

RESEARCH LETTER

Serial measurements of fractional exhaled nitric oxide at home and at work: A useful tool for monitoring workers with platinum salt allergy after exposure reduction

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In a recent publication, we have shown that serial FeNO measurements off and at work provide complementary information for the diagnosis of occupational asthma (OA).¹ This result prompted us to assess whether this method is particularly suitable for tertiary prevention, that is, to monitor workers in platinum (Pt) industry with diagnosed OA to Pt salts after exposure reduction.

Pt salt allergy is a major health problem in precious metals refineries and catalyst productions. Skin prick test with Pt salts (SPT_{Pt}) is a useful tool for early detection of Pt salt sensitization.² Medical surveillance programs have a long tradition in these industries, and it is known that immediate removal from exposure after SPT_{Pt} conversion from negative to positive results in an excellent prognosis and reversion of positive SPT_{Pt} to negative.³ Whereas a large number of sensitized workers are transferred from their workplace where they acquired allergy (“high exposure”; air concentrations of soluble Pt greater than about 200 ng/m³) to areas within the plants with at most negligible exposure (“very low exposure”; air concentrations of soluble Pt below 20 ng/m³) or leave the company (“no exposure”), it is common practice to perform other preventive measures, for example, working with an airstream helmet or transfer especially highly qualified operators to adjacent departments (“low exposure,” air concentrations of soluble Pt about 20–200 ng/m³).⁴

The exact exposures in “(very) low-exposure” areas are unknown; the above-mentioned exposure ranges were provided by industry. In addition, so far no data are available on a tolerable Pt air concentration for sensitized workers.

A sensitive and objective method could allow to monitor the effects of persistent low occupational allergen exposure. It is known that increased levels of fractional exhaled nitric oxide (FeNO) represent a marker of eosinophilic airway inflammation which is a feature of OA.^{5,6} In a recent study, serial FeNO measurements in subjects with suspected OA, but a negative result in specific inhalation challenge (SIC) resulted in about a quarter of cases in significant FeNO increases at work providing complementary information for the diagnosis of OA.¹ Therefore, the aim of the present study was to examine whether serial FeNO measurements are also suitable for monitoring workers with known OA after interventions.

The study was approved by the ethic's committee of the Ruhr University, Bochum. Workers were referred to our institute by the plant physician of one single precious metals refinery and catalyst production. In this plant, yearly examinations including SPT_{Pt} were performed. A pilot study was performed in three workers with Pt salt allergy who had been transferred to “very low-exposure” areas (subjects D and E in Table 1; very-low-exposure areas in this study were defined as workplaces within the plant that were not in the vicinity of high exposure areas, and all available air concentrations of soluble Pt were measured below 20 ng/m³) or to “low-exposure” areas (subject A in Table 1).

After the successful pilot study workers with a new diagnosis of Pt salt allergy (which was made by our institute) were transferred prospectively from 2014 onwards as soon as possible to “low-exposure” areas. These workers were offered to participate in this study which included serial daily FeNO measurements for 2 weeks at home and at work as described in detail earlier.¹ Workers who agreed to

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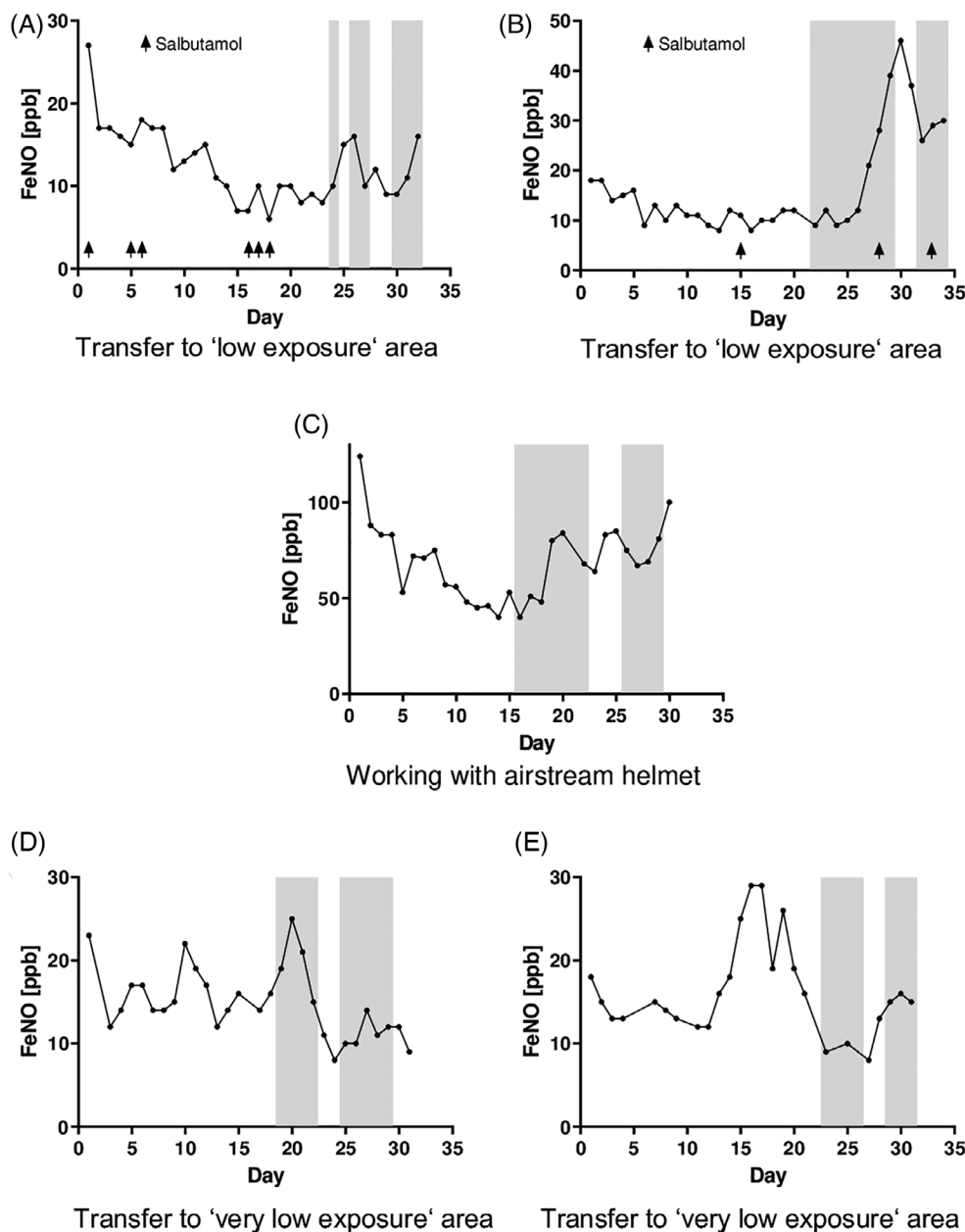
TABLE 1 Characteristics, symptoms, and test results of subjects with a diagnosis of occupational asthma due to platinum at the time of serial FeNO measurements which was performed after exposure reduction (intervention)

Subject	Kind of Intervention	Time since Intervention (month)	Symptoms	Age	Sex	Smoking	Total IgE (kU/L)	Atopy	SPT _{Pt} ^a	FEV ₁ % pred	FEV ₁ /FVC	BHR
A	Transfer to "low"	77	R, C, A	57	m	Ex	15.8	neg.	neg. ^b	113.6	79.8%	pos.
B	Transfer to "low"	2	R, C, A, skin	20	f	7/day	74.0	neg.	10 ⁻⁴	105.7	89.4%	pos.
C	"airstream-helmet"	6	R	49	m	Never	122.0	pos.	10 ⁻⁴	115.2	81.0%	neg.
D	Transfer to "very low"	45	None	45	m	Ex	62.8	neg.	10 ⁻³	91.1	81.4%	neg.
E	Transfer to "very low"	12	None	29	m	10/day	121.0	neg.	10 ⁻³	96.2	84.4%	pos.

Abbreviations: A, asthmatic symptoms; BHR, bronchial hyperresponsiveness; C, conjunctivitis; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; R, rhinitis; SIC, specific inhalation challenge (with platinum); SPT_{Pt}, skin prick test with platinum salt.

^aIf SPT pos.: lowest Pt concentration (g/ml) inducing wheal diameter ≥4 mm is mentioned.

^bSPT conversion from pos. to neg. occurred 65 month after intervention.



participate were taught how to perform the FeNO measurements with a portable device (NioxMino, Aerocrine, Solna, Sweden) which they had to perform for 2 weeks once daily about 1 hour after work or at about the same time during periods off work.

During the prospective study, 10 workers showed SPT_{Pt} conversion. In eight of these subjects, FeNO was measured before and 24 hours after SIC_{Pt}. With the exception of one smoker in whom FeNO was not measurable before and after SIC_{Pt} (<5 ppm), there was an increase in FeNO after SIC_{Pt} (Δ_{FeNO} median: 36 ppb [9–127 ppb]). One subject had to be hospitalized after an asthma attack at work and was excluded. Only two of nine eligible workers agreed to participate. Thus, in total, five subjects completed the study protocol. The subjects were told to use inhaled short-acting beta agonists (SABA) on demand, but no further asthma medication. Actually, only two subjects used SABA during the study period (subjects A and B, Figure 1).

Three of the five subjects reported ongoing work-related symptoms after the intervention (two workers had been transferred into “low-exposure” areas and one worker was equipped with an airstream helmet; Table 1). In accordance with this, these subjects exhibited work-congruent differences in serial FeNO (Figure 1A–C). In particular, subjects A and C needed approximately 14 days until the FeNO level—which was elevated from the previous work period—decreased to normal. In all three cases, the grouped FeNO values were significantly higher at work than during periods off work (data not shown), indicating an ongoing exposure to Pt salts at the workplace. Therefore, further interventions (exposure cessation) were recommended to the three workers. In contrast to this, both workers who had been transferred to “very-low-exposure” areas and who reported a disappearance of symptoms after intervention showed no higher FeNO values at than off work (Figure 1D,E).

There is a weak epidemiological evidence that ongoing tasks in low-exposure areas cannot be advocated as an alternative to the cessation of exposure.⁷ In line with this, only the two subjects who had been transferred to “very-low-exposure” areas showed no symptoms and no increases in FeNO. Due to the fact that all three subjects with ongoing symptoms after exposure reduction showed significant FeNO increases at work, serial FeNO measurements seem to be a particularly suitable objective tool to monitor subjects with OA after interventions at work. In particular, the fact that subject A became negative in SPT_{Pt} 4 years after transfer to “low”-exposure area, but still showed symptoms and increased FeNO levels at the workplace, indicates high sensitivity of the method.

Limitations of the study are the small number of participants, the inter- and intraindividual variation of FeNO values and the fact that FeNO measurements in current smokers are still under debate as the cigarette smoke itself may influence the results. With regard to the last two points; however, it must be kept in mind that performing serial FeNO measurements allows each subject to act as his/her own control. The high number of subjects who did not agree to participate may be explained by the paucity of symptoms during the early stages of Pt salt allergy in these workers and the fear of social disadvantages and income loss.

Although only five subjects agreed to participate, this study suggests that transfer to “low-exposure” areas or intensified respiratory protection are actually not an option. This view is strengthened by the case of a worker who had to be hospitalized after an asthma attack at his workplace after transferal to a “low-exposure” area. In contrast, transfer to “very-low exposure”, that is, to areas outside the metal refining building, was associated with cessation of work-related symptoms and a lack of FeNO increases in both workers.

In conclusion, serial measurements of FeNO off and at work represent an obviously sensitive, and, unlike the declaration of symptoms, an objective tool to assess the efficacy of tertiary prevention measures in workers with Pt salt allergy.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Rolf Merget, Hendrik Mertens, Vera van Kampen, Thomas Brüning

Project Administration: Vera van Kampen, Rolf Merget

Investigation: Rolf Merget, Hendrik Mertens

Writing: Original draft preparation: Vera van Kampen, Rolf Merget

Writing: Review and editing: Vera van Kampen, Rolf Merget, Hendrik Mertens, Thomas Brüning

All authors had read and approved the final version of the manuscript.

Vera van Kampen had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS STATEMENT

This study was carried out in accordance with the Declaration of Helsinki. All procedures were reviewed and approved by the ethic's committee of the Ruhr University, Bochum. A signed informed consent form was obtained from each participant prior to inclusion in this study.

TRANSPARENCY STATEMENT

Vera van Kampen affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request and in compliance with privacy or ethical restrictions.

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REFERENCES

1. van Kampen V, Brüning T, Merget R. Serial fractional exhaled nitric oxide measurements off and at work in the diagnosis of occupational asthma. *Am J Ind Med*. 2019;62:663-671.
2. Merget R, Gautrin D. Metals. In: Malo JL, Chan-Yeung M, Bernstein DI, eds. *Asthma in the Workplace*. 4th ed. London/New York: CRC Press/Taylor & Francis Group; 2013:290-304.
3. Merget R, Caspari C, Dierkes-Globisch A, et al. Effectiveness of a medical surveillance program for the prevention of occupational asthma due to platinum salts. A nested case-control study. *J Allergy Clin Immunol*. 2001;107:707-712.
4. Merget R, Pham N, Schmidtke M, et al. Medical surveillance and long-term prognosis of occupational allergy due to platinum salts. *Int Arch Occup Environ Health*. 2017;90:73-81.
5. Lemiere C, NGuyen S, Sava F, D'Alpaos V, Huaux F, Vandenplas O. Occupational asthma phenotypes identified by increased fractional exhaled nitric oxide after exposure to causal agents. *J Allergy Clin Immunol*. 2014;134:1063-1067.
6. Engel J, van Kampen V, Lotz A, et al. An increase of fractional exhaled nitric oxide after specific inhalation challenge is highly predictive of occupational asthma. *Int Arch Occup Environ Health*. 2018;91:799-809.
7. Vandenplas O, Dressel H, Wilken D, et al. Management of occupational asthma: cessation or reduction of exposure? A systematic review of available evidence. *Eur Respir J*. 2011;38(4):804-811.

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