

Pulmonary Inflammatory Mediators After Sevoflurane Anaesthesia in Tobacco Smoking and Non-Smoking Patients

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Abstract: *Purpose:* Volatile anaesthetics modify pulmonary immune and inflammatory reactions per se and in smokers anaesthetics appear to suppress the immune and inflammatory responses. Our hypothesis was that a more reduced amount of inflammatory responses would be observed in the smoking patients than in the non-smoking patients during surgery under sevoflurane anaesthesia.

Methods: We compared pulmonary inflammatory responses in 20 non-smokers and 9 smokers during prostatectomy under sevoflurane anaesthesia. Bronchoalveolar lavage (BAL) fluids were collected after anaesthesia induction and at the end of the surgery.

Results: Non-smokers demonstrated higher BAL LTC₄ concentrations than smokers postoperatively. Smokers had a tendency to have increased IL-6 and IL-8 concentrations after surgery whereas the opposite was observed in non-smokers, contradicting our hypothesis.

Conclusion: Pulmonary inflammatory mediators differ slightly between smokers and non-smokers during surgery under sevoflurane anaesthesia. Most likely these mediators have minor relevance to the postoperative pulmonary complications in smokers.

Keywords: Volatile anesthetics, sevoflurane, inflammation, cytokine, leukotriene, nitric oxide, bronchoalveolar lavage, prostate cancer.

INTRODUCTION

Tobacco smoking is a significant risk factor for postoperative pulmonary complications [1] and for intensive care admittance [2]. Exposure to tobacco smoke reduces the number of cilia [3] and during general anaesthesia smokers have both increased intraoperative excretion volume [4] and slower bronchial mucus transport [5] than non-smokers. These factors are known to be associated with postoperative atelectasis [6] which may delay the recovery and predispose to pneumonia [7].

Anaesthetic agents seem to suppress pulmonary immune responses [8]. The pulmonary inflammatory responses are attenuated further when anaesthesia is combined with previous smoke exposure [9, 10]. The suppressed pulmonary inflammatory responses may contribute to the susceptibility of smokers to develop pulmonary complications, as an adequate proinflammatory response is necessary for example in

pneumonia to prevent bacteraemia [11]. In addition, also volatile anaesthetics are known to modulate the inflammatory responses [12]. We have previously observed significant increases in BAL leukotriene C₄ (LTC₄), nitrate (NO₃⁻), and nitrite (NO₂⁻) concentrations [13] and decreased gene expression of tumour factor- α (TNF- α) and interleukin-1 β (IL-1 β) [14] after sevoflurane anaesthesia when compared to thiopentone anaesthesia.

The main purpose of this study was to compare the pulmonary inflammatory responses in smoking and non-smoking patients during sevoflurane anaesthesia. Our hypothesis, based on previous studies after smoke exposure [9, 10], was that a more reduced amount of pulmonary inflammatory responses would be observed in the smoking patients than in the non-smoking patients undergoing major surgery under sevoflurane anaesthesia.

MATERIALS AND METHODOLOGY

This study protocol was approved by the hospital Ethics Review Committee. After written informed consent, 33 patients scheduled for total prostatectomy due to prostate cancer were recruited.

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Inclusion criteria included: smoking history of more than 10 pack-years (daily cigarette consumption x number of years smoked) / 20 [2] and present smoking for the smoking group or non-smoking for at least 1 year preceding the study for the non-smoking group, scheduled to total prostatectomy, ASA physical status I-III, age 18-75 years and written informed consent from the patient. Preoperative exclusion criteria were: chronic or short-term use of anti-inflammatory medication (NSAID, COX-2 inhibitors or corticosteroids) preceding fourteen days prior to surgery, contraindication to the use of sevoflurane, history of serious mental illness, ASA physical status IV-V, viral or bacterial pneumonia during the last four weeks preceding surgery and chronic pulmonary disease. Pulmonary function tests were not performed before the surgery, thus leaving minor degree of COPD possibly undiagnosed. Intraoperative exclusion criteria were: adverse airway reactions, i.e. aspiration, bronchial obstruction, major blood loss (more than 50% of the estimated blood volume) with massive blood transfusion and hypothermia, defined as nasopharyngeal temperature less than 35 °C.

None of the smokers received nicotine patches perioperatively. All patients were premedicated with oral diazepam 10 mg. Before induction of anaesthesia, thoracic epidural catheter was placed at Th 9-10 or Th 10-11 level for postoperative analgesia. Epidural analgesia with 0.125% bupivacaine and fentanyl (0.01 mg.ml⁻¹) was commenced at a rate of 3 ml.h⁻¹ after the baseline sample collection and prior to surgery in all the patients. The infusion rate was kept constant throughout surgery. The epidural infusion was maintained for 2-3 days postoperatively.

Anaesthesia was induced with fentanyl (3 µg.kg⁻¹) and propofol (2 mg.kg⁻¹). Neuromuscular relaxation was achieved with rocuronium (1 mg.kg⁻¹). During induction of anaesthesia patients were breathing 80% oxygen in air. Anaesthesia was maintained with 0.7-1.5 Minimal Alveolar Concentration (MAC) sevoflurane in 40-60% oxygen in air and 1.5 l.min⁻¹ fresh gas flow to comply with peripheral arterial blood oxygen saturation > 95%. The actual exposure of the lungs to sevoflurane was determined by using the MAC hour concept (amount of anaesthetic gas equivalent to 1 MAC given over 1 hour). During surgery Ringer acetate was used as the maintenance fluid with an infusion rate of 10 ml.kg⁻¹.h⁻¹.

Ventilation was adjusted to maintain the end expiratory carbon dioxide (CO₂) between 4.0-4.5%. Used tidal volume was 6-8 ml.kg⁻¹ and respiratory rate was determined by the end expiratory CO₂. In all patients 4 cmH₂O positive end expiratory pressure was used.

Arterial blood pressure, heart rate and electro cardio graph (ECG), peripheral oxygen saturation (SpO₂) and end expiratory CO₂ were monitored continuously. Radial artery was cannulated after induction of anaesthesia for invasive blood pressure monitoring and sampling of blood for gas analyses (arterial partial pressure of oxygen (PaO₂) and arterial partial pressure of carbon dioxide (PaCO₂)) and leukocyte count and differential. Depth of anaesthesia was monitored using auditory evoked potentials (AEP) (AEP Monitor, Danmeter a/s, Odense, Denmark) and surgical anaesthesia was considered achieved when AEP A-line ARX-index (AAI) was below 20. Nasopharyngeal temperature was

measured continuously. Patients were kept normothermic using a heating blanket, warm fluids and a heating pad.

Bronchoalveolar lavage (BAL) was performed in all patients immediately after induction of anaesthesia and tracheal intubation. BAL was repeated upon completion of surgery while the patients were still under sevoflurane anaesthesia. The same individual performed both baseline and after the surgery BAL. The baseline BAL was performed according to predetermined randomisation code either to the right or left lung and the second BAL to the other side. Fiberscope was introduced into the trachea and the main bronchus through the tracheal tube. The bronchus was then lavaged three times with 20 ml of normal saline (0.9% NaCl). Harvested BAL fluid was placed into the sample tubes and placed on ice. Samples were then immediately transferred to the laboratory for centrifugation and the supernatant was then frozen immediately until further analysis. Inflammatory mediators, interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tumour necrosis factor-α (TNF-α), leukotriene C₄ (LTC₄), nitrite (NO₂⁻) and nitrate (NO₃⁻) were assessed from the BAL fluid.

Cytokines were quantified using a commercial immunoassay kit LINCoplexKIT (LINCO Research Inc., Millipore, Billerica MA, USA) and applying Luminex[®]100 system (Austin TX, USA). Sensitivities for the assays were 0.06 pg.ml⁻¹ for IL-1β, 0.10 pg.ml⁻¹ for IL-6, 0.11 pg.ml⁻¹ for IL-8, 0.15 pg.ml⁻¹ for IL-10 and 0.05 pg.ml⁻¹ for TNF-α.

LTC₄ was quantified by a commercial enzyme immunoassay kit (Cayman Chemical, Ann Arbor, MI, USA) according to the manufacturer's instructions. Nitrite and nitrate were quantified fluorometrically by a commercial assay kit (Cayman Chemical, Ann Arbor, MI, USA) according to the manufacturer's instructions.

Samples for number of leukocytes and leukocyte differentiation and blood gas analyses were obtained from the arterial blood. They were collected immediately after anaesthesia induction, during surgery at 1 and 2 hours and immediately before the second BAL and in the post anaesthesia care unit 2 hours after the surgery. Arterial blood samples for number of leukocytes and leukocyte differentiation were drawn into a tube containing ethylenediamine tetraacetic acid and analysed within 2 hours using an automatic analyser (Advia 120 Hematology System, Technicon Ltd., Tarrytown, NY, USA). Blood gas analysis was performed bedside using i-STAT[®] 1 (Abbott Laboratories, Abbott Park, IL, USA).

All variables, except BAL inflammatory mediator concentrations were normally distributed. SYSTAT 10.2 (SYSTAT software Inc, San Jose, CA, USA) statistical package was used for parametrical studies. Paired t-test and two way ANOVA were applied for comparison of airway pressure readings and number of leukocytes and leukocyte differentiation. These results are expressed as mean ± SD. Pearson's chi-square test was performed to compare the ASA class between the groups. The trends of changes of BAL inflammatory mediator concentrations were compared by classifying whether concentrations increased or decreased by the end of surgery. The comparison was performed using Pearson's chi-square test. Mann Whitney U was performed to compare the BAL inflammatory mediator concentrations between smokers and non-smokers and to compare the difference of

baseline and end of surgery BAL inflammatory mediator concentrations between smokers and non-smokers. Wilcoxon Signed Rank test was performed to compare the BAL inflammatory mediator concentrations between the baseline and end of surgery. These tests were performed using SAS/STAT 9.1 (SAS Institute Inc., Cary, NC, USA). These results are expressed as median (range; minimum-maximum). $P < 0.05$ was considered significant.

RESULTS

Altogether 13 patients were recruited in the smoking group where as the non-smoking group consisted of 20 patients. However, 4 smokers had to be excluded during the study due to anti-inflammatory medication. Thus the smoking group consisted of 9 patients. The demographic characteristics of the study groups were similar (Table 1). None of the patients were preoperatively diagnosed with chronic obstructive pulmonary disease or asthma.

Table 1. Characteristics of the Study Groups, Mean \pm SD

	Non-Smokers (n=20)	Tobacco Smokers (n=9)	P-Value
ASA II/ASA III	10 / 10	6 / 3	0.404
Age	61.1 \pm 6.1	59.4 \pm 5.9	0.513
Weight kg	85.0 \pm 10.7	85.8 \pm 10.3	0.847
Height cm	178.4 \pm 5.6	180.8 \pm 6.0	0.301
Duration of surgery min	180.3 \pm 40.7	174.2 \pm 18.7	0.589
Intraoperative fluids ml	3580 \pm 1696	3711 \pm 941	0.792
Blood loss ml	845 \pm 684	528 \pm 162	0.063

There were no statistically significant differences between the groups.

Despite monitoring the depth of anaesthesia by AEP and no difference in the duration of the surgery between the groups, there was a statistically significant difference in the MAC hour values between the non-smokers 2.6 ± 0.4 MAC hours and the smokers 3.0 ± 0.7 MAC hours, $P < 0.05$.

There were no differences during or after surgery in the blood pressure, heart rate, SpO₂, PaO₂ and PaCO₂ between the groups (data not shown). There were no differences in the tidal volume, breathing frequency, inspired fraction of oxygen or end tidal CO₂ between the groups.

In both groups the total numbers of leukocytes increased uniformly during surgery (Table 2). The increase in neutrophil count during surgery accounted for the increase in total leukocyte count in both groups. However, the increases in the total leukocytes and neutrophils were not statistically different between or within the groups. The smokers had a tendency for higher neutrophil count and lower lymphocyte count than the non-smokers.

There were no differences in the aspirated BAL sample volumes between the groups.

Most of the patients in both the smokers and non-smokers had BAL IL-1 β , TNF- α and IL-10 concentrations below the sensitivity level.

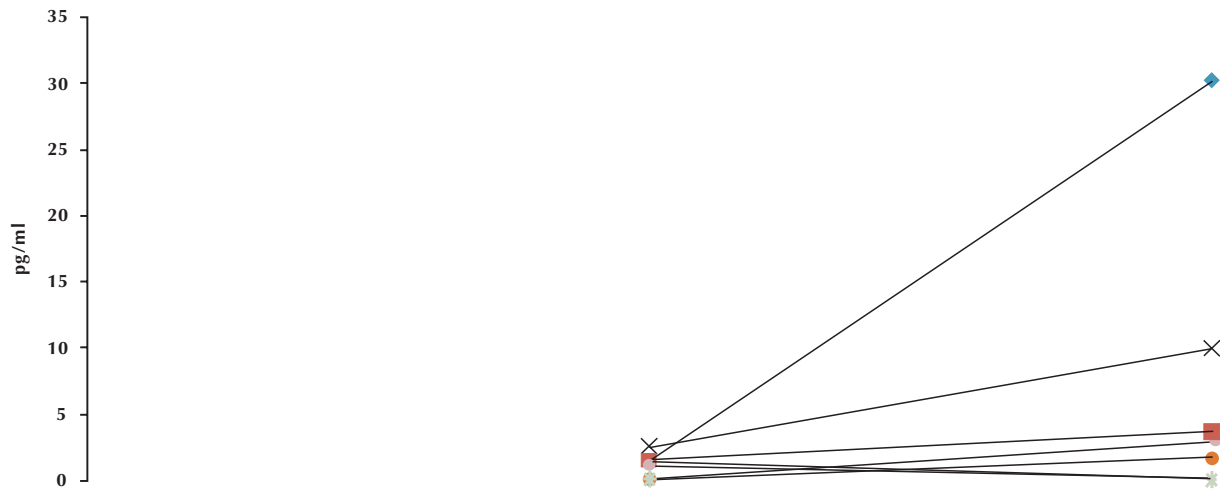
No differences were observed within or between the smokers and the non smokers in the preoperative and post-operative BAL IL-6 (Fig. 1) and IL-8 (Fig. 2) concentrations. BAL IL-6 increased in most of the smokers whereas BAL IL-6 decreased in most of the non-smokers, $P = 0.049$. However, the magnitude of the change in the concentrations was not statistically significant (Table 3). Similarly to IL-6, BAL IL-8 concentration increased in most of the smokers whereas

Table 2. Total Blood Leukocyte Count and Differential, Mean \pm SD. All the Values are $\times 10^6 \text{ l}^{-1}$

Leukocytes	Pre op	1 Hour	2 Hours	End of Surgery	Post op	Change %
Non-smokers	4.7 \pm 1.4	5.2 \pm 1.4	5.8 \pm 1.7	7.1 \pm 3.1	12.6 \pm 4.3	168 %
Tobacco smokers	5.7 \pm 1.8	6.4 \pm 2.0	6.9 \pm 1.9	8.5 \pm 0.9	13.1 \pm 1.7	130 %
Neutrophils	Pre op	1 Hour	2 Hours	End of Surgery	Post op	Change
Non-smokers	2.7 \pm 0.9 56.9 \pm 9.2 %	3.0 \pm 0.9 57.3 \pm 8.6 %	3.6 \pm 1.0 61.5 \pm 6.2 %	4.8 \pm 2.7 66.9 \pm 8.5 %	10.3 \pm 4.0 81.3 \pm 6.2 %	281 % 43 %
Smokers	4.0 \pm 1.2 64.1 \pm 6.1 %	4.5 \pm 1.9 65.2 \pm 8.8 %	4.6 \pm 1.8 65.5 \pm 7.9 %	6.2 \pm 1.0 72.7 \pm 5.0 %	11.3 \pm 1.7 84.0 \pm 2.2 %	183 % 31 %
Lymphocytes	Pre op	1 Hour	2 Hours	End of Surgery	Post op	Change
Non-smokers	1.5 \pm 0.5 31.5 \pm 9.6 %	1.6 \pm 0.5 30.9 \pm 7.1 %	1.7 \pm 0.7 28.7 \pm 5.4 %	1.7 \pm 0.6 24.8 \pm 7.3 %	1.5 \pm 0.5 12.1 \pm 3.9 %	0 % -62 %
Smokers	1.4 \pm 0.4 24.0 \pm 5.7 %	1.5 \pm 0.2 23.3 \pm 7.2 %	1.6 \pm 0.4 24.5 \pm 7.3 %	1.6 \pm 0.3 18.7 \pm 5.0 %	1.3 \pm 0.2 9.8 \pm 2.7 %	7 % -59 %
Monocytes	Pre op	1 Hour	2 Hours	End of Surgery	Post op	Change
Non-smokers	0.3 \pm 0.1 5.9 \pm 1.8 %	0.3 \pm 0.1 6.1 \pm 2.1 %	0.3 \pm 0.1 5.1 \pm 1.9 %	0.3 \pm 0.1 4.6 \pm 1.2 %	0.5 \pm 0.2 3.8 \pm 1.1 %	67 % -36 %
Smokers	0.4 \pm 0.1 7.2 \pm 1.7 %	0.4 \pm 0.1 6.8 \pm 1.9 %	0.3 \pm 0.1 5.8 \pm 1.3 %	0.4 \pm 0.1 5.1 \pm 1.2 %	0.6 \pm 0.2 4.4 \pm 1.1 %	50 % -39 %

There were no differences between non-smokers and tobacco smokers.

Pre- and postoperative IL-6 in smokers



Pre- and postoperative IL-6 in non-smokers

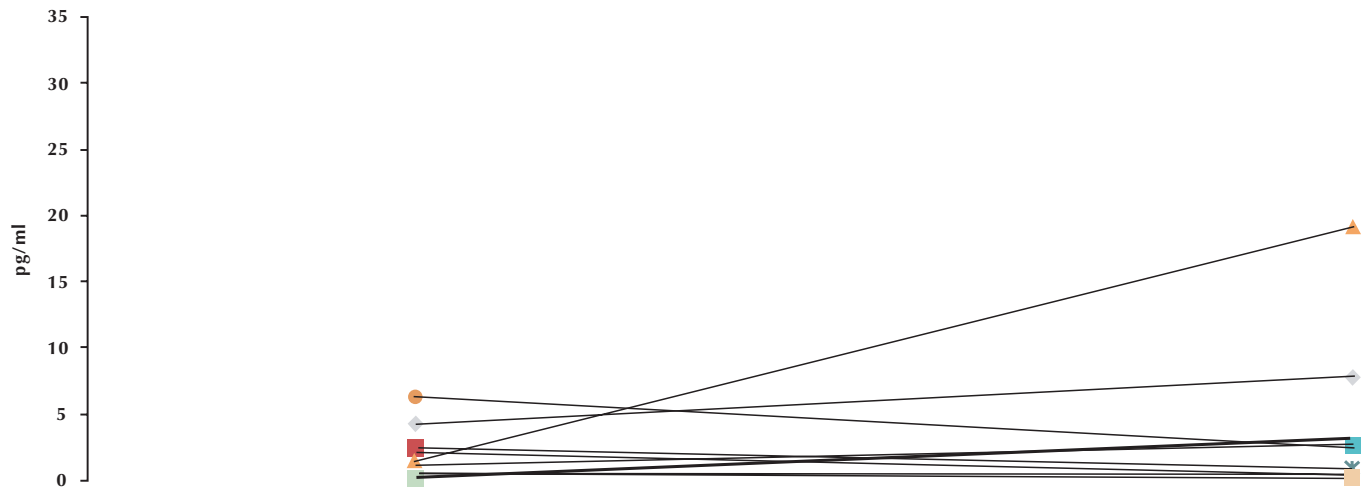


Fig. (1). Individual time course of IL-6 in smokers and non-smokers. IL-6 increased in 6 smokers and decreased in 3 smokers. IL-6 increased in 5 non-smokers and decreased in 14 non-smokers. In one of the non-smokers, there was no change in the IL-6 concentration, Pearson chi-square test, $P=0.049$.

BAL IL-8 decreased in most of the non-smokers, $P = 0.055$. The magnitude of the change in the concentrations, however, was not statistically significant (Table 3).

There were no differences between the preoperative and postoperative BAL LTC₄ concentrations within the smokers and non smokers. However, there was statistically significant difference between the non smokers and the smokers in the postoperative LTC₄ concentrations. The non-smokers had significantly higher postoperative LTC₄ concentrations than the smokers 170 (92-252) pg ml⁻¹ and 102 (46-234) pg/ml respectively, $P < 0.05$. This magnitude of the change of LTC₄ during the time course was also different between the groups, $P < 0.05$ (Fig. 3).

There were no differences in the preoperative or postoperative concentrations of NO₃ between or within the non smokers and smokers (Table 3). Although in most of the smokers NO₃ levels decreased and in most of the non-smokers NO₃ levels increased during the surgery, this was

not statistically different between the groups, $P = 0.094$. The concentration of NO₂ was undetectable in most of the patients.

Two patients in the tobacco smoking group developed a postoperative adverse event. One had pulmonary atelectasis and the other developed infectious abdominal haematoma.

DISCUSSION

The aim of our study was to investigate, whether the pulmonary inflammatory response would be less in smokers than in non-smokers under sevoflurane anaesthesia. Based on previous studies [9, 10] and our earlier observations [13, 14], the concentrations of proinflammatory cytokines (TNF- α , IL-1 β , IL-6 and IL-8), anti-inflammatory cytokine (IL-10), nitrous oxide metabolites (NO₃ and NO₂) and the 5-lipoxygenase pathway metabolite (LTC₄) were chosen for assessment of the inflammatory response.

Pre-and postoperative IL-8 in smokers



Pre-and postoperative IL-8 in non-smokers

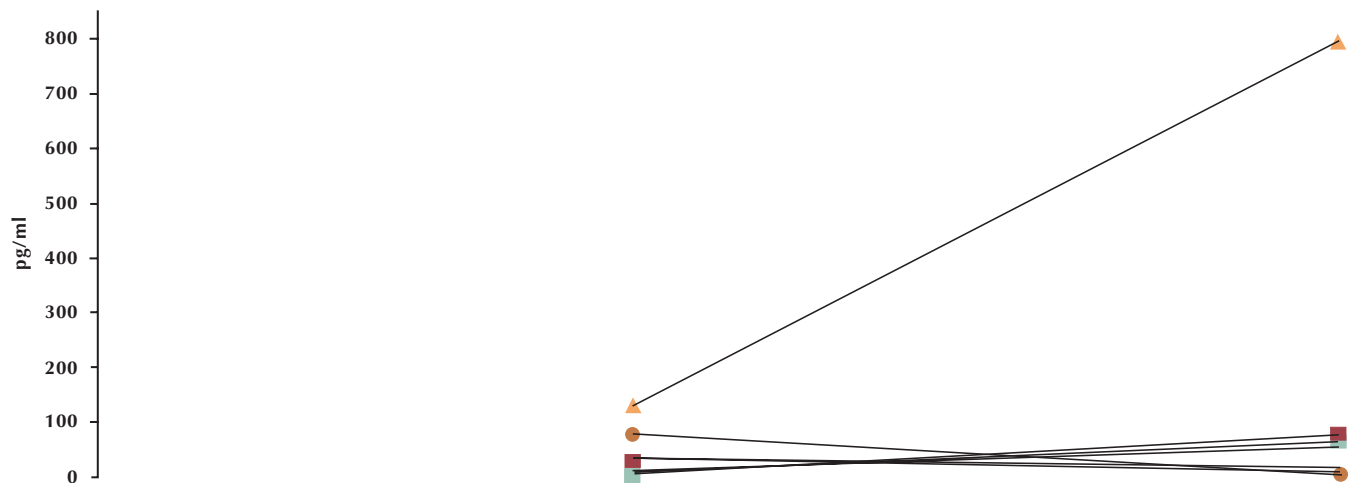


Fig. (2). Individual time course of IL-8 in smokers and non-smokers. IL-8 increased in 6 smokers and decreased in 3 smokers. IL-8 increased in 7 non-smokers and decreased in 13 non-smokers, Pearson chi-square test, P=0.055.

Table 3. BAL IL-6, IL-8 and NO₃. Concentrations (pg.ml⁻¹) Before and after the Surgery, Median (Range)

	IL-6 Pre op	IL-6 Post op
Non smokers	0.6 (0.07-6.29)	0.3 (0-19.1)
Smokers	1.2 (0-2.4)	1.8 (0.01-30.1)
	IL-8 Pre op	IL-8 Post op
Non Smokers	10.5 (2.43-129.1)	4.2 (0-793.3)
Smokers	22.8 (0-42.0)	32.5 (0.03-503.8)
	NO ₃ . Pre op	NO ₃ . Post op
Non smokers	1.3(0.1-5.6)	0.8 (0-7.7)
Smokers	4.2 (0-7.5)	0.9 (0-3.5)

Only minor differences in the pulmonary inflammatory mediators between the smoking and the non-smoking pa-

tients were detected. Smokers had a tendency of increased IL-6 and IL-8 concentrations after the surgery whereas non-smokers had an opposite tendency. Compared to the smokers, the non-smokers had significantly increased LTC₄ concentration after the surgery.

The cell sources of measured cytokines were not determined in our study. Neither the total cell number nor differentiation from BAL fluid were measured as previous reports have demonstrated increased number of total cells and macrophages in the BAL fluid of smokers compared with that of the non-smokers [15, 16]. Yet, alveolar macrophages from smokers seem to secrete less IL-1, IL-6 and TNF- α than those of non-smokers [15, 16]. The antimicrobial functions of alveolar macrophages decrease significantly and the gene expression of proinflammatory cytokines is suppressed in smoke exposed animals after halothane and isoflurane anaesthesia [9]. Similarly in smoking patients during propofol anaesthesia, the proinflammatory responses and antimicrobial activities of alveolar macrophages are attenuated [10, 17]. Differences between our study and these earlier studies

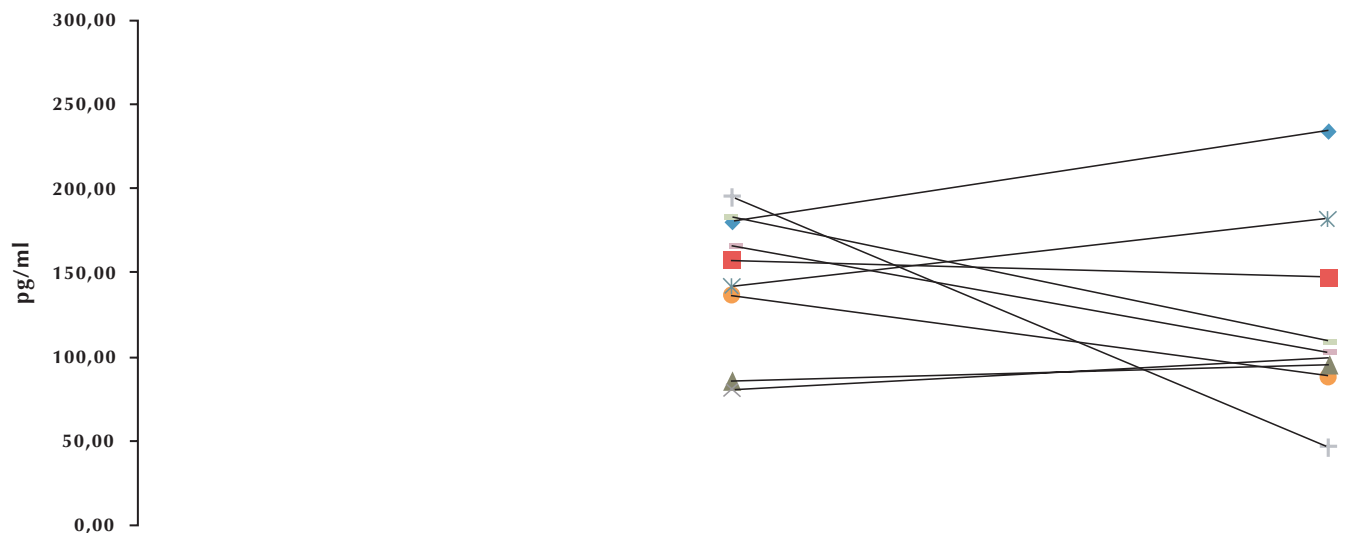
can be explained by different study objects and study settings. In addition, the duration of anaesthesia remained shorter in our study than in those reported previously.

The LTC₄ concentration in the non-smokers was increased postoperatively whereas the LTC₄ concentration in the smokers was decreased. Alveolar macrophages of smokers are known to release less arachidonic acid, PGE₂ and TXB₂ [18] and LTB₄ [19, 20] than those of non-smokers. However, there is no difference between the smokers and non-smokers in the BAL LTC₄ concentration in a previous study [21], which is in accordance with our baseline measurement. Smokers are proposed to have an enzymatic defect in the lipoxygenase pathway [18-20, 22] and our findings could suggest that sevoflurane might augment this enzymatic defect further. Another explanation, although entirely specu-

lative, for the postoperatively decreased LTC₄ in smokers could be that the conversion of LTC₄ to LTD₄ and LTE₄ is enhanced in smokers during sevoflurane anaesthesia. Unfortunately, we did not measure the LTD₄ and LTE₄ concentrations.

A higher, although not statistically significant, baseline concentration of NO₃⁻ was observed in this study in the smokers compared with the non-smokers. Reversibly decreased levels of exhaled NO have been detected in smokers [23] and in non-smokers exposed to passive tobacco smoke inhalation [24]. On the other hand, acute smoking increases transiently the level of NO₃⁻, reflecting oxidation of NO by tobacco smoke [23]. Although NO₃⁻ and NO₂⁻ are stable metabolites of NO [25], we are not able to draw conclusions about the exhaled NO levels in our patients as this was not

Pre- and postoperative LTC₄ in smokers



Pre- and postoperative LTC₄ in non-smokers

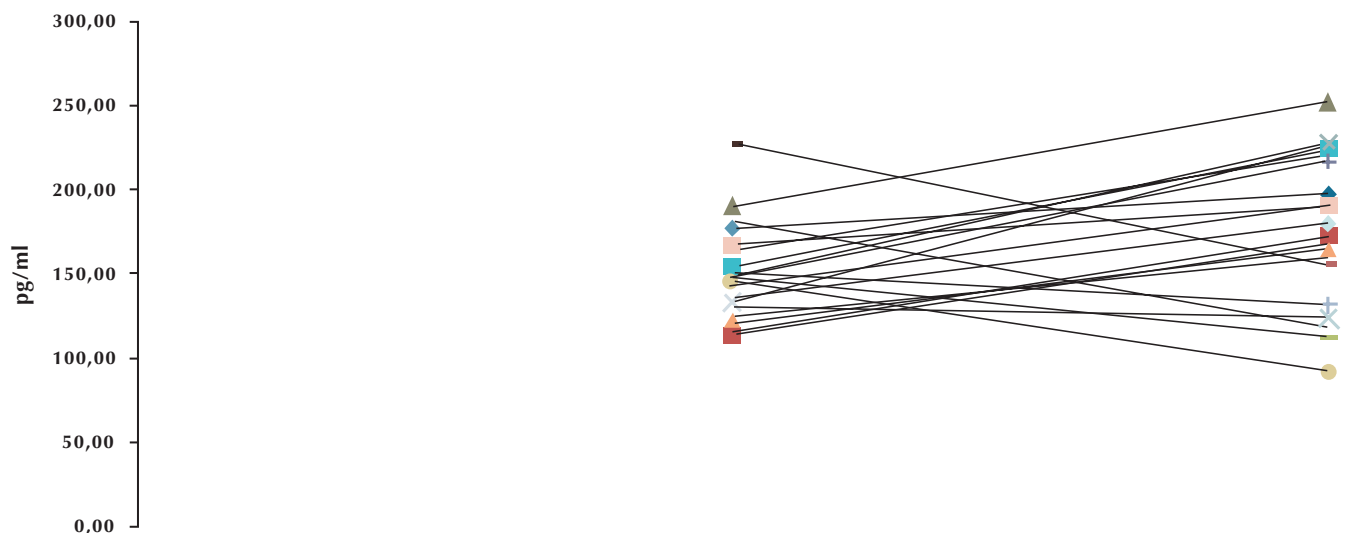


Fig. (3). Individual time course of LTC₄ in smokers and non-smokers. Non-smokers had significantly higher postoperative LTC₄ concentrations than smokers, $P < 0.05$. The magnitude of the change of LTC₄ during the time course was also different between the groups, $P < 0.05$.

measured. In animal studies volatile anaesthetics have both reduced [26] and increased [27] the mRNA and protein levels of inducible NO-synthase and NO-synthase activity in stimulated macrophages. In human neutrophils, halothane has been shown to decrease NO synthase activity [28]. In contrast, sevoflurane has been proposed both to enhance NO generation [29] and inhibit NO production from endothelial cells [30]. On the other hand, irrespective of the choice of the anaesthesia, decreased systemic level of NO has been observed during surgery and anaesthesia [31]. Nevertheless, systemic levels of NO do not necessarily correlate with local pulmonary NO levels, at least not when the compartmentalisation of the inflammatory reaction is maintained [32].

To standardise the surgical trauma and the severity of tissue injury, which affects the inflammatory reaction [33], this study was performed on prostatectomy patients only. We also aimed to standardise the exposure of sevoflurane but the MAC hour turned out be significantly higher in smokers than in non-smokers. This is likely a consequent of smokers requiring greater doses of anaesthesia agents for loss of consciousness [34] and suggested higher arousal level in auditory evoked potentials in smokers [35].

Atelectasis due to a rapid collapse of alveoli is a common phenomenon upon induction of anaesthesia [36]. To diminish atelectasis formation and consequent repetitive opening and closure of the alveoli, 80% oxygen was used during the induction [37] and 4 cmH₂O PEEP was applied during mechanical ventilation. The lungs of our patients were ventilated with tidal volumes between 6 and 8 ml.kg⁻¹ in order to avoid an inflammatory response induced by over stretching of the alveoli [38]. Local pulmonary increases of TNF- α and IL-6 concentrations are observed after 2 hours mechanical ventilation with a tidal volume of 10 ml.kg⁻¹ under sevoflurane anaesthesia [39]. As smoking status does not seem to have any effect on the inflammatory response with various ventilation strategies [40] and as both of our study groups were under similar low tidal volume ventilation, it is unlikely that the ventilation *per se* would have contributed to our results.

There are limitations in our study. We managed to include only 9 smokers. The number of Finnish men smoking tobacco has gradually decreased during the past two decades. In 2007 of Finnish men in the age group of 45-64, 23% smoked [http://www.stat.fi/til/tup/2007/tup_2007_2008-12-18_tie_001.html (accessed 03/01/2009)], whereas of men older than 64 years, only 12% smoked [http://www.stat.fi/til/tup/2005/tup_2005_2006-11-02_tie_001.html (accessed 03/01/2009)]. This fact resulted in slow recruitment and eventually termination of our study due to expiring of the study approval. Due to the limited number of patients, the study may be underpowered, leaving place for type II error. However, as the individual changes in the inflammatory mediators were fairly small, as presented in Figs. (1-3), it is unlikely that the here obtained results would change even if we had managed to recruit 20 smokers. Furthermore, we are not able to state that the here observed changes are due to sevoflurane as this was not specifically investigated.

CONCLUSION

There are only minor differences in the pulmonary inflammatory mediators between smokers and non-smokers

during prostatectomy under sevoflurane anaesthesia. Accordingly, the here investigated mediators have probably minor relevance on the postoperative pulmonary complications in smokers.

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