

Cross-shift Reduction in Fractional Exhaled Nitric Oxide among Cement Workers

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Abstract

Objective: Assessment of changes in fractional exhaled nitric oxide (FENO) across the shift was performed among cement production workers and controls. FENO was used as a possible marker of eosinophilic inflammation in the airways. In addition, the relations between personal total dust exposure and FENO changes across the work shift were examined.

Methods: Pre-and post-shift FENO levels were determined among 55 non-smoking dust exposed cement production workers and among 31 non-smoking mineral water factory workers as controls. The FENO levels were examined for three consecutive days among the exposed and two consecutive days among controls. Personal total dust levels were collected in the breathing zone of each participant using cellulose acetate filters on the first day of FENO examination. A three-piece Millipore cassette was used to place the filters and the cassette was connected to a Side Kick Cassella pump at a flow rate of 2 l/minute.

Results: There was a statistically significant reduction in FENO levels among exposed workers, but not among controls. The reduction in FENO levels among the exposed was observed on each day of FENO examination. The cross-shift reduction in FENO levels among the exposed did not show possible associations with personal total dust exposure levels ($r=-0.175$, 95% CI: -0.36, 0.04). The geometrical mean for total dust exposure were 8.3 mg/m³ and 0.28 mg/m³, among exposed workers and controls, respectively.

Conclusion: The results show a cross-shift reduction of FENO among cement workers and indicate that dust exposure is not associated with this finding. The reason for the reduction in FENO across the shift is unknown. Researchers in this field should be aware of potential unknown confounders when performing future studies.

Keywords: Cement; Dust exposure; Airway inflammation; Fractional exhaled nitric oxide; Cross-shift

Introduction

Studies on respiratory health among cement workers have shown that cement dust exposure is likely to result in adverse respiratory effects. A study among 4265 European cement factory workers showed higher prevalence of respiratory symptoms and reduced dynamic lung volumes among dust-exposed cement factory workers compared to administrative workers [1]. A study among highly exposed Ethiopian cement production workers shows a reduction in lung function and an increase in chronic respiratory symptoms among the exposed than among controls [2]. Furthermore, cross-shift reduction in peak expiratory flow rate, forced expiratory volume in 1 second (FEV1) and the ration between FEV1 and forced vital capacity (FVC) ratio after an 8 h exposure to cement dust have been observed in previous studies [3,4]. Previous studies among cement workers in Tanzania have reported high prevalence of respiratory symptoms, reduced forced expiratory volume in 1 second (FEV1), reduced forced vital capacity

(FVC), and increased prevalence of chronic obstructive pulmonary disease (COPD) [5,6]. Despite these previously reported health effects of cement dust exposure, the underlying mechanisms are still unknown. Activation of inflammatory responses following exposure to cement dust has been suggested in previous studies. An experimental study reported stimulation of tumor necrosis factor α (TNF- α) production in rat alveolar macrophages following exposure to cement dust [7]. Studies on biomarkers of inflammatory response among cement workers are scarce and the results are not clear [8,9]. A study among Norwegian cement workers found an increase in percentage of neutrophils and interleukin levels in induced sputum of cement exposed workers [9].

As fractional exhaled nitric oxide (FENO) can be used as a possible marker of inflammatory responses [10], studies on FENO among cement workers have been performed to evaluate whether an inflammatory response is present. One of these studies among cement production workers showed a significant reduction of FENO, not an increase, when baseline levels were compared with FENO levels 32 hours later [11], but this study did not have a control group. Another

study found no difference in FENO levels between non-smoking cement production workers and non-smoking controls at the end of the day shift [12]. Thus, it is not clear whether eosinophilic inflammatory responses may occur following exposure to total dust among cement workers.

Therefore, this study aimed at assessing possible cross-shift changes in FENO dust exposed among cement production workers compared with non-exposed mineral water factory workers as controls. Furthermore, we determined possible associations between total dust exposure levels and changes in FENO across an 8 hour shift.

Methods

Study design and setting

The cross shift study was conducted among cement production workers (exposed) and mineral water factory workers (controls) in 2011, Dar es salaam, Tanzania. The cement factory had a total of 495 workers. Of these, 411 worked in the production section. The mineral water factory is located in the same city as the cement factory. The mineral water factory had a total of 679 workers. Of these, 349 worked in the manufacturing section. The shift arrangements for workers in the cement factory were in three 8h work-shifts: morning, afternoon and night shifts. Controls had day and night shifts (12 hr shift), each shift operating for two days consecutively.

Study participants

The study involved only males because due to lack of females in the production line in the cement factory. We invited 171 exposed workers and 82 controls. The response rate for the invited workers was 78.4% among exposed workers (n=134) and 76.8% among controls (n=63).

Participants eligible for FENO examinations were non-smokers, they had been off work for at least two days before the first day of FENO examination, had no history of childhood or current asthma, and had no history of chronic obstructive airway disease. Totally, 103 exposed workers and 41 controls fulfilled the criteria above. Four to five of the eligible participants were daily selected at random for FENO examination using the participants' list and the workers' day shift list. The FENO examinations were performed in a period of four weeks among exposed workers and in a period of two weeks among controls. A total of 60 exposed workers and 31 controls were randomly selected for FENO examination. Five exposed workers refused FENO examination, thus remaining 55 and 31 participating exposed workers and controls, respectively.

Interviews on participants' background information and eligibility for FENO examination were conducted by the first author using structured Swahili questionnaire. The information obtained the interview included age and level of education (primary education or higher education levels). Information regarding duration of employment in the factory, work section and whether they had worked in other dusty industries previously were obtained. In the cement factory, were asked if they usually wore respiratory protective equipment (RPE) during work (yes/no). Participants were asked whether they had ever been treated for (yes/no): chest injury or operation on the chest, heart disease, bronchitis, pneumonia, pulmonary tuberculosis, and asthma. Furthermore, the use of medications for chest treatment such as steroids (yes/no) or any other medications was asked.

Smoking was assessed by asking whether participants had ever-smoked cigarettes (yes/no), currently smoking cigarettes (yes/no), and the duration since the participant had stopped cigarette smoking (less than 1 year/more than 1 year). Participants who were current smokers or those who had stopped smoking within less than 1 year prior the study were categorized as smokers. Never-smokers or those who had stopped smoking more than 1 year prior the study were categorized as non-smokers.

Exposure assessment

We assessed personal total dust levels on each worker on the first day of participation in FENO examinations. The dust samples were obtained from the breathing zone of each participant. Pre-weighed 37 mm cellulose acetate filters, pore size of 0.8 μ m, were placed in a three-piece Millipore-cassette. The cassettes were connected to SKC pumps (Sidekick Casella; SKC Limited, Blandford Forum, U.K.) at a flow rate of 2.0 l/min. Calibration of the SKC pumps was done daily before dust sampling using a rotameter. A sampling checklist was used to record flow rates at start and stop, and the sampling time. The average dust sampling durations were 371 min (range: 221–463 min) and 293 min (range: 97–432 min) among exposed workers and controls, respectively. Gravimetric analysis for personal total dust level was conducted using a Mettler scale AT 261 at the Eurofins laboratory (Eurofins Products Testing, Denmark). A total of two and three dust samples among exposed workers and controls, respectively, were not analysed due to low pump flow rate.

Fractional exhaled nitric oxide

FENO was examined before the workers started (Pre-shift) and after the workers stopped working (post-shift). FENO examinations (in parts per billion, ppb) were conducted using a hand held electro-chemistry based device (Niox Mino[®], Aerocrine AB, Solna, Sweden) for three days consecutively among exposed workers and two days consecutively among controls. FENO examination device was pre-calibrated by the manufacturer, hence there were no further calibrations needed when collecting data.

FENO examinations were performed in accordance with the American Thoracic Society/European Respiratory Society procedure, [13] with the exception only measurement was needed for each participant when using the hand held analyzer due to high reproducibility of this method [14,15]. Each participant exhaled through an automatically closing velum at a flow rate of 50 ml/s. Weight in kilograms was measured using a weighing scale and height was measured in centimeters. Participants were advised not to take food or drink some beverages within one hour before the FENO examination were conducted [13]. Rooms provided at the Health and Safety Office in the cement factory and in a dispensary in the mineral water factory were used for FENO examinations. Room nitric oxide (room-NO) was examined before pre-shift examinations were conducted every day, and random measurements were taken before post-shift FENO examinations. The examination rooms did not differ in pre- and post-shift room-NO.

Statistical analysis

Total dust exposure and FENO levels were loge-transformed. Geometric Mean (GM) for total dust exposure and FENO were obtained using descriptive statistics. Comparison of total dust

exposure between exposed workers and controls was conducted using independent t-test.

Pre and post-shift FENO were compared using paired t-test on each day of examination among exposed workers and controls, respectively. Mixed effects model analyses were used in comparing pre- and post-shift FENO, respectively, for all days of examination between exposed workers and controls, using examination time (pre-shift=0 or post-shift=1) and day of examination (day=1, 2 or 3) as fixed factors, while personal identity number (ID number) was used as a random factor. Comparison of pre- and post-shift FENO among exposed workers and controls, respectively, was conducted using group (exposed=1 or controls=0), day of examination and height as fixed factors, while ID number was used as a random factor.

A change in FENO across the shift for each day of examination was assessed by subtracting pre-shift FENO from post-shift FENO (Post-shift FENO - Pre-shift FENO). The arithmetic mean (AM) for the cross-shift change in FENO was also calculated.

Correlation between total dust exposure and the cross-shift change in FENO on the first day of examination was assessed using correlation test. Linear regression analysis was conducted to assess possible associations between personal total dust exposure and the cross-shift change in FENO. The linear regression analysis included all FENO

changes among exposed workers and controls on the first day of examination. In the regression analysis, FENO change on the first day of examination was used as a dependent variable adjusting for age and height. A similar regression analysis was repeated among the exposed workers alone. Variables were included in the linear and mixed effects models, respectively, when the significance level was less than 0.2 (p<0.2). Data was entered and analyzed using IBM SPSS Statistics version 19 for Windows. A statistical significance was set at 95% confidence interval (CI).

Results

Study participants

There was no significant difference in baseline characteristics between exposed workers and controls. However, the controls had lower education level but were taller than the exposed workers (Table 1). The proportion of workers who reported using respiratory protective equipment (face masks) among the exposed workers was high (98%). All participants did not have history of childhood or current asthma and/or history of heart diseases, and none used any medication for chest treatment during the study.

Variable	Exposed (N=55)			Controls (N=31)		
	AM (SD)	Median	Range	AM(SD)	Median	Range
Age(years)	34 (9)	32	21-57	34 (7)	34	23-53
Duration of employment(years)	6.4 (7.5)	3.2	1-32	8.3 (6.7)	6	1-27
Height(m)	1.63 (0.8)	1.62	1.44-1.80	1.66 (0.7) [¶]	1.66	1.54-1.79
Weight(kg)	68 (13)	65	46-110	66 (13)	66	47-102
	n(%)			n(%)		
Primary school only	35 (64)			26 (84) [§]		
Non-smokers	55 (100)			31 (100)		
Use of RPE	54 (98)			-		

N: total number; n(%): number(percentage); AM(SD): arithmetic mean (standard deviation);[¶]independent t-test, (p=0.024); [§] χ^2 Test (p=0.033)

Table 1: Characteristics of study participants among exposed and controls.

Total dust exposure

Total dust exposure level among exposed workers and controls was 8.3 mg/m³ (range: 0.31-4500) and 0.28 mg/m³ (range: 0.05-1.80), respectively (Table 2). Cement mill workers had the highest exposure

(GM: 11.1 mg/m³). However, there was no significant difference in dusts exposure levels between the sections in the cement factory. Among exposed workers, the proportion of dust exposure levels above the recommended value [13] of 10 mg/m³ was 43%.

Category	nw	ns	AM (SD)	Range	GM (GSD)	TLV >10	p
Controls	28	28	0.39 (0.4)	0.05-1.80	0.28 (2)	0	Ref
All exposed	53	53	101 (616)	0.31-4500	8.30 (5)	23 (43)	<0.001 [†]
Crusher	11	11	423 (1352)	0.31-4500	6.51 (17)	4 (36)	<0.001 [§]
Crane	2	2	6.4 (3)	4.2-8.6	6.0 (1.7)	0	0.057 [§]

Kiln/RM	4	4	6.35 (4)	2.4-12	5.38 (2)	1 (40)	0.003 [§]
Cement mill	12	12	19 (16)	0.7-48	11.1 (4)	7 (58)	<0.001 [§]
Packing	24	24	18 (25)	1.1-110	8.85 (5)	11 (46)	<0.001 [§]

Nw, number of workers; ns, number of samples; AM(SD), arithmetic mean (standard deviation); GM(GSD), geometric mean (geometric standard deviation); [†]independent t-test between exposed and controls; [§]ANOVA test between controls and the different sections in the exposed group; TLV>10 =dust levels above the Threshold Limit Value of 10mg/m³ for particles not otherwise specified; p, significance level

Table 2: Personal total dust exposure (mg/m³) among controls and exposed cement workers.

Fractional exhaled nitric oxide

Post-shift FENO levels were lower than pre-shift FENO on each of the three days of examination among the exposed workers (t-test; p<0.001, p=0.001, p=0.003, respectively), but not for the two days among controls (t-test; p=0.078, p=0.823, respectively). The cross-shift reduction in FENO among exposed workers was significant among those who participated in pre- and post-shift FENO examinations for at one day, and for those who completed all FENO examinations (Table 3). The overall AM (standard deviation, SD) for the reduction in FENO

among exposed workers (n=134) and controls (n=55) was -3.16 (8.8) ppb and -0.64 (4.7) ppb, respectively. Mixed effects model analyses for all FENO values among the exposed workers and controls, separately, indicated significantly lower post-shift FENO than pre-shift FENO among exposed workers ($\beta=0.12$, 95% CI; 0.064 to 0.18), but not among controls ($\beta=0.05$, 95% CI; -0.04 to 0.14). Age, day of examination, duration of employment and height did not enter the mixed effects model (p>0.2).

Day	Exposed (N=55)									Controls (N=31)								
	Pre-shift FENO			Post-shift FENO			Change in FENO			Pre-shift FENO			Post-shift FENO			Change in FENO		
	n ^a	GM (GSD)	Range	n ^b	GM (GSD)	Range	AM	Range	p [†]	n ^a	GM (GSD)	Range	n ^b	GM (GSD)	Range	AM	Range	p [†]
1	55	20 (2.1)	5-162	48	18 (2.1)	5-159	-4	-23, 6	0.001	31	16 (1.8)	5-71	29	14 (1.9)	5-77	-1	-6, 11	0.078
2	46	20 (2.0)	5-102	42	18 (2.1)	5-90	-3	-33, 9	0.001	27	15 (2.0)	5-62	26	15 (1.7)	6-70	0	-13, 11	0.823
3	47	19 (2.1)	5-147	43	16 (2.1)	5-82	-5	-65, 16	0.003	NA								
1	31 [‡]	20 (2.2)	5-162	31	18 (2.2)	5-159	-3	-23, 6	0.023	24 [‡]	16 (1.9)	5-71	24	15 (1.9)	5-77	-1	-11, 6	0.338
2	31 [‡]	20 (2.1)	5-102	31	18 (2.1)	5-90	-3	-33,9	0.002	24 [‡]	15 (1.9)	5-62	24	15 (1.8)	6-70	-1	-13, 6	0.617
3	31 [‡]	20 (2.3)	5-147	31	17 (2.2)	5-82	-5	-65,16	0.033	NA								

FENO: fractional exhaled nitric oxide; N: total number of participants; n^a: number of pre-shift FENO participants; n^b: number of post-shift FENO participants; GM (GSD): geometric mean (Geometric standard deviation); ppb: parts per billion; †: paired t-test between pre- and post-shift FENO; ‡: participants who performed a total of six FENO measurements among exposed and four FENO measurements among controls during examination period; NA: Not applicable.

Table 3: Pre-and post-shift FENO (ppb) measurements among exposed cement workers among controls.

We found no association between individually measured total dust exposure obtained on the first day of examination and the cross-shift reduction in FENO among exposed workers and controls (n=77) (Pearson correlation, r=-0.175, 95% CI; -0.36, 0.04). In a linear regression analysis including the exposed workers and controls, total dust exposure, age and height had no effect on the cross-shift change in FENO (p>0.2). In a similar linear regression analysis among the exposed workers only, while adjusting for age there was no association between the cross-shift decrease in FENO on the first day of examination and total dust exposure.

Discussion

We found a cross-shift reduction in FENO among cement workers that was not related to the cement dust exposure. Our results are partly in line with a study among Norwegian cement production workers [11]

where a reduction of 2 ppb of FENO was reported when baseline FENO values were compared to those measured 32 hours later. However, dust exposure level in the Norwegian study was lower than in our study, and the study showed no significant difference between pre and post-shift FENO values measured on the same day among Norwegian cement workers.

The reduction in FENO among exposed workers can possibly be explained by cross-shift decrease in PEF, FEV1 and FVC [3,4,11] following acute dust exposure, due to possible constriction of airways [16] thus causing lower FENO output. Another possible explanation for cross shift reduction in FENO among exposed workers can be due to impairment of IL-8 (Interleukin 8) release from epithelial cells that may be exerted by cement particles, [15] thus affecting trans membrane eosinophil migration due to failure of IL-8 activated neutrophils mobilization; [17] hence reducing FENO production.

However, the lack of correlation between personal dust exposure and decrease in FENO indicates that the cement dust might not be the cause of the decrease in FENO. Other unknown factors might have influenced the results, such as local food habits in the cement factory, which could be different from the control factory. Other studies are needed to obtain more information about the workers to find the cause of the decrease in FENO.

Another possible explanation for the reduction in FENO across the shift could be due to diurnal variations in FENO. However, this explanation is less likely, since there was no cross-shift reduction in FENO in the control group. Also, the lower post-shift FENO compared to pre-shift FENO is in contrast with previous studies which indicate higher FENO values in the afternoon than in the morning [18-21], and also with studies which have reported lack of any diurnal variation in FENO [22,23]. To our knowledge, there are no other studies assessing cross-shift changes in FENO among cement production workers and controls.

The use of a control group and inclusion of only non-smokers strengthen our study. Moreover, we accounted for age, previous diseases, day of examination, height and sex in the analysis. Examination of FENO after study participants have been off work for at least two days reduced the effects of previous dust exposure at work. In addition, measurement of personal total dust exposure levels on the first day of FENO examination allowed exploration of possible associations between individually measured total dust exposure and the cross-shift decrease in FENO occurring on same day. However, the dust exposure levels were assessed on the first day of FENO examination only, thus associations between FENO and the subsequent days of examination could not be determined. The use of RPEs may have reduced the strength of association between dust exposure, thus affecting possible inflammatory changes in the airway, and possibly the magnitude of cross-shift FENO reduction. However, disposable masks (type FFP1) that are considered to be inefficient in protection against dust exposure were used by cement workers. Other limitations of our study include lack of skin prick test and serum Immunoglobulin E to identify atopic individuals. However, exposed workers and controls were located in the same geographical area, thus it is likely that both were exposed to the same risk of allergy development, hence minimizing bias due to the effect of atopy. Also, workers with childhood or current asthma were not included in this study.

The consistent and statistically significant cross-shift reduction in FENO poses questions that need explanations. Also, it is unclear whether the decrease is of any clinical relevance. Both pre- and post-shift FENO mean values were below 25 ppb, indicating a lack of eosinophilic inflammation. Further population studies of FENO are needed to address to the present findings. It seems that there is an unknown factor present in this group of workers, influencing their respiratory health. This should be considered when performing future studies on respiratory health among cement production workers.

Conclusion

Our results indicate a cross-shift reduction in FENO among cement production workers that does not seem to be associated with the cement dust exposure. The reason for the reduction in FENO is not known.

Ethical Consideration

The study was approved by Muhimbili University of Health and Allied Sciences Research and Publications Committee in Tanzania, and the Regional Committee on Medical and Health Research Ethics West in Norway and the. Participants gave written informed consent. Information about each study participants was not disclosed to the employers.

Authors' Contributions

AMT planned the study, collected and analyzed data, and revised the manuscript after consultation with the other authors. MB, SHM and BEM participated in planning, data collection and data analysis, provided scientific support throughout the study and reviewed the manuscript. All authors have read and approved the final manuscript for publication.

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Competing Interests

The authors declare that they have no competing interests.

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