Comparison of the effects of xenon and sevoflurane anaesthesia on leucocyte function in surgical patients: a randomized trial†

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Editor's key points

- While volatile anaesthetics generally have anti-inflammatory effects, the immune effects of xenon are controversial.
- In healthy subjects undergoing elective surgery, the immune effects of xenon or sevoflurane were compared.
- Xenon and sevoflurane had similar effects on immune function providing small anti-inflammatory, and no pro-inflammatory, effects.

Background. While most anaesthetics are known to suppress immune reactions, data from experimental studies indicate the enhancement of reactivity to inflammatory stimulators under xenon treatment. We investigated the effect of xenon anaesthesia on leucocyte function in surgical patients.

Methods. We performed a subgroup analysis of subjects undergoing xenon or sevoflurane anaesthesia in a randomized clinical trial. After oral premedication with midazolam, two separate blood samples were obtained from subjects undergoing elective abdominal surgery, directly before and 1 h after induction of anaesthesia. General anaesthesia was maintained with either 60% xenon or 2.0% sevoflurane in 30% O₂. Leucocyte count, phagocytotic function, and pro-inflammatory cytokine release after ex vivo lipopolysaccharide (LPS) stimulation were determined.

Results. Except for lymphocyte numbers, leucocyte subpopulations did not differ between the groups. Phagocytosis and oxidative burst of granulocytes were reduced in both groups after 1 h of anaesthesia, whereas monocytes were not affected. Pro-inflammatory cytokine release in response to LPS was not affected.

Conclusions. In vivo, xenon and sevoflurane anaesthesia did not have a pro-inflammatory effect, at least in combination with the types of surgery performed in this study. Notably, the impact of xenon anaesthesia did not differ significantly from sevoflurane anaesthesia with regard to leucocyte function. However, an underestimation of treatment effects due to limited sample sizes cannot be fully excluded.


Keywords: anaesthetics, inhalation; leucocytes; sevoflurane; xenon

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Surgery is a stressor for the human body, resulting in a major activation of the immune system that involves cytokine release, activation of complement cascades, and mobilization of leucocytes.¹ ² The role of anaesthesia in this context has not been fully elucidated: different study results range from no effect to modulation of inflammatory activation.¹ ³ ⁴ The impact of anaesthesia on immune function differed between the anaesthetics used. In particular, volatile anaesthetics such as sevoflurane appear to mitigate pro-inflammatory stimuli such as surgery, extracorporeal circulation, or trauma, thereby potentially exerting protective effects.⁵ There is additional evidence about anti-inflammatory effects from several in vivo and in vitro models.⁶–⁸

The noble gas xenon is an anaesthetic with many advantageous properties,⁹ for example, its haemodynamic stability¹⁰–¹² and its neuroprotective effects.¹³ While other volatile anaesthetics seem to suppress immune reactions, data from experimental xenon studies are controversial: xenon treatment alone and in combination with extracorporeal membranes did not enhance inflammatory mediators in vitro,¹⁴ ¹⁵ whereas other studies indicated the enhancement of reactivity to the inflammatory stimulus bacterial lipopolysaccharide (LPS).¹⁵ ¹⁶ The impact of these findings on general anaesthesia in humans has not yet been examined.

The aim of this study was to investigate a potential pro-inflammatory effect of xenon anaesthesia on leucocyte
function in patients and compare it with sevoflurane anaesthesia, which has been shown to exert a predominantly anti-inflammatory potential. As a further stimulus of inflammation ex vivo, we used LPS, because in vitro studies showed an enhancement of immune reactivity under xenon treatment, whereas it was attenuated by sevoflurane.

Methods
Study design
We studied blood samples from 60 subjects allocated to receive xenon or sevoflurane anaesthesia for elective abdominal surgery in a randomized, controlled, double-blind clinical trial (EudraCT No.: 2008-004132-20; NCT No.: 00793663 at http://clinicaltrials.gov). The study was designed as a subgroup analysis by amendment to the above-named randomized controlled trial and approved by the local clinical ethical review committee and the German authority for supervision and approval of pharmaceuticals (BfArM). Subjects did not receive any other study intervention than the above-mentioned anaesthesia before blood sampling took place.

Subjects
Subjects were enrolled between October 2010 and March 2011. All patients undergoing elective abdominal surgery (gynaecological, urological, or middle-sized general surgery, conducted either open or laparoscopic) with a planned duration > 60 min and a planned admission to the ward after post-anæsthesia care unit stay were screened. Exclusion criteria were: severe cardiac, respiratory, liver or kidney disorders, history of hyper-sensitivity, suspicion of malignant hyperthermia, pregnancy and lactation, and legal incapacity to give informed consent. The described screening technique led to a screening rate of approximately five patients per day and a total of 650 patients over the recruitment period. A screening log was not listed. After written informed consent, 60 subjects 18–75 yr of age and ASA status I–III were enrolled. The study IDs of subjects enrolled in the trial were randomly assigned to one of the two study groups using a randomization-software (RandList version 1.2, DatInf) and blinded to receiving either sevoflurane or xenon.

Trial procedure
Medical quality xenon in steel cylinders was provided by Air Liquide Santé International (Paris, France). Sevoflurane was provided by Abbott (Wiesbaden, Germany). Both anaesthetic agents were administered using a closed-circuit respirator (Felix Dual offenders, Taema, France) with appropriate software, which allowed the use of xenon only under closed-circuit conditions. Anaesthetic end-tidal concentrations were assessed by a respirator-incorporated thermo-conductivity meter (accuracy ± 3 vol%) with automatic calibration.

A sketch of the study procedure is displayed in Figure 1A. All subjects received premedication with 7.5 mg midazolam orally 45 min before admission to the operating theatre. After standard monitoring and epidural anaesthesia when indicated, the first blood sample was acquired directly before induction of anaesthesia. After 3 min preoxygenation, general anaesthesia was induced by propofol (2.0 mg kg⁻¹ initially, repeating dose if necessary 0.5–1.0 mg kg⁻¹) and 0.5 µg kg⁻¹ min⁻¹ remifentanil by infusion over a period of 60 s. Rocuronium 0.6 mg kg⁻¹ was administered to facilitate tracheal intubation. Xenon or sevoflurane wash-in was started with a target end-tidal concentration of 60 (5) vol% xenon or 2 (0.2) vol% sevoflurane in 30% oxygen. General anaesthesia was maintained by inhalation of xenon or sevoflurane and supported by remifentanil infusion titrated to clinical needs (baseline 0.1 µg kg⁻¹ min⁻¹). Standard monitoring included pulse oximetry, three-channel ECG, non-invasive arterial pressure measurement, control of tracheal tube cuff pressure, neuromuscular function, body core temperature, and oxygen, carbon dioxide, and end-tidal anaesthetic gas concentration. Ventilation control assured normoxia, physiological carbon dioxide concentration, and normothermia. Depth of anaesthesia was maintained according to physiological parameters (heart rate, arterial pressure, coughing, etc.), and BIS values were logged every 5 min. Standard treatment of blood loss, fluid replacement, and haemodynamic support were applied if necessary. One hour after wash-in of xenon or sevoflurane, the second blood sample was acquired. The postoperative examination was uneventful for all subjects.

Blood samples
Blood samples were harvested in lithium-heparin gel tubes (16 IE heparin ml⁻¹; Sarstedt-Monovetten®, Sarstedt AG & Co., Nümbrecht, Germany) and immediately processed.

Analysis of leucocyte subsets
Total leucocyte numbers were quantified with a CASY1 cell counter after lysis of erythrocytes with moly-lyse lysis solution (MöLab, Langenfeld, Germany). In parallel, whole blood samples (100 µl) were incubated with Simultest Leucocyte antibodies (BD Biosciences, Heidelberg, Germany) against CD14 (PE) and CD45 (FITC) or the respective isotype-matched controls for 15 min at room temperature in the dark, followed by lysis with BD FACS lysis solution according to the manufacturer’s instructions. Flow cytometric analysis was performed on a FACSCalibur flow cytometer using Simulset software (Becton Dickinson, Heidelberg, Germany) to calculate monocyte, lymphocyte, and granulocyte numbers.

Cytokine assay
Heparinized whole blood was diluted (1:1) with cell culture medium (RPMI 1640 containing 10% fetal calf serum, 2 mM L-glutamine, 100 U ml⁻¹ penicillin, and 100 µg ml⁻¹ streptomycin) and incubated in sterile polypropylene tubes with 0, 25, or 1000 ng ml⁻¹ LPS (Escherichia coli strain 0111:B4, Sigma Aldrich, Taufkirchen, Germany) for 4 h at 37°C. Subsequently, samples were centrifuged at 500g for 5 min; supernatants were harvested and stored at ~80°C until further use. For quantification of TNF-α, IL-1β, and IL-6, OPT-EIA ELISAs from BD Biosciences (Heidelberg, Germany) were used according
to the manufacturer's protocol and analysed with a spectrophotometer (Sunrise™; Tecan, Crailsheim, Germany).

**Western blotting**

Leucocytes were obtained by erythrocyte removal with ammonium chloride lysis. Briefly, 1 ml blood was incubated (5 min, 4 °C) with 15 ml ice-cold lysis-solution (0.67 M NH₄Cl, 0.01 M KHCO₃, 0.1 mM Na₂EDTA, pH 7.2–7.4), followed by centrifugation (300g, 5 min) and washing the leucocytes with phosphate-buffered saline twice. Cells were counted and taken up in 20 vol% of Laemmli sample buffer. An equivalent of 2 × 10⁵ cells per lane was separated on 10% polyacrylamide gels at 150 V and blotted to nitrocellulose membrane with 0.45 μm
pore size (BioRad, Munich, Germany). Uniform loading of gels was confirmed by staining with Ponceau S. After destaining, membranes were blocked with TBS-T [20 mM Tris/HCl, pH 7.6, 136 mM NaCl, 0.1% (v/v) Tween-20] containing 5% fat-free dry milk at room temperature for 1 h, and incubated with primary antibodies against phosphorylated p38 (Thr180/Tyr182), phosphorylated ERK1/2 (Thr202/Tyr204), or total β-actin (all from New England Biolabs, Frankfurt, Germany) at 1:1000 dilution in TBS-T containing 5% fat-free dry milk overnight at 4°C. Subsequently, membranes were washed three times with 25 ml TBS-T and incubated for 1 h with goat anti-rabbit-HRP followed by detection with Lumiglo Reagent (New England Biolabs, Frankfurt, Germany) on a Fuji-film LAS3000 imager. Band intensities were quantified with ImageJ software (http://rsb.info.nih.gov/ij/download.html).

Phagocytosis and oxidative burst
Heparinized whole blood (100 µl) was pre-incubated for 15 min at either 4°C (negative control) or 37°C, followed by the addition of E. coli (strain BL-21) that had been transformed with the vector pGEX-4T-1 containing the DsRed gene, and DHR 123 (Dihydrorhodamine 123, final concentration 1 µg ml⁻¹). After 30 min, erythrocytes were removed by ammonium chloride lysis. Phagocytosis and oxidative burst were analysed by flow cytometry using a BD FACSCalibur (Becton Dickinson). Forward and side light scatter were used to distinguish between monocyte and granulocyte populations.

Data evaluation and statistical analysis
Subjects who had received steroid medication before sample acquisition were secondarily excluded from data analysis. We expected the xenon group to show higher cytokine levels after immune response triggering compared with the sevoflurane group. Cytokine levels during sevoflurane anaesthesia + surgery were hypothesized to show up to a 50% reduction after exposure to the anaesthetic in relation to baseline.

A doubling of cytokine levels after xenon anaesthesia + surgery compared with baseline would be considered to be a clinically significant difference to sevoflurane. Given an effect size of 0.9, a total of 21 subjects per group would have to be evaluated to achieve an α-error of 0.05 and a β-error of 0.2 (i.e. 80% power) to prove the above hypothesized effect. The power calculation was performed using nQuery Advisor® Version 7.0 (Statistical Solutions, Saugus, MA, USA). For both groups, n = 30 subjects were included to compensate for possible drop-outs.

Parametric patient characteristic and anaesthesia data were analysed by one-way analysis of variance (ANOVA). Categorical subject data were analysed with the two-tailed Pearson χ² test and given as numbers. P-values from subject data were adjusted for multiple comparisons with a post hoc Bonferroni correction for 11 independent tests. Parametric data derived from blood samples were tested with a two-way ANOVA with corrections for paired samples, followed by a post hoc Bonferroni test for multiple comparisons. If not otherwise stated, parametric data are presented as mean (standard deviation). Differences were considered statistically significant at a P-value of <0.05. Statistical analysis was performed using IBM SPSS statistics software version 19.0 (IBM Corporation, Armonk, NY, USA) and GraphPad PRISM® (GraphPad Software Inc., La Jolla, CA, USA).

Results
Subject characteristics
A detailed study flow is presented in Figure 1a. Twenty-two subjects in the xenon group and 20 subjects in the sevoflurane group were included in the analysis. Subjects in both groups were comparable with respect to age, height, body mass index, gender, ASA classification, smoking status, scheduled surgery, additional epidural anaesthesia, average depth of anaesthesia, and average remifentanil doses (Table 1). The delay between the start of surgery and the second blood sampling was equally distributed.

Table 1. Subject characteristics. A detailed listing of the subject and anaesthesia characteristics sorted by treatment is given. Values in parentheses are mean and minimum—maximum range. Subjects in both groups were comparable with respect to age, height, body mass index (BMI), sex, ASA status, smoking status, type of scheduled surgery, additional epidural anaesthesia, the delay between start of surgery and sample II, and average BIS values during anaesthesia. The P-value threshold was post hoc adjusted with a Bonferroni correction for 11 independent comparisons, with an adjusted significance level of P=0.0045. No significant difference was found between the groups.

<table>
<thead>
<tr>
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<th>Xenon (n = 22)</th>
<th>Sevoflurane (n = 20)</th>
<th>P-value</th>
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<tr>
<td>Age (yr)</td>
<td>55.5 (17.0)</td>
<td>59.1 (12.4)</td>
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<tr>
<td>Height (m)</td>
<td>1.75 (10.7)</td>
<td>1.72 (8.6)</td>
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<tr>
<td>BMI (kg m⁻²)</td>
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<td>27.1 (7.3)</td>
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<tr>
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<td>11/9</td>
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<td>3/16/1</td>
<td>0.440</td>
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<td>4/16</td>
<td>0.691</td>
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<td>8/12/0</td>
<td>0.749</td>
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<tr>
<td>Epidural: none/thoracic/lumbar</td>
<td>12/1/9</td>
<td>13/0/7</td>
<td>0.550</td>
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<tr>
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<td>29.2 (10.2)</td>
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<tr>
<td>Average dose of remifentanil (µg kg⁻¹ min⁻¹)</td>
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<td>0.025</td>
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<td>Average BIS value</td>
<td>47</td>
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<td>0.856</td>
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Leucocyte counts and subpopulations

In subjects with xenon anaesthesia, leucocyte numbers did not differ between sampling time points. Subjects with sevoflurane anaesthesia had significantly fewer leucocytes after 1 h of anaesthesia compared with the baseline measurement (Fig. 2A). There were significant differences concerning lymphocyte and granulocyte numbers before and 1 h after induction of anaesthesia in the sevoflurane group (Fig. 2B and D). Monocyte numbers in the sevoflurane group and leucocyte subpopulations in the xenon group did not differ significantly (Fig. 2C). There were significantly fewer lymphocytes in subjects anaesthetized with xenon than in those anaesthetized with sevoflurane before and 1 h after induction of anaesthesia (Fig. 2B).

Cytokine response to LPS stimulation

All samples treated with LPS showed significantly higher cytokine levels than untreated controls (Fig. 3A–C). Significant differences in TNF-α release were noted after treatment with low (25 ng ml⁻¹) and high (1 µg ml⁻¹) concentrations of LPS in both study groups and at both sampling times (Fig. 3A). IL-1β release was significantly higher after stimulation with 1 µg ml⁻¹ LPS compared with 25 ng ml⁻¹ LPS only at baseline (Fig. 3B). IL-6 release was elevated in a significant manner when stimulated with 1 µg ml⁻¹ at 1 h of xenon anaesthesia and at baseline after sevoflurane anaesthesia compared with stimulation with 25 ng ml⁻¹ LPS (Fig. 3C). Anaesthetic treatment did not significantly affect cytokine release in all cases (Fig. 3A–C).

Phagocytotic activity and oxidative burst

Phagocytosis- and oxidative burst-positive granulocytes were slightly but significantly reduced after 1 h in the xenon group (Fig. 3D). Granulocytes after sevoflurane anaesthesia and monocytes in both groups were equally distributed at both sampling times (Fig. 3D and F). There was a significant decrease in the degree of granulocyte phagocytotic capacity and ability to perform an oxidative burst after 1 h of anaesthesia in both groups (Fig. 3E and F). In monocytes, phagocytotic and oxidative burst capacities were not affected (Fig. 3I and J). No significant differences were found comparing xenon and sevoflurane.
**Fig 3** Cytokine release and phagocytosis/oxidative burst capacity. After 4 h of incubation with 25 ng ml\(^{-1}\) and 1 \(\mu\)g ml\(^{-1}\) LPS, cytokine release from leucocyte preparations was assessed by ELISA (A–C). Samples treated identically except for LPS addition served as controls (0 ng ml\(^{-1}\) LPS). TNF-\(\alpha\) (A), IL-1\(\beta\) (B), and IL-6 (C) release was significantly elevated after LPS stimulation compared with controls in all experimental settings. Significantly higher concentrations of TNF-\(\alpha\) were found in all groups after stimulation with 1 \(\mu\)g ml\(^{-1}\) compared with 25 ng ml\(^{-1}\) LPS (A). IL-1\(\beta\) concentrations were significantly elevated after stimulation with 1 \(\mu\)g ml\(^{-1}\) compared with 25 ng ml\(^{-1}\) LPS only at baseline sampling in the xenon group (B). Significant differences in IL-6 release when comparing 25 ng ml\(^{-1}\) and 1 \(\mu\)g ml\(^{-1}\) LPS were found after 1 h of anaesthesia in the xenon group and at baseline in the sevoflurane group (C). No statistically significant differences were detected between xenon and sevoflurane treatment, or between different sample times. Results are given as mean (standard deviation). (*) \(P<0.05\); (**) \(P<0.01\); (***) \(P<0.001\). Phagocytotic and oxidative burst capacity before and after 1 h of xenon or sevoflurane anaesthesia is given in (D–F) for granulocytes and in (G–I) for monocytes. The total number of active granulocytes was slightly but significantly reduced in the xenon group but not after sevoflurane (G). Active monocyte numbers did not differ between the groups or between the two sampling times (H). Phagocytotic and oxidative burst capacity (I) were significantly reduced in both groups after 1 h of anaesthesia. In monocytes, neither phagocytotic (\(\dagger\)) nor oxidative burst capacity (\(\ddagger\)) was affected by anaesthesia. With both cell types, no significant differences were found regarding the anaesthetic regimen. Results are given as mean (standard deviation). (* \(P<0.05\); ** \(P<0.01\).)
Mitogen-activated protein kinase phosphorylation

Sevoflurane or xenon anaesthesia had no significant effect on p38 phosphorylation (Fig. 4A and B). In contrast, ERK1/2 phosphorylation was significantly reduced after 1 h of xenon anaesthesia (Fig. 4A and C).

Discussion

Previous in vitro studies have shown pro-inflammatory effects of xenon in LPS-mediated immune reactivity. In contrast, our results did not find any elevation of pro-inflammatory cytokines or augmented phagocytic/oxidative burst activity after xenon anaesthesia when compared with sevoflurane anaesthesia. On the contrary, our clinical data show that xenon does not have pro-inflammatory features in vivo when applied in ASA I and II individuals undergoing elective surgery. Subjects receiving xenon anaesthesia did not show any differences in leucocyte function in peripheral blood compared with those receiving sevoflurane anaesthesia, neither in baseline measurements nor after stimulation with LPS. In contrast, both anaesthetic regimens showed a slight anti-inflammatory effect after in vitro stimulation at 1 h after induction, probably counteracting a pro-inflammatory primary response to surgical stress.

This has been shown before for sevoflurane, but not for xenon. Potential bias resulting from side-effects of non-equally distributed immunosuppressive medication was avoided by excluding subjects with steroid medication from data analysis. The immunomodulatory effect of benzodiazepines is well described. Therefore, benzodiazepine premedication was applied to all subjects at the same dosage. Opioid doses were marginally higher in the xenon group, which might possibly mask a pro-inflammatory effect of xenon because of an intrinsic anti-inflammatory effect. Depth of anaesthesia and the additional use of epidural anaesthesia, which have been attributed effects on the immune response to surgical stress, were comparable between the groups. However, this study has its limitations. Conceived and performed as a subgroup analysis by amendment to another randomized controlled trial evaluating xenon or sevoflurane anaesthesia in ASA I and II patients, study subjects were not primarily evaluated for inflammation-modifying medication and pre-existing immunological co-morbidities. Since only subjects without compromising chronic diseases (ASA status I–II, rarely III) were included in the trial, biasing effects through further non-study-related medication are not expected, but cannot be definitely excluded. The surgical trauma and thereby the extent of surgical stress might have differed between individuals, since a large panel of medium-size surgical interventions, either open or laparoscopic, was applied. However, the second sampling took place 1 h after induction of anaesthesia, a time where surgery had started about 30 min earlier in both groups, and factors such as length of surgery and personal factors of the performing surgeon were not expected to differ between the groups. The types of surgery were equally distributed between xenon and sevoflurane anaesthesia, so surgical trauma and eventual loss of blood were expected to be comparable at the time of the second sampling.

Apart from surgical trauma, further inflammatory stimulation of blood cells was performed ex vivo. With its very low blood–gas partition coefficient of 0.686, xenon is quickly lost by diffusion. The solubility of sevoflurane (blood–gas partition coefficient of 0.115–0.14) is greater than that of xenon. A delay of LPS stimulation due to experimental processes might have been a reason for an attenuated reactivity after xenon treatment compared with sevoflurane. However, stimulation of cytokine release with different LPS concentrations was equivalent in both groups at both sampling times, so attenuation of xenon’s or sevoflurane’s effects by diffusion seems unlikely.

A difference in leucocyte numbers during sevoflurane anaesthesia could result from a reduction in average arterial pressure compared with xenon anaesthesia and treatment thereof (haemodilution through fluid therapy). In the study protocol, fluid therapy was neither restricted nor specially logged. However, differences between the groups in baseline lymphocyte counts have to be regarded as mainly subject-determined differences unknown at randomization, and thus an incidental finding, given random distribution within the study population. After stimulation with LPS, monocytes are...
the primary source of the examined cytokines in the blood.

As monocyte numbers were not affected by either study treatment, this possible bias is precluded as well. This clinical trial gives the first hint that xenon anaesthesia in vivo might also be safe during infectious and inflammatory diseases; at least during short periods of anaesthesia (longer periods of anaesthesia have not been investigated). However, an underestimation of treatment effects due to limited sample sizes cannot be fully excluded. An investigation concentrating on patients with active inflammatory processes would be a further step in evaluating the safety of xenon anaesthesia. A lack of inflammatory activation during xenon treatment in models of trauma and inflammation has also been found in animal models of acute pulmonary hypertension and also during cardiopulmonary bypass.

Several in vitro studies indicate that activation of mitogen-activated protein kinases (MAPKs) by xenon is involved in its organ protective properties and cellular effects. We did not find an equivalent activation of the MAPKs p38 and ERK1/2 in leucocytes during anaesthesia. Instead, we found a significant reduction in ERK1/2 phosphorylation and a reduced p38 phosphorylation after 1 h of xenon anaesthesia. Sevoflurane is known for its organ protective properties and cellular effects. Sevoflurane appeared to reduce the phosphorylation of ERK1/2 as well, although there was no significant effect. This might be due to the fact that leucocytes missed a stimulating analogue as in experimental trauma models.

In contrast, xenon treatment in vitro activated ERK1/2 without further stimulus, an effect that was not confirmed in our study. Further in vitro experiments would be desirable to elucidate the target cells, circumstances, and mechanisms of MAPK activation by xenon or volatile anaesthetics.

Summary

Xenon or sevoflurane anaesthesia did not have a pro-inflammatory effect 1 h after anaesthesia induction, at least in combination with the types of surgery performed in this study. The impact of xenon anaesthesia did not differ significantly from sevoflurane anaesthesia with regard to leucocyte function. However, underestimation of treatment effects due to limited sample sizes cannot be fully excluded.

Authors’ contributions

A.V.F., M.C., and H.H. conceived and performed the study and drafted the manuscript. R.R. and C.S. helped to perform the study and draft the manuscript.

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Declaration of interest

M.C. and R.R. received lecture and consultant fees and project funding for clinical trials from Air Liquide Santé International, a company interested in developing clinical applications for medical gases, including xenon. A.V.F. received travel reimbursement from Air Liquide Santé International.

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