

Bronchoalveolar mastocytosis and lymphocytosis after nitrogen dioxide exposure in man: a time-kinetic study

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ABSTRACT: The combination of environmental chamber exposure and bronchoalveolar lavage (BAL) was used to study the time-course of the cell response in the human lung to nitrogen dioxide (NO₂). Healthy subjects were exposed for 20 min to 7 mg NO₂·m⁻³ (4 ppm), a concentration which occurs indoors in industries and is below the peak exposure limit for work places in most countries, 10 mg·m⁻³ (5.5 ppm). BAL was performed in all subjects several weeks before exposure and 4, 8, 24 and 72 h after exposure, in eight subjects at each time. Mastocytosis and lymphocytosis were found in BAL fluid 4-24 h after exposure, with normalization after 72 h. A mild increase in lysozyme positive macrophages was found 24-72 h after exposure. The time-course of the human pulmonary cell response to NO₂, demonstrated in BAL fluid, represents a new and previously not reported finding after exposure to this common air pollutant. Our findings are diverging from results obtained in animal studies, using approximately the same NO₂ concentrations, indicating that the results from the animal studies may not be transferable to man.

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Much attention has been focussed on the role of nitrogen dioxide (NO₂) as a causative agent of morbidity in respiratory disease. This air pollution is most common in urban and suburban areas. It is mainly emitted from traffic and various industries, but also occurs in homes using gas-fired appliances. The highest concentrations are encountered in work places in chemical plants and industries using combustion processes. Pulmonary effects of NO₂ in man have mainly been studied with epidemiological methods [1-5] and tests of lung function and airway responsiveness in inhalation experiments [6-10]. Whereas increased airway resistance has been demonstrated in healthy subjects after short-term exposure with 2.9 mg NO₂·m⁻³ [7, 8], asthmatics have been found to respond to concentrations below 1 mg·m⁻³ [9, 10].

Bronchoalveolar lavage (BAL) has recently been included as an instrument in investigations of intrapulmonary effects of NO₂ in man. Increased lavage levels of α₂-macroglobulin and impaired inactivation of influenza virus were demonstrated after exposure to 1.1 mg NO₂·m⁻³ for 3 h [11, 12].

Decreased α₁-protease inhibitor activity in bronchoalveolar lavage fluid (BALF) was found 3.5-4 h after

3 h exposure with 5.4 and 7.2 mg NO₂·m⁻³ [13]. While no cellular changes were reported in these studies, we have found mastocytosis and lymphocytosis in a recent dose-response study with BAL 24 h after exposure to 4, 7 and 10 mg NO₂·m⁻³ (2.25, 4.0 and 5.5 ppm) [14]. Thus, inflammatory cell responses were found in BALF even below the peak exposure limits for work places which, in most countries, is around 10 mg NO₂·m⁻³.

The noxious effects of NO₂ have largely been attributed to its oxidating and free radical properties [15-18]. The cellular mechanisms involved in the pathogenesis of NO₂-induced lung effects are not known. We reasoned that studying the cell response pattern in BALF over a period of time after exposure to NO₂, including the early and late phases of response, could yield valuable information on the reactive processes in the human lung induced by NO₂. Therefore we have performed this time-kinetic study on changes in the cell population in the lungs after NO₂ exposure, as reflected in BALF. The exposure level is based on conditions in work places and results from recent BAL investigations [13, 14]. The time intervals are based on a dose-response study with BAL after NO₂ exposure and a time-kinetic study with BAL after SO₂ exposure [19].

Table 1. — Cell numbers and albumin concentrations in bronchoalveolar lavage fluid 4, 8, 24 and 72 h after controlled chamber exposure with 7 mg NO₂·m⁻³. The values are expressed as median with interquartile range.

	Total cells × 10 ⁷ ·l ⁻¹	Lymphocytes × 10 ⁷ ·l ⁻¹	%	Macrophages/monocytes × 10 ⁷ ·l ⁻¹	%	Lysozyme positive macrophages/monocytes × 10 ⁷ ·l ⁻¹	% of macrophages	Neutrophils × 10 ⁷	%	Mast cells × 10 ⁴ ·l ⁻¹	%	Albumin mg·l ⁻¹
Before exposure	n=32 8.0 6.6–12.4	0.6 0.4–1.4	7 5–12	7.2 5.5–11.6	91 86–92	0.8 0.4–1.8	12 6–16	0.10 0.04–0.16	1 1–2	2.8 0.8–10.0	0.03 0.03–0.08	41 29–51
4 h after exposure	n=8 9.2 7.4–11.7	1.7* 1.3–1.9	20** 13–23	7.2 5.7–10.1	78* 77–86	0.9 0.6–1.0	12 8–14	0.08 0.06–0.18	1 1–2	14.5** 11.1–19.1	0.15** 0.10–0.22	34 30–42
8 h after exposure	n=8 11.3 8.5–16.8	1.2* 0.6–3.8	10* 7–20	9.7 5.9–15.2	89* 79–92	1.0 0.7–2.0	13 9–14	0.13 0.07–0.24	1 1–1	7.1* 3.8–30.0	0.08 0.03–0.26	33 22–60
24 h after exposure	n=8 7.9 6.7–9.0	1.4* 0.7–2.0	16* 12–24	6.4 5.0–7.6	79* 68–85	0.8 0.7–1.1	14* 11–18	0.14 0.9–0.18	2 1–2	11.7* 6.9–13.6	0.14*** 0.11–0.22	48 42–55
72 h after exposure	n=8 8.8 7.9–12.0	0.8 0.7–3.2	10 7–29	7.1 6.4–8.1	90 70–92	1.3 0.9–2.2	16* 14–28	0.09 0.08–0.12	1 1–1	11.7 7.3–27.4	0.12 0.07–0.29	42 39–73

*: p<0.05; **: p<0.01; ***: p<0.001.

Methods

Subjects

We evaluated the pulmonary response to NO₂ in 32 healthy, nonsmoking male volunteers with a mean age of 25 yr (range 21–37 yr). All were free from symptoms of airway infection within at least six weeks prior to the study and none had a history of asthma. Pre-exposure dynamic spirometry was normal in all subjects. Informed consent was obtained from the subjects and the study was approved by the Ethics Committee of the University of Umeå.

Design of the study

Environmental chamber exposure to 7 mg NO₂·m⁻³ (4 ppm) for 20 min was performed in all subjects. The exposure protocol had previously been described in detail [20]. This included light work on a bicycle ergometer with a work load of 75 W during the last 15 min of the exposure, and recordings of symptoms and dynamic spirometry. Flexible fiberoptic bronchoscopy with BAL was performed 3 weeks or more before NO₂-exposure in all subjects in order to obtain reference BALF (table 1). Re-examination with BAL was performed 4, 8, 24 and 72 h after the end of exposure to NO₂. At each time, eight subjects were re-examined. Each subject was used as his own reference in calculations of changes in the BALF content, after exposure compared with before exposure.

Nitrogen dioxide exposure

The exposure chamber has recently been described in detail [20]. Ambient air was drawn continuously through the chamber at 150 m³·h⁻¹, resulting in one air exchange approximately every six min. During the exposures the chamber air temperature was kept at 21°C. The relative humidity was 45% as measured with an RH&T indicator HMI 14, Vaisala. The desired NO₂ concentration in the exposure chamber was achieved by adding a gas stream from a tube containing 1% NO₂ gas into the chamber air inlet. The gas flow was maintained evenly by a Mass Flowmeter, Brooks 5850 Tr. The chamber air was continuously analysed with a direct indicating equipment, Nitrogen oxides analyser 8440 B, Monitor Labs.

Bronchoalveolar lavage

The method of flexible fiberoptic bronchoscopy with BAL and the processing of the BALF has previously been described in detail [21]. In short, all BAL were performed by one investigator under local anaesthesia with lidocaine together with atropine as a pre-medication. Four boluses of 60 ml phosphate buffered saline (PBS-A) at 37° were infused in the right middle lobe and gently suctioned back to a siliconized vessel placed in ice water. The fluid was chilled during all

processing steps. Cytocentrifugal specimens were stained with May-Grünwald-Giemsa for standard differential counts, acid toluidine blue counterstained with Mayer's acid haematoxylin for mast cells [22] and Lysozyme[®] antibody and immunoperoxidase technique for lysozyme positive macrophages. The ratio T-helper/cytotoxic-suppressor cells was determined using Simultest T Helper/Suppressor Test[®]. Albumin was measured with electroimmuno assay [23] change.

Statistics

Wilcoxon's non-parametric signed rank test for paired observations was used for comparison of BAL parameters before and after exposure. A p-value of <0.05 was considered significant.

Results

Bronchoscopy

Normal tracheal and bronchial mucosa were found in all subjects at the bronchoscopy before exposure. All subjects examined 4 and 8 h after exposure had a prominent mucosal erythema in the trachea and main bronchi. A mild erythema was observed in these areas in four of the eight subjects examined 24 h after exposure while all subjects examined at 72 h displayed a normal mucosa.

Bronchoalveolar lavage

The median amount of recovered BALF at the pre-exposure BAL was 75% with an interquartile range of 67–77%. No significant differences in the amount of recovered BALF was found at the various times after exposures. The counts for eosinophils, neutrophils, epithelial cells, total cell number and T-helper/suppressor-cytotoxic cell ratio was not significantly affected after different exposures. Eosinophil counts were never above 2% and neutrophil counts never above 4% of the total cell counts in BALF. The cell counts for total cells, neutrophils, lymphocytes, alveolar macrophages/monocytes and mast cells are given in table 1. The relative changes in cell numbers after exposure are given in figure 1, expressed as ratio after/before exposure.

Mastocytosis was found in the recovered BALF 4, 8, and 24 h after exposure ($p < 0.01$ – 0.05). No significant elevation of mast cells was found at 72 h.

The total number and the percentage of lymphocytes of all cells was significantly increased 4 h after exposure ($p < 0.02$ and $p < 0.05$ respectively). The increase remained 8 and 24 h after exposure ($p < 0.05$) while no significant elevation was found at 72 h.

The significant decreases of alveolar macrophages in percent of all cells 4, 8 and 24 h after exposure were due to the corresponding increases in other cells. The total macrophage counts were not significantly changed.

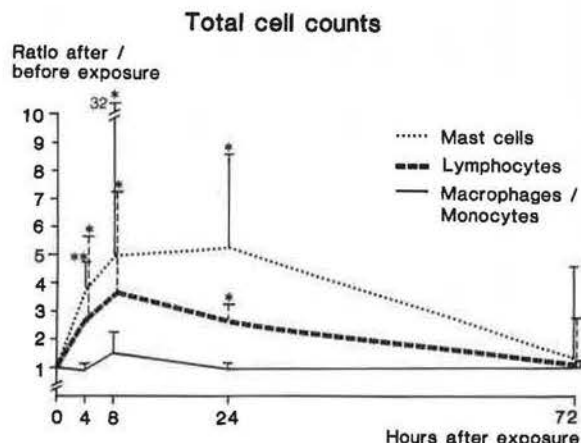


Fig. 1. — The relative changes in total cell counts for mast cells, lymphocytes and macrophages before exposure compared with 4, 8, 24 and 72 h after 20 min exposure to 7 mg NO₂. The values are expressed as ratio of the respective total cell counts after/before exposure. *: $p < 0.05$ **: $p < 0.02$

A tendency to increase in lysozyme positive macrophages in percent of all macrophages was found 8 h after exposure ($p = 0.052$). A modest but statistically significant increase was found at 24 h and this persisted even 72 h after exposure ($p < 0.05$ respectively).

Albumin concentrations in BALF were not significantly altered after exposures.

Spirometry

Lung function recordings with Vitalograph[®] immediately after exposure and before BAL showed small and non-significant decreases in FEV₁ < 8% of initial values.

Symptoms

An unpleasant smell and very mild irritation in the nose and throat were reported during exposure.

Discussion

An inflammatory cell response was found in BALF from healthy volunteers after 20 min exposure to 7 mg·m⁻³ NO₂ during light bicycle ergometer work. This finding is supported by a recent dose-response study in our laboratory, with BAL after different NO₂ concentrations [14]. Apart from these two studies, there are, to our knowledge, no published reports of data on inflammatory cell response to NO₂ *in vivo* in man. In the present study, we found lymphocytosis as early as 4 and 8 h after exposure. This is in conflict with a study by MOSHENIN and GEE [13] where no cell changes were found in BALF 4 h after a 3 h exposure with 5.4 and 7.2 mg NO₂·m⁻³ (3 and 4 ppm). However, they lavaged their subjects only once, *i.e.* after exposure, and the findings were compared with a small separate control group. We believe it to be advantageous to use each subject as his

own control because of the inter-individual differences in BALF cell counts. The total cell counts in BALF were lower in the above mentioned study compared with studies in our laboratory [14, 19, 21, 24]. Difference in BAL technique and processing of the recovered fluid may therefore also be responsible for the differences between the studies. In two recent studies by FRAMPTON *et al* no cell changes were found in BALF after exposure to 1.1 mg NO₂·m⁻³ (0.6 ppm), which is probably due to the low exposure concentration. The lymphocytosis that we found in BALF was not associated with changes in the Leu₃a+/Leu₂a+ (helper/cytotoxic) T-cell ratio, which is in agreement with previous studies with NO₂ and SO₂ exposure in our laboratory [14, 19, 21, 24]. We consider the lymphocytosis to be an unspecific inflammatory response.

The mastocytosis that was demonstrated in the present study is in agreement with our preceding investigation [14]. Mast cell stains were, however, not used in the three previously discussed BAL studies in man [11–13]. Even though mastocytosis has been demonstrated in BALF after exposure to both NO₂ [14] and SO₂ [19, 24], its role in the inflammatory cell response to air pollutants is unclear. The mast cell has clearly been shown to have chemotactic properties in IgE mediated reactions, such as asthma [25, 26], but the pattern of cell response to NO₂ and SO₂ does not resemble that type of reaction. It remains to be shown whether the mast cells are immunologically active and may play a chemotactic role in the pulmonary response to air pollutants. Even though the physical presence of mast cells in the bronchoalveolar airspaces after NO₂ exposure is a recent finding [14], involvement of mast cells has previously been suggested in a study where increased airway resistance after NO₂ exposure was blocked by antihistamine [27]. Mastocytosis and rupture of mast cells following NO₂ exposure has, furthermore, been observed in a morphologic study in rodents [28].

The modest but significant increase in lysozyme positive macrophages is in agreement with our preceding study [14]. Even though the macrophage is an immunologically highly capable cell, the late appearance of response, *i.e.* a modest increase in lysozyme positive macrophages at 24–72 h, probably indicated a minor role in the pathogenesis of NO₂-induced inflammation. It is interesting to see that there is a significant difference in the bronchoalveolar cell response between the poorly water soluble gas NO₂, which is believed to be deposited peripherally and the highly water soluble gas SO₂ with its pronounced proximal deposition. The response in the alveolar macrophages was considerably less pronounced after exposure to NO₂ than after SO₂, where macrophages constituted the largest part of the total cell increase in BALF [19, 21, 24]. It has previously been shown that increased lysozyme production may occur in macrophages after a variety of stimuli [29–31]. We believe that the increase in lysozyme positive macrophages that has been demonstrated after both SO₂ and NO₂ exposure is an unspecific response to noxious stimuli.

Neutrophilia has been a prominent finding in studies of lung morphology and BAL in rodents [32–35] and increased neutrophil chemotaxis has been demonstrated after *in vitro* challenge of human macrophages [36]. Neutrophils have, however, still not been demonstrated to be significantly involved in the response in human lungs to occupational concentrations of NO₂.

Numerous animal studies have investigated the effects of long term exposure to relatively high NO₂ concentrations but relatively few studies have investigated the effects of short-term exposure with low levels of NO₂ (table 2) [28, 33–35, 37]. Only two studies have reported use of mast cell staining. One reported mastocytosis and signs of degranulation [28] while the other was not able to confirm this [32]. Neutrophilia, macrophage increase and occasionally lymphocytosis have been

Table 2. – Animal studies with changes in inflammatory cell numbers after nitrogen dioxide exposure.

Exposure concentration	Exposure duration	Lymphocytes	Neutrophils	Macrophages	Mast cells	Animal	Histologic/BAL examination	Reference
0.5–1 ppm	1 h	nr	nr	nr	+	Rat	Histologic	[28]
12–27 ppm	28 h	nr	+	+	0	Syrian hamster	Histologic/BAL	[32]
7–30 ppm	24 h	nr	+	+	nr	Syrian hamster	Histologic	[33]
30 ppm	48h–6w	+	+	+	nr	Rat	Histologic/BAL	[34]
28 ppm	6–48 h	nr	+	+	nr	Syrian hamster	Histologic	[35]
2+17 ppm	24–72 h	nr	nr	0 - +	nr	Rat	Histologic	[37]

+ = increase; 0 = unchanged; nr = not reported

demonstrated in both histological and BAL cell examinations [32–35]. The partly conflicting results, compared with the present study, could be due to species differences and differences in exposure level and time. Anatomy and size of airways may give different deposition patterns of NO₂ compared with humans. In rodents, cells from central airways are lavaged which may partially mask more peripheral changes in cell numbers. Differences in duration of exposure and time between exposure and BAL in the animals may also be of importance. The relatively high concentrations of NO₂ used in several animal studies may have induced severe toxic lung effects that are qualitatively different from what may occur in man at the presently studied concentrations. We find it difficult to transfer the knowledge from previous animal studies to humans.

It is interesting to note the similarities between NO₂ and SO₂ regarding the time-kinetic response for mast cells and lymphocytes, as demonstrated in BALF [14, 19, 21, 24]. Four hours after exposure inflammatory response had been induced by both gases with peak cell counts occurring after 8–24 h. The magnitude of the mast cell and lymphocyte increases caused by the gases was also relatively similar, in the investigated dose intervals. The magnitude of the macrophage response differed considerably between the two gases, as discussed above. Furthermore, SO₂ caused an early increase in lysozyme positive macrophages that had ceased 72 h after exposure, while NO₂ caused a late increase that persisted at 72 h.

In the present study we did not find any significant change in FEV₁ and FVC. Earlier studies [6–8] have shown increased airway resistance after exposure to similar NO₂ concentrations. It is probable that more sensitive equipment would have revealed an increased airway resistance in our studies as well.

It is concluded that mastocytosis and lymphocytosis were found in BALF 4–24 h after exposure to 7 mg NO₂·m⁻³. A mild increase in lysozyme positive macrophages was found 24–72 h after exposure. The consequences of the inflammatory response demonstrated after a brief exposure to an NO₂ concentration below the peak exposure limit of most countries remains to be established. Our findings do not support the hypothesis that the inflammatory changes demonstrated in animal models after NO₂ exposure are directly transferable to humans.

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Mastocytose et lymphocytose broncho-alvéolaire après exposition au NO₂ chez l'homme: une étude de cinétique dans le temps. T. Sandström, M. C. Andersson, B. Kolmodin-Hedman, N. Stjernberg, T. Ångström.

RÉSUMÉ: Pour étudier le développement dans le temps de la réponse cellulaire du poumon humain au dioxyde d'azote (NO₂), nous avons utilisé la combinaison d'une exposition dans une chambre environnementale et du lavage broncho-alvéolaire. Des sujets sains ont été exposés pendant 20 minutes à 7 mg de NO₂/m³ (4 ppm), concentration qui existe à l'intérieur dans certaines industries et est inférieure à la limite d'exposition de pointe pour les lieux de travail dans la plupart des pays: 10 mg/m³ (5.5 ppm). Le lavage broncho-alvéolaire a été exécuté chez tous les sujets plusieurs semaines avant l'exposition, ainsi que 4, 8, 24 et 72 h après l'exposition, chaque fois chez huit sujets. La mastocytose et la lymphocytose ont été décelées dans les liquides de lavage alvéolaire de 4 à 24 h après l'exposition, avec une normalisation après 72 h. Une légère augmentation des macrophages lysozyme positifs a été décelée de 24 à 72 h après l'exposition. Le décours de la réponse cellulaire pulmonaire humaine au NO₂, démontré dans le lavage alvéolaire, représente une observation nouvelle non rapportée jusqu'ici, après exposition à ce polluant commun de l'air. Nos observations divergent des résultats obtenus dans les études animales, utilisant approximativement les mêmes concentrations de NO₂, ce qui indique que les résultats chez l'animal peuvent ne pas être valables chez l'homme.

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