48	1.98	2.59
Male										
GM		28.35	32.46	30.63	16.24	30.43	49.61	39.75	49.59	37.83
GSD		3.18	2.33	2.36	2.60	1.31	2.24	1.99	2.72	2.12
Hypersusceptibility										
GM		65.50	49.84	56.65	72	41.69	17	54.77	93	43.81
GSD		2.95	1.88	1.59	–	2.47	–	3.03	–	1.92
Non-Hypersusceptibility										
GM		22.51	24.41	16.71	15.90	20.81	40.10	34.39	25.46	28.34
GSD		2.84	2.25	2.20	2.41	1.60	2.25	2.00	2.39	2.41

of the students in the reference island was 27.7 ppb. No significant difference was observed between the two groups ($p=0.92$).

4. DISCUSSION

We previously conducted epidemiological studies on volunteers and residents of Miyake who were exposed to SO_2 from volcanic gas across a 10-year period and reported the presence of a quantitative reaction between SO_2 exposure and subjective symptoms. For example, Ishigami *et al.* (2008) conducted a follow-up study on 611 healthy volunteers, on a person-hour basis (28,413 person-hours), who visited Miyakejima Island to provide support to residents and stayed anywhere from a few to 15 days from February to July 2005. The hourly incidence of irritative symptoms showed clear exposure-response relationships with hourly average SO_2 concentrations, and exposure to 20–30 ppb SO_2 or above increased the rate ratio of irritative symptoms such as sore throat. This result was consistent with the acute effect. However, our study differs from this study as respiratory effect of child in Miyakejima.

In addition, Iwasawa *et al.* (2015) found clear dose-response relationships in child Miyakejima residents. The subjects of that study were residents aged 6–18 years who were enrolled in a Miyake elementary school, middle school, or high school at the time of each medical checkup. Applying a logistic regression model, age-, sex-, and hypersusceptibility-adjusted prevalence odds ratios to the reference population showed clear exposure-dependent increases in some irritative symptoms such as "Irritation and/or pain in throat" and "in eyes", and approximately 30 ppb seemed to be the threshold concentration. This result was consistent with child in Miyakejima. However, our study differs from this study in the respiratory effect assessed by fractional exhaled nitric oxide concentration.

Further, Kochi *et al.* (2017) found clear dose-response relationships in adult Miyakejima residents. To assess the exposure-effect and exposure-response relationships between SO_2 exposure and effects on respiratory system in adult Miyakejima residents. In this study, they observed minor health effects on the respiratory system and irritation symptoms. They also observed clear dose-response relationships and determined an apparent threshold concentration of approximately 70 ppb. This result was consistent with adult in Miyakejima. However, our study differs from this study in the respiratory effect assessed by fractional exhaled nitric oxide concentration.

FeNO concentration has attracted attention as a marker of airway inflammation and has been measured on child in Miyakejima as a respiratory effect of SO_2 exposure since 2008.

Although emission rates of SO_2 have been gradually decreasing since the initial eruption, levels remain high (Tokyo Metropolitan Government and the Cabinet Office of Japan, 2003), especially in comparison with current levels around Sakurajima in Japan (Uda *et al.*, 1999), Kilaueu in Hawaii (Mannino *et al.*, 1996), and Stromboli and Etna in Italy (Durand *et al.*, 2001).

A nitrate-rich diet and contamination with nasal NO can increase FeNO values and should therefore be avoided or taken into account when measuring FeNO. In this study, consumption of a nitrate-rich diet (Miyake 4.8%, reference 0%) was not statistically significantly different between the two populations.

Fujisawa (2012) previously reported the GM of FeNO concentration. FeNO was measured using NIOX-MINO for Japanese volunteers of general junior high school students and high school students. The presence or absence of allergic disease in the subjects was classified using the Japanese version ISAAC questionnaire. In the analysis excluding allergic rhinitis, the geometric mean value of 79 male was 21 ppb. On the other hand, including allergic rhinitis, the cut-off value was 40 ppb at male subject. Additionally, FeNO is affected by age. Generally, the FeNO becomes higher as the age increases. This study covers second-year junior high school students aged 13–14 years and is close to the median of Fujisawa's studies.

In contrast, we found that the concentration was 28.3 ppb among children on Miyakejima and 27.7 ppb among children on the reference island. This discrepancy may be due to the persistent presence of salt particles, which can contribute to airway inflammation.

Airway irritative pollutants other than SO_2 may influence FeNO. Tokyo Metropolitan Government and the Cabinet Office of Japan (2003) measured SPM from November 2002 to February 2003 at three sites in Miyakejima Island and average concentrations were 13 to 20 $\mu g/m^3$, which were lower than JEStd. In the referent island, $PM_{2.5}$ was measured from 2011 to 2014 and was lower than the annual JEStd (Kagoshima prefecture, 2019). Horie *et al.* (2017) and the Okinawa Prefecture Environment White Paper (2016) reported SO_2, SPM and NO_2 were lower than JEStd in the Southwest Islands area in Japan where the reference island belongs. $PM_{2.5}$ has dose dependent health effects even in a very low level. For example, Fan *et al.* (2018) described that an interquartile range (IQR) change in personal exposure to $PM_{2.5}$ (16.4 $\mu g/m^3$) was positively associated with 12.8% increase in FeNO (95% confidence interval, CI: 5.5–20.7%), while nil association was found for ambient $PM_{2.5}$. Therefore, airway irritative pollutants other than SO_2 may confound FeNO in this study.

Rapid changes of temperature and atmospheric pressure may affect airway obstruction in asthmatics and wheezers. In Miyakejima island, difference in mean temperature (°C) on the FeNO measurement day and the previous day was 0 in 2008, 0.5 in 2009, 0.1 in 2010, −5.7 in 2011, −0.9 in 2012, 2.6 in 2013 and −2.9 in 2014. In the referent island, that was 1.6. The maximal difference was −5.7°C in 2011 but we could not observe abnormal FeNO deflection.

Our study has some limitations. First, we did not investigate smoking. According to ATS/ERS recommendations (2005), chronically reduced levels of FeNO have been demonstrated in cigarette smokers in addition to acute effects immediately after cigarette smoking. Despite the depressant effect of smoking, smokers with asthma still have a raised FeNO. Subjects should not smoke in the hour before measurements, and short- and long-term active and passive smoking history should be recorded. Since we target children, there should be no smokers. However, the influence of passive smoking could not be denied.

Second, we have not investigated the length of stay in the target and control island. However, this study targets acute respiratory effects. Presence or absence of exposure at the time of survey is important. These data are unlikely to affect exposure to SO_2.

In conclusion, there was no clear significant difference in GM FeNO concentration between students from Miyakejima and a reference island, when the average concentration of SO_2 over a period of 3 months was 22 ppb or less.

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The authors have declared that no competing interests exist.

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