

RESEARCH ARTICLE

Serial fractional exhaled nitric oxide measurements off and at work in the diagnosis of occupational asthma

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Abstract

Background: Fractional exhaled nitric oxide (FeNO) before and after specific inhalation challenge has been postulated as an additional tool in the diagnosis of occupational asthma (OA), but little is known about serial FeNO measurements at home and at work. The aim of the present study was to assess the contribution of serial measurements of FeNO off and at work toward the diagnosis of OA.

Methods: Forty-one subjects with suspected ($n = 35$) or diagnosed ($n = 6$) OA performed FeNO measurements once daily during a 2-week holiday and a subsequent 2-week work period. A work-related increase in FeNO by 20 ppb (parts per billion) or more was considered positive. Subjects with negative or doubtful specific inhalation challenge but a FeNO increase of 20 ppb or more were evaluated individually by an overall expert rating taking into account all available information.

Results: Seven of 35 subjects (20%) with suspected and three of six subjects (50%) with diagnosed OA showed a work-related FeNO increase of 20 ppb or more. Six of the seven with suspected OA were reclassified as having an OA diagnosis by the overall expert rating which also considered these FeNO changes.

Conclusions: Serial FeNO measurements off and at work provide complementary information in the diagnosis in about one-fifth of cases with suspected OA, especially if specific inhalation challenges are negative or cannot be performed.

KEYWORDS

asthma, fractional exhaled nitric oxide, occupational, serial measurements

1 | INTRODUCTION

Specific inhalation challenge (SIC) with suspected occupational agents is considered the gold standard for the diagnosis of occupational asthma (OA).^{1,2} However, false-negative SIC results can occur for example, due to reduced bronchial reactivity to the causal agent after prolonged removal from exposure or due to a wrong or underdosed test agent.² Thus, a negative test in a worker with otherwise good evidence of OA is not sufficient to exclude the diagnosis.³ In addition, in some cases the performance of SIC is not possible, that is, when contraindicated in patients with severe airway obstruction, when the responsible allergen is not found, or when the workplace conditions are too complex to perform SIC. In those

cases, serial self-measurements of forced expiratory volume in 1 second (FEV₁) or peak expiratory flow (PEF) during periods at and off work using portable instruments have been used to document the relationship between the workplace and the occurrence of asthma.³ However, there are clear limitations of PEF and FEV₁ monitoring that include the need for patient motivation and cooperation, as well as the possibility that patients may falsify the measurements.²

In contrast to PEF and FEV₁, the measurement of fractional exhaled nitric oxide (FeNO) is largely independent of the patient's collaboration. The FeNO measurement is noninvasive and easy to perform. Increased levels of FeNO represent eosinophilic inflammation in asthma,⁴ and in clinical practice, FeNO is recommended for

the monitoring of airway inflammation in patients with asthma. A diagnostic role for FeNO measurements has also been postulated for the diagnosis of OA.⁵⁻⁸ Increases in FeNO after SIC with occupational allergens have been previously reported⁹⁻¹¹; however, not all subjects with an asthmatic response showed increases in FeNO. To date, limited information is available about serial FeNO measurements during work and nonwork periods,¹²⁻¹⁴ suggesting that serial FeNO measurements may provide complementary information in individual cases.

Therefore, the aim of this study was to assess whether serial FeNO measurements both off and at work might add to the accuracy of diagnosing OA when SIC cannot be performed, or when the SIC result is negative in a worker with otherwise good evidence of OA. Although it is known that FeNO is influenced by factors such as atopy, age, height, sex, smoking, and respiratory tract infection,¹⁵ performing serial measurements allows each subject to act as his/her own control. With the exception of two of our own case reports,^{12,13} there is only one previous study on serial FeNO measurements (in subjects exposed to laboratory animals) before and after a week-end.¹⁴ These authors described one sensitized subject who exhibited increasing FeNO during the week at work and concluded that serial FeNO measurements may be helpful in the assessment of occupational airway disease.

2 | MATERIALS AND METHODS

Forty-one subjects were included in this study, all of whom suffered from work-related respiratory symptoms, and were examined within the scope of claims for compensation due to occupational airway disease (suspected OA) in our outpatient clinic between 2008 and 2016. As in 35 cases, OA was considered doubtful after using conventional diagnostic tests, serial FeNO measurements were performed.

Additionally, six persons with positive SIC performed serial FeNO measurements. In one case, serial FeNO measurement should demonstrate whether sensitization to a ubiquitous allergen (mold) was relevant for the patient's complaints at the workplace. The other five SIC-positive subjects underwent serial FeNO measurements because of ongoing work-related symptoms despite preventive measures being instituted at the workplace. In these cases, FeNO increases at work would indicate ongoing allergen exposure. In the following, the six SIC-positive subjects are referred to as positive controls.

Personal data, as well as both work and medical history, were obtained by a questionnaire. The subjects underwent a physical examination, specific immunoglobulin E (sIgE) antibodies were measured using ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden), and skin-prick testing (various manufacturers) was performed with environmental and occupational (if available) allergens. Atopy was defined by at least one wheal reaction 3 mm or more with any environmental allergen. Methacholine testing, lung function, and where possible SIC with occupational agents were performed.

2.1 | Lung function and methacholine testing

Lung function was recorded using body plethysmography¹⁶ and spirometry¹⁷ with MasterLab (CareFusion, Wuerzburg, Germany). Reference values according to the European Community for Steel and Coal¹⁸ were used. Methacholine testing was performed as described previously.¹⁹

2.2 | Specific inhalation challenges

Specific inhalation challenges (SIC) was performed according to different protocols. Particulate allergens such as flour were dispersed and the inhalable dust was measured. For complex exposures (eg, hay and stable dust) a workplace-simulating test was performed. Inhalations with soluble allergens were performed as described by the ATS for methacholine challenges, with minor modifications.^{20,21} Isocyanate challenges were performed according to a four-step, 1-day whole-body challenge protocol.²²

A positive SIC was assumed if FEV₁ decreased by 20% or more and specific airway resistance (sRt) increased 100% or more to 2 kPa-s or more. A challenge was considered negative if there was not a decrease of FEV₁ by 20% or more and not an increase of sRt 100% or more to 2 kPa-s or more. Challenges which could not be assigned as positive or negative were considered doubtful.

2.3 | Serial measurements of FeNO and FEV₁

During their visit at our outpatient clinic, the patients were acquainted with the performance of FeNO measurements (NioxMi-no; Aerocrine, Solna, Sweden) and spirometry (SpiroPro; CareFusion, Wuerzburg, Germany). Spirometry was obtained from three maneuvers by choosing the highest FEV₁ for final analysis. The devices were given to the patients who were instructed to perform FeNO and spirometry measurements (in this order) once a day during a 2-week holiday, directly followed by once a day during a 2-week working period. Measurements were to be done daily between 4:00 and 6:00 PM, and if necessary at a different time (that was after the shift) on days with shift work. All drugs affecting the respiratory tract were to be taken without changes during periods off and at work. Patients were asked to record their exact working hours, and the use of asthma medication during the study period. In addition, new or special working tasks and exposures, as well as the occurrence of symptoms, were to be documented. All data were recorded electronically.

2.4 | Data analysis

Serial FeNO and FEV₁ measurements were plotted by times off and at work. Due to the fact that after allergen exposure FeNO increases progressively with its maximum after 24 to 48 hours,²³ data for both FeNO and FEV₁ from the first 2 days off work were excluded from further analysis because it was unknown whether the patients were previously exposed. In addition, the first 2 days after a working

period were rated as working time (FeNO) or excluded (FEV₁). According to the finding of Lemiere et al⁹ that a post-SIC increase in FeNO level of 17.5 ppb (parts per billion) or more was highly specific (90% specificity) for a positive SIC, serial FeNO measurements were considered positive if any work-related increase was documented as 20 ppb or more.

To obtain a final diagnosis, subjects with negative/doubtful or missing SIC but a work-related increase of FeNO of at least 20 ppb were evaluated individually by the same experienced occupational health physician (RM) in an overall expert rating. This took into account all available information and examinations like anamnesis, improvement of symptoms on days away from work, specific allergen sensitization, results of serial FeNO and FEV₁ measurements and—in cases when SIC was performed—whether SIC reaction was clearly negative or near positive or whether symptoms such as rhinitis occurred during SIC.

To avoid carry-over effects from working periods into the periods off work, the values from the last week off work were compared with those from the first work week using the Mann-Whitney test. A $P < .05$ was considered statistically significant. Data were analyzed and visualized using GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego, CA).

3 | RESULTS

In 19 of the 41 subjects included in the study, no SIC could be performed due to severe airway obstruction ($n = 5$) or due to unknown allergens ($n = 14$). Out of the 22 subjects who underwent SIC, six showed a positive test (positive controls), 15 negative, and one doubtful (Table 1).

All 41 subjects performed serial FeNO measurements during periods off and at work. Eleven subjects (27%) could not be evaluated due to missing FeNO values and were excluded (Table 1). Sixteen cases (39%) complied with the predefined scheme of measurements (2-weeks off work followed by a 2-week work period); whereas 14 subjects (34%) were unable to comply fully with the predefined scheme (eg, starting with work period). They were nevertheless

included in the assessment, because periods of at least 10 days off and at work were available, resulting in 30 cases with sufficient data. In 13 of them (43%), the measurements did not show any FeNO increase of at least 20 ppb and they were considered negative (Table 1). Although the increase of FeNO of at least 20 ppb could be detected in the remaining 17 cases (57%), in seven cases those peaks appeared during periods off work. Overall, there were 10 cases with an increase of FeNO of at least 20 ppb that were work-related (Table 1).

While three of the six SIC-positive subjects showed positive serial FeNO measurements (work-related increases of FeNO of at least 20 ppb), one was negative and in two SIC-positive subjects FeNO measurements could not be evaluated (Table 1). Out of the 35 subjects with negative/doubtful or missing SIC, seven subjects showed work-related FeNO increases of at least 20 ppb, which provided an additional contribution to diagnosis.

Characteristics of the 10 subjects with work-related increases in FeNO of at least 20 ppb are shown in Table 2. In eight cases, statistically significant differences in FeNO values off and at work could be detected with the Mann-Whitney test (Table 2).

Measurements of serial FEV₁ could only be obtained in eight (80%) subjects, because two subjects were unable to perform FEV₁ measurements. Interestingly, serial FEV₁ was negative (no significant differences between periods off and at work) in two subjects with positive results in SIC (positive controls, nos. 1 and 2 in Table 2) as well as in serial FeNO measurement. The overall expert rating resulted in a final diagnosis of OA (in one case, early-onset OA) in six patients with negative/doubtful or missing SIC (nos. 4–9 in Table 2).

Table 3 summarizes the characteristics of the 13 subjects who did not show any significant FeNO increase; neither off nor at work. This group includes one of the positive controls which showed a positive serial FEV₁ measurement in addition to the positive SIC (no. 11 in Table 3). In comparison to the subjects with work-related FeNO increases 20 ppb or more (Table 2) the subjects listed in Table 3 were more frequently exposed to complex, unspecified mixtures, showed fewer agent-specific sensitizations (50% vs 8%), and more often a reduced ($<70\%$) FEV₁/FVC ratio (38% vs 20%). In addition, more subjects without work-related FeNO increase used inhaled corticosteroids (85% vs 50%) (data not shown).

TABLE 1 Overview of SIC results and serial FeNO measurements in 41 study subjects

Results of serial FeNO measurements	SIC result ($n = 22$)			SIC not done ($n = 19$)	Total ($n = 41$)
	Positive ($n = 6$)	Negative ($n = 15$)	Doubtful ($n = 1$)		
1. Missing values Not enough days off/at work; defect of devices; lack of cooperation	1	4	0	6	11
2. Negative No increase of FeNO by 20 ppb or more	1	3	0	9	13
3. Not work related Increases in FeNO during days off work (eg, due to infections)	1	4	0	2	7
4. Positive Work-related increase of FeNO by 20 ppb or more	3	4	1	2	10

Note. Results of positive controls are in italics.

Abbreviations: FeNO, fractional exhaled nitric oxide; SIC, specific inhalation challenge.

TABLE 2 Characteristics and diagnostic results of subjects with suspected occupational asthma showing work-related increases in FeNO of 20 ppb or more

ID	Age	Sex	Smoking	Atopy	Agent	Agent-specific sensitization	FEV ₁ % pred.	FEV ₁ /FVC	BHR	SIC	Baseline FeNO [ppb]	Serial FEV ₁	Final diagnosis
Positive (significant work-related FeNO increase of at least 20 ppb)													
1	43	m	Never	neg.	MDI	neg.	104.4	79.9%	neg.	pos.	44	neg.	OA
2	27	m	Never	pos.	Rhodium	+ (SPT)	97.0	73.2%	pos.	pos.	41	neg.	OA
3	36	m	Ex	pos.	<i>Aspergillus fumigatus</i>	+ (slgE, SPT)	84.1	73.9%	pos.	pos.	10	pos.	OA
4	55	w	Never	pos.	Flour	+ (slgE)	113.1	80.1%	pos.	neg.	49	pos.	OA
5	43	m	Ex	pos.	HDI	neg.	114.0	86.8%	neg.	neg.	11	n.d.	OA
6	44	m	Never	neg.	HDI	neg.	92.1	74.2%	pos.	doubtful	9	n.d.	OA
7 [§]	51	m	5-10 cgts	neg.	Flour	+ (slgE, SPT)	60.6	59.1%	n.d.	n.d.	25	pos.	OA
8 [§]	29	m	Never	pos.	Triticale	+ (SPT)	111.1	77.3%	pos.	n.d.	47	pos.	OA
Difficult to interpret (work-related but non-significant FeNO increase of at least 20 ppb)													
9	39	w	Ex	pos.	MDI	neg.	99.6	74.5%	neg.	neg.	16	neg.	Early-onset OA
10	35	m	Ex	neg.	HDI	neg.	110.9	76.9%	neg.	neg.	16	neg.	No OA

Positive controls

Abbreviations: BHR, bronchial hyperresponsiveness; cgts, cigarettes; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; HDI, hexamethylene diisocyanate; IgE, immunoglobulin E; MDI, methylene diisocyanate; n.d., not done; OA, occupational asthma; SIC, specific inhalation challenge; slgE, specific IgE antibodies; SPT, skin-prick test.

[§]Cases published earlier^{12,13}

TABLE 3 Characteristics and diagnostic results of subjects with suspected occupational asthma without increases in FeNO of 20 ppb or more

ID	Age	Sex	Smoking	Atopy	Agent	Agent-specific sensitization	FEV ₁ % pred.	FEV ₁ /FVC	BHR	SIC	Agent used for SIC	Baseline FeNO [ppb]	Serial FEV ₁	Final diagnosis
11	40	w	15 cgts.	neg.	Cobalt	neg.	86.1	57.5%	pos.	pos.	Cobalt	13	pos.	OA
12	24	m	Never	neg.	Plastic dust/Formaldehyde	neg.	94.5	67.5%	pos.	n.d.	-	16	pos.	Early-onset OA
13	59	m	Never	neg.	Grain dust	neg.	94.1	77.8%	neg.	n.d.	-	11	neg.	No OA
14	55	w	Never	pos.	Dusts	n.d.	101.6	76.7%	pos.	n.d.	-	21	neg.	No OA
15	48	m	Ex	neg.	Plastics, chemicals	neg.	111.0	81.4%	neg.	neg.	TDI	11	neg.	No OA
16	24	m	Never	neg.	Baking allergens	neg.	114.7	87.4%	neg.	n.d.	-	4	neg.	No OA
17	28	m	Never	neg.	Lacquers	neg.	104.3	83.1%	pos.	neg.	HDI	25	n.d.	OA
18	34	m	Ex	pos.	Silica dust	neg.	78.3	72.3%	n.d.	n.d.	-	20	n.d.	No OA
19	33	m	Never	pos.	Chemicals	n.d.	100.6	67.7%	pos.	n.d.	-	44	pos.	No OA
20	64	m	Ex	neg.	Isocyanates	neg.	105.4	72.6%	pos.	n.d.	-	5	neg.	No OA
21	46	w	Never	neg.	Horse stable dust	neg.	112.4	82.5%	pos.	neg.	Hay, stable dust	23	neg.	No OA
22	52	m	Ex	pos.	Isocyanates	neg.	54.3	64.6%	pos.	n.d.	-	27	neg.	No OA
23	60	m	5 cgts.	pos.	Detergent enzymes	+ (slgE, SPT)	91.9	63.8%	pos.	n.d.	-	6	n.d.	OA

Positive control

Abbreviations: BHR, bronchial hyperresponsiveness; cgts, cigarettes; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; HDI, hexamethylene diisocyanate; IgE, immunoglobulin E; n.d., not done; OA, occupational asthma; SIC, specific inhalation challenge; slgE, specific IgE antibodies; SPT, skin-prick test; TDI, toluene diisocyanate.

In contrast, subjects with work-related FeNO increases showed slightly higher baseline FeNO values (median, 20.5 vs 16 ppb) and more often baseline FeNO values 25 ppb or more (50% vs 23%). However, these differences were not significant ($P > 0.2$). On the basis of all available information and examinations, out of the 12 subjects with negative or missing SIC and without any FeNO increase at work, three subjects (nos. 12, 17, and 23 in Table 3) were rated as OA cases (in one case early-onset OA) in the overall expert rating.

3.1 | Description of single cases

One example of positive control (positive SIC) is a 43-year-old nonsmoking forklift operator with work-related respiratory symptoms who was on sick leave for 2 months (no. 1 in Table 2). The transfer to another factory hall had not resulted in an improvement of the complaints. He had been exposed to methylene diphenyl

diisocyanate (MDI) and OA was confirmed by a positive SIC with MDI. As shown in Figure 1A,B, FeNO values were significantly lower in the last days off work than those at work (maximum: 114 ppb), but work relatedness was not reflected in the FEV₁ measurements.

Because the subject was absent from work for a long time, the initial small FeNO increase observed during the work-free period (Figure 1A: days 5-7) was inexplicable. On request it was discovered that during this time a staircase was installed in the worker's private house and strong-smelling glue had been used. FEV₁ measurements were performed by the subject (nonsequentially) only on 32 instead of 45 days. While in the progression graph (Figure 1C), there is a clear decrease in FEV₁ on day 23, the statistical analysis of the grouped values off and at work did not show any significant differences (Figure 1D). On the basis of these results, the worker was advised to give up his job on the basis of a positive SIC and positive serial FeNO measurements.

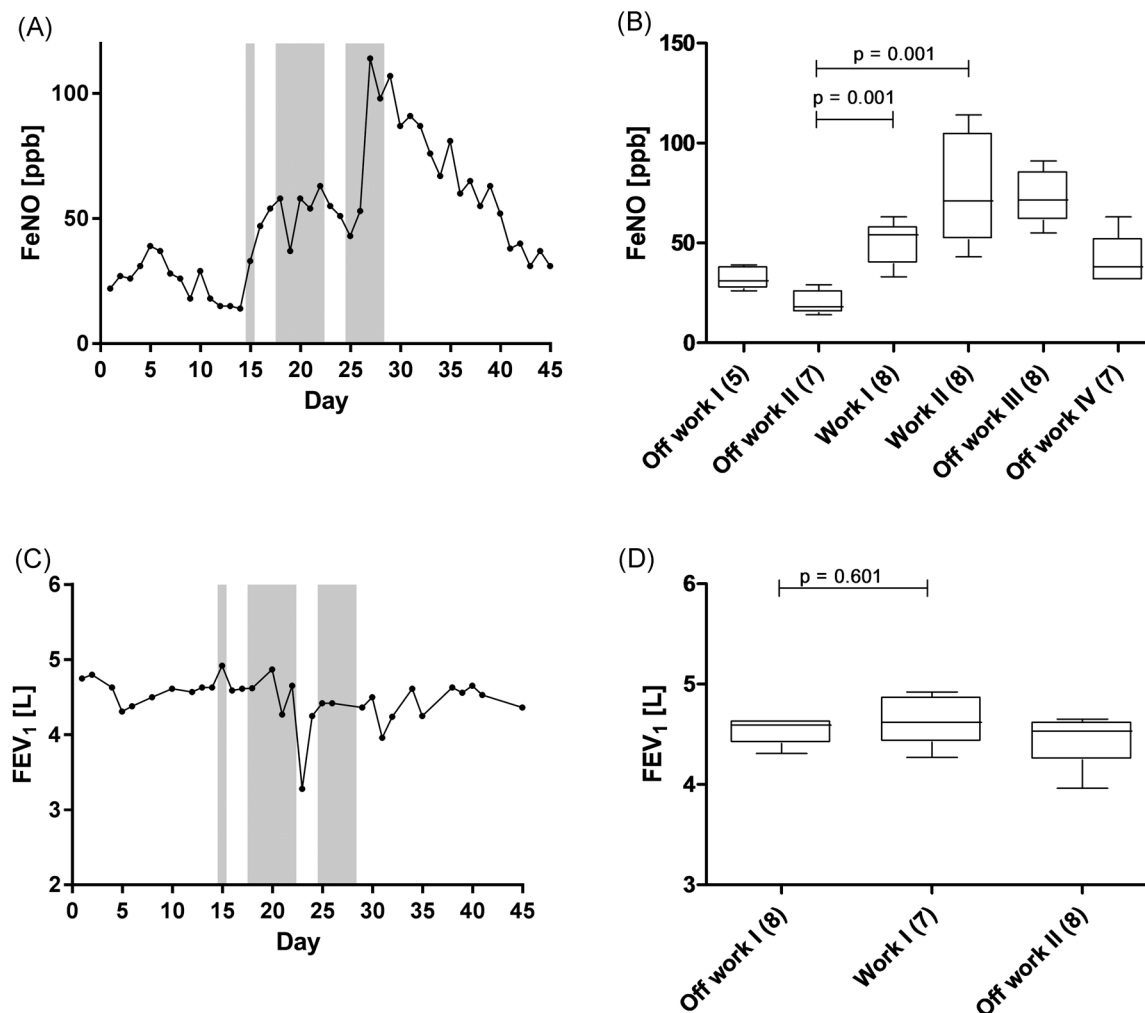


FIGURE 1 Subject no. 1 in Table 2: Serial daily measurements of FeNO (A) and FEV₁ (C—subject omitted FEV₁ measurement on 13 nonsequential days) in a forklift operator at work (gray areas) and off work. This subject showed a positive SIC with methylene diphenyl diisocyanate (MDI) and served as a positive control. Box-plots represent median and fifth to 95th percentile distributions of FeNO (B) and FEV₁ (D) grouped as weeks off and at work. Numbers in brackets indicate the number of considered days. Values from the last week off work were compared with those from a work week using the Mann-Whitney test. FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; SIC, specific inhalation challenge

An example of a negative SIC but positive serial FeNO test is a 55-year-old bakery shop assistant (no. 4 in Table 2). The female subject had suffered from hay fever since adolescence and had developed work-related perennial rhinoconjunctivitis and asthma. She showed sensitization to wheat and rye flour (sIgE, both CAP class 2), with stronger responses to grass and tree pollen (both CAP class 5). SIC with rye flour was negative. The observation time started with a period at work. However, Figure 2A,C show a decrease in FeNO and a small increase in FEV₁ after cessation of exposure. For both parameters, the grouped values of the last work week and the second week off work were significantly different (Figure 2B,D). This case was accepted as an occupational disease by the workers' compensation board on the basis of the positive serial FeNO and FEV₁ measurements, despite a negative SIC test. Approximately 1 year after exposure cessation, the patient reported an improvement in her symptoms.

In a further case, a significant FeNO increase was observed after day 41, while during the first 40 days, no significant changes in FeNO off and at work were detected. Importantly, on day 41 an accidental exposure to "chemicals" (probably isocyanates) occurred after maintenance work. In another case (no. 10 in Table 2), FeNO was modified by infections which may occur off and at work (data not shown in detail).

4 | DISCUSSION

In a recent study, it was shown that the results of FeNO measurements before and after SIC with occupational agents are highly predictive of OA.⁷ In addition, cross-shift FeNO measurements of 150 spice mill workers showed a delayed increase in FeNO 24 hours after exposure to elevated inhalable spice dust on

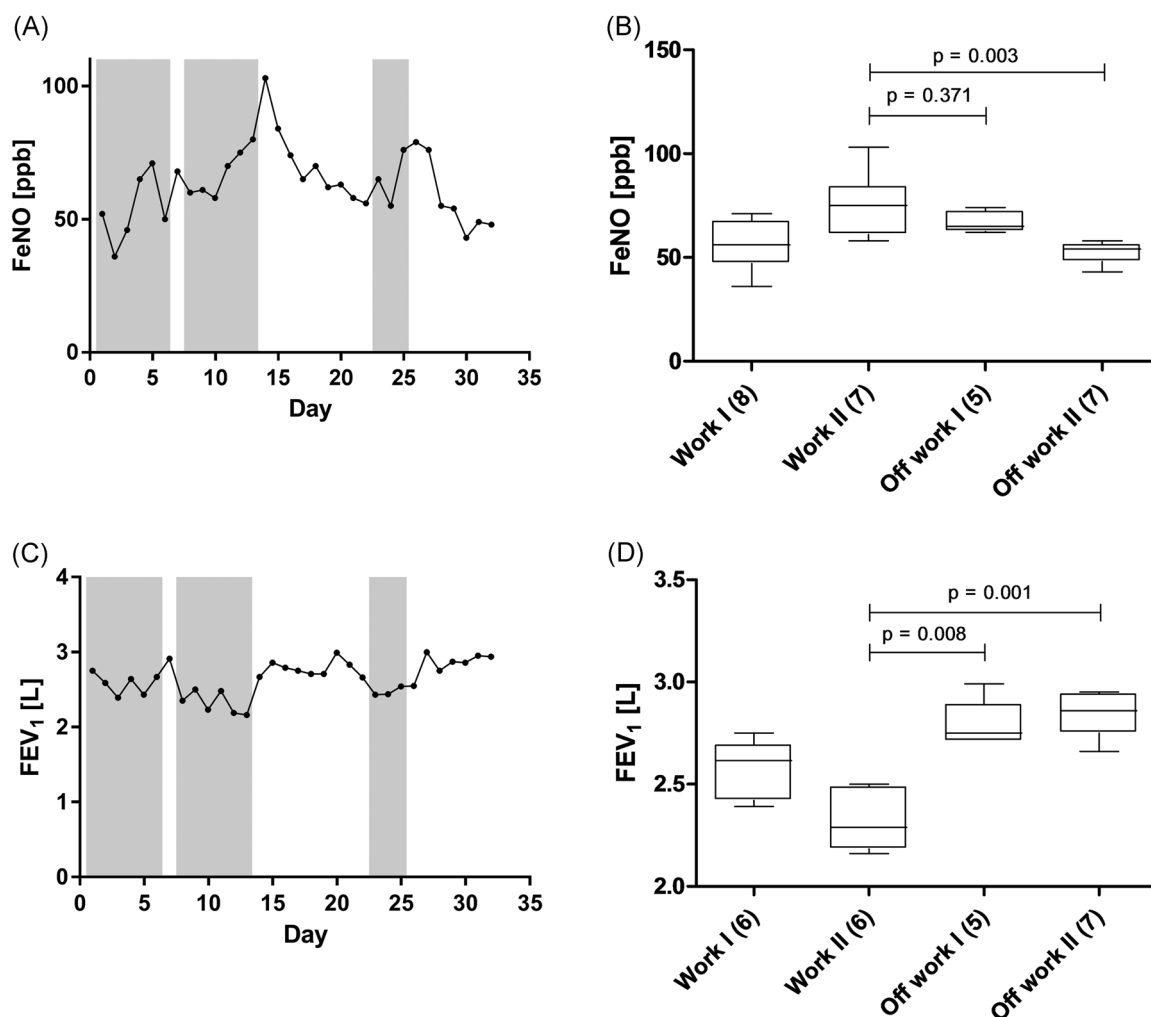


FIGURE 2 Subject no. 4 in Table 2: Serial daily measurements of FeNO (A) and FEV₁ (C) at work (gray areas) and off work in a bakery shop assistant. The grouped values for both FeNO (B) and FEV₁ (D) of the last working week and the second week of holidays were significantly different. Box-plots represent median and fifth to 95th percentile distributions of FeNO (B) and FEV₁ (D) grouped as weeks off and at work. Numbers in brackets indicate the number of considered days. Values from the last week off work were compared with those from a work week using the Mann-Whitney test. FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; SIC, specific inhalation challenge

commencement of the work week preceded by an exposure-free 48 hours of no work during the weekend.²⁴

Therefore, it was plausible to assess the diagnostic value of serial measurements of FeNO off and at work for the diagnosis of OA, especially since it also allows testing in the case of complex exposures where simulation of occupational exposure in the laboratory is not possible. A further advantage of serial measurements may be the repetitive exposures at work, which may result in higher sensitivity than single allergen exposures commonly used in SIC.²⁵

To date, there are limited data on the use of this method in literature, thus we chose daily measurements in order not to miss relevant short-term changes. On the basis of the findings of previous studies with cut-offs of 13 ppb⁷ and 17.5 ppb,⁹ a FeNO increase of 20 ppb or more as the criterion for a positive response was used. This slightly higher cutoff was chosen to ensure the highest possible specificity in this study which was supplemented by a higher number of measurements but also potentially encountered a higher number of possible confounders than during SIC.

The advantages of serial FeNO measurements must be weighed against their technical effort, as well as the restriction on those subjects who are still at work. The major result of this study is that considering serial FeNO measurements together with other available information enabled a positive diagnosis of an additional six (17%) of 35 subjects with negative/doubtful or missing SIC, although in 10 of the 35 cases the FeNO measurements could not be evaluated due to missing data. The expert rating that was performed by an experienced occupational physician taking into account all available information may be criticized, but it is difficult to obtain a valid gold standard for diagnosing OA, especially in cases where a SIC could not be performed. Furthermore, other authors reported these difficulties in "real life" of occupational medicine practice and confirmed the importance of experienced and trained occupational health physicians for a precise final diagnosis of OA.²⁶ Although this study shows that serial FeNO measurements may help to diagnose OA in individual cases, an estimation of the precise number of false-negative cases or calculations of sensitivity and specificity cannot be made. One reason for this is that the results of the serial FeNO measurement were taken into account during expert rating of the final diagnosis.

The optimal design of a study which aims to introduce a new diagnostic tool for the diagnosis of OA would be to compare the results of this tool (here, serial FeNO measurements) in subjects with positive and negative SICs. However, the question is whether it is ethically acceptable to instruct subjects with positive SIC to perform serial FeNO measurements at work. Especially since the subjects have to agree with this additional investigation which does no longer serve for the diagnosis and keeps them longer at work for study purposes. Thus, serial FeNO measurements in SIC-positive subjects are only indicated in certain circumstances, for example, to demonstrate the relevance of ubiquitous allergens at the workplace or for subjects with exposure reduction but ongoing work-related symptoms.

The lack of increase in serial FeNO concentrations in half of the six subjects with a positive SIC corroborates the finding that FeNO before and after SIC has low sensitivity in subjects with diagnosed OA.^{7,9} The reasons for this are many, but the asthma phenotype of each subject seems to play a role. Piipari et al²⁷ showed that FeNO increase mainly occurred in subjects with late asthmatic reactions and elevated FeNO baseline levels. However, since the results of recent studies^{7,9} showed that baseline FeNO was not significantly associated with an increase in FeNO above the cutoff after SIC and that the absolute FeNO values performed slightly better than relative values, in the present study the baseline FeNO was not factored into assessing the increase in FeNO.

Previous studies have also observed that the increase in FeNO may depend on the type of allergen. While in the study of Lemiere et al⁹ a FeNO increase was associated with asthmatic reactions induced by high-molecular-weight (HMW) agents, other authors found a significant association with low-molecular-weight (LMW) agents.²⁸ In the present study, increases in FeNO occurred only with substances known to induce immunologic OA, thus the detection of new responsible allergens after a complex exposure was not possible. It could be shown that both LMW and HMW allergens may induce FeNO increase. A significant difference in the baseline FeNO levels between subjects with and without work-related increases in FeNO was not detectable in the present study. However, this finding could be limited by the low number of subjects. In addition, regarding a lack of FeNO increases it is relevant to note that workers may not always be exposed on a regular basis, but rather sporadically, for example, during specific activities or production steps.

False-positive results of serial FeNO measurements due to respiratory infections or nonoccupational allergen exposure may also occur. Both findings demonstrate the importance of accurate documentation of working hours, symptoms, and leisure activities during the study period. In addition, these diverse potential confounders make clear that a standardized statistical algorithm of serial FeNO measurements is not possible, and that the individual course of the FeNO measurement has to be interpreted separately for each subject.

Serial measurements of FEV₁ were missing in 12% of the study participants, most probably due to the more demanding performance of FEV₁ measurement. Out of the eight subjects with positive results in serial FeNO measurement and a final OA diagnosis, only four showed positive results in serial FEV₁ measurement. Hewitt et al¹⁴ have presented a case with absent changes in peak flow but work-related increases in FeNO. However, the evaluation of the usefulness of the serial FEV₁ measurements for the diagnosis of OA was not the primary aim of this study.

While the performance of FeNO measurement is simple, the compliance with the measuring scheme (at least 2-weeks off work and an immediately subsequent 2-week work period), regarding regularity, as well keeping the exact documentation is arduous. Overall, only half of all study participants were able to comply with the predefined scheme. In addition, 23% of the data sets could not be evaluated due to missing values. Thus, serial FeNO measurements are complex, time-consuming, and sometimes difficult to interpret.

Independent of the mentioned difficulties and pitfalls, serial FeNO measurements, off and at work, provided complementary information for the diagnosis of OA in about one-fifth of cases with suspected OA. However, the combination of all available results and information seems to be the best strategy for the diagnosis of OA, especially when SIC cannot be performed.

5 | CONCLUSION

Serial FeNO measurements at home and at work could be considered in subjects with missing, doubtful, or negative SIC but work-related airway symptoms. A prerequisite is ongoing exposure to potential airway sensitizing substances at work. In this study the consideration of serial FeNO measurements together with other available information enabled a positive diagnosis in six of 35 subjects with suspected OA.

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CONFLICT OF INTERESTS

The authors are employed at the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (IPA), which is financed by the German Social Accident Insurance (DGUV) and which is also an Institute of the Ruhr University of Bochum.

DISCLOSURE BY AJIM EDITOR OF RECORD

Rodney Ehrlich declares that he has no conflict of interest in the review and publication decision regarding this article.

AUTHOR CONTRIBUTIONS

RM and VVK participated in conception and design of the study, in the analysis and interpretation of data and drafting the article. RM and TB performed the collection of medical data and TB assisted in drafting the manuscript. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICS APPROVAL AND INFORMED CONSENT

The Ethics Committee of the Ruhr University Bochum gave the approval to perform the study and all subjects gave written informed consent.

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