Sevoflurane in Exhaled Air of Operating Room Personnel

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Evidence on potential health hazards arising from exposure to volatile anesthetics remains controversial. Exposure may, in principle, be supervised by monitoring of ambient air or, alternatively, *in vivo*. We used the Proton Transfer Reaction-Mass Spectrometry to screen the breath of 40 operating room staff members before operating room duty, 0, 1, 2, and 3 h after duty, and before commencing duty on the consecutive day, and control persons. Staff members exhibited significantly increased sevoflurane levels in exhaled air after duty, with a mean of 0.80 parts per billion as compared with baseline values of 0.26 parts per billion ($P < 0.05$). Analysis of variance with adjustment for within correlation (repeated measurements) showed a statistically significant time-effect ($P < 0.001$). We conclude that (a) Proton Transfer Reaction-Mass Spectrometry biomonitoring of exhaled sevoflurane can serve as a simple and rapid method to determine volatile anesthetic excretion after occupational exposure, and (b) significant concentrations of sevoflurane may be continuously present in persons exposed to sevoflurane on a daily basis.

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Several studies on occupational exposure to trace anesthetic gases have been conducted. Evidence concerning the effects of volatile anesthetics on human reproduction and chromosomal integrity is inconclusive (1–3). Furthermore, inhalation of volatile anesthetics has been implicated in peripheral lymphocyte apoptosis and may thus, in principle, contribute to perioperative leukopenia (4). Considerable risks after occupational exposure to volatile anesthetics cannot therefore be excluded safely. National public health authorities such as the National Institute of Occupational Safety and Health have introduced threshold values of 2 parts per million volume (ppmv) for ambient air regulating occupational exposure over a given time period (5).

Occupational exposure to volatile anesthetics has been determined by gas chromatographic (6) and infrared spectrometric measurements of ambient air (5). However, thus far, direct *in vivo* measurements of volatile anesthetic kinetics have only been performed in tracheally intubated patients under controlled ventilation (7) and using gas chromatography in the urine of exposed personnel (8,9). No investigations concerning the time-course of exhaled air composition in exposed persons have been performed, probably because of technical difficulties, although the potential importance of such measurements has been highlighted (9).

Proton Transfer Reaction-Mass Spectrometry (PTR-MS) has been established as a new method for the real-time analysis of volatile anesthetics and constituents of ambient air in operating room (OR) (10) and postanesthesia care unit (PACU) settings (11). Furthermore, PTR-MS allows for accurate measurements of exhaled volatile organic compounds in both single and real-time measurements (12). Therefore, it was the aim of the present open, observational, nonrandomized trial to investigate the exhaled breath of OR personnel by PTR-MS.

Methods

The present investigation was approved by the Ethics Committee of the Leopold-Franzens-University of Innsbruck. Written and informed consent was sought from 40 persons working in the local OR (anesthesiologists, surgeons, or nurses), performing routine duty within the otorhinolaryngology ORs from 7:30 AM until 4:00 PM. Three-hundred-seventy persons

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without occupational exposure to anesthetic gases attending a public health fair served as controls. Demographic data of volunteers are summarized in Table 1. Based on OR volume and air exchange capacity, it was calculated that ambient air was exchanged 14.23 times per hour. Mean concentrations of sevoflurane in the surveyed OR zone under the same conditions have been reported to be 103.6 ppbv (10). After IV induction, sevoflurane was used for the maintenance of anesthesia in combination with nitrous oxide and fentanyl. Patients were endotracheally intubated after a mask time of 2 min. Inspired concentrations of sevoflurane were titrated to effect and thus not standardized. All persons had comparable levels of occupational exposure.

Specimen were collected before the start of OR duty, at the end of OR duty, 1, 2, and 3 h after clinical duty, and on the consecutive day before commencing OR duty. Exhaled air samples were collected from these persons in Tedlar® bags (Gasco, Sarasota, FL), as previously described (12). Parallel evaluation of ambient air was performed. In PTR-MS measurements, sevoflurane is ascribed to protonated mass 181 (11).

PTR-MS allows on-line monitoring of volatile organic compounds (VOCs) with volume mixing ratios as small as a few parts per trillion (13). Chemical ionization is applied based on proton-transfer reactions, with H_3O^+ as the primary reactant ion, which is most suitable when air samples containing a wide variety of traces of VOCs compounds are to be analyzed (13). Almost all VOCs have proton affinities larger than H_2O, and therefore, proton transfer occurs on every collision with rate constants k that are well known, having typical values of 1.5×10^{-9} $cm^3s^{-1} < k < 4 \times 10^{-9}$ cm^3s^{-1}. A decisive advantage of using primary H_3O^+ ions is that many of their proton transfer processes are nondissociative, so only one product ion species occurs for each neutral reactant. In cases where dissociation does occur, it frequently follows a straightforward pattern, e.g., the ejection of a H_2O-molecule from protonated alcohols.

A simple mean imputation method was used to replace missing values. To fulfill the conditions for the analysis of variance (ANOVA) (normal distributed), the dependent variable was log transformed. ANOVA for repeated measurements (general linear model) was performed, with exhaled sevoflurane concentrations as dependent variable and time as factor. Statistical significance was defined as $P < 0.05$. SPSS for Windows 11.0 software (SPSS, Chicago, IL) was used for all analyses.

Results

In OR staff, mean exhaled concentrations of mass 181 were 0.26 ± 0.37 ppbv before starting the study. After the working day, the mean expired concentration was 0.80 ± 1.12 ppbv. In the measurements 1, 2, and 3 h after duty and on the consecutive morning, the mean concentrations were 0.34 ± 0.29, 0.27 ± 0.23, 0.28 ± 0.19, and 0.11 ± 0.07 ppbv, respectively (Fig. 1). No significant correlation between the rate of sevoflurane decay and body mass index was found.

Table 1. Demographic Data of Test Persons Given as mean ± SD Where Applicable

Age	35.6 ± 7.4
Body mass index	23.2 ± 3.2
Male/female subjects	19/22

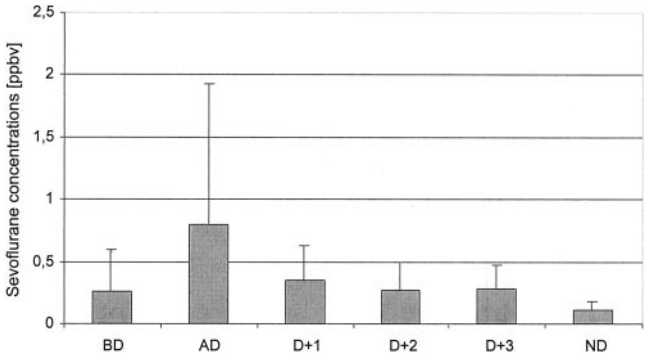

Figure 1. Time-course of sevoflurane in exhaled air of operating room personnel. Analysis of variance (ANOVA) with adjustment for within correlation showed a highly significant time-effect. Data are given as mean ± SD. BD = before duty; AD = after duty; D + 1/2/3 = duty plus 1/2/3 h, respectively; ND = next day.

A baseline value of mass 181 in control persons was 0.019 ± 0.003 ppbv. Exhaled sevoflurane in the breath of OR staff members was significantly more at all times as compared with controls. ANOVA with adjustment for within correlation (repeated measurements) showed a highly significant time-effect ($P < 0.001$). The time profile in exhaled air is depicted in Figure 1.

Discussion

The principal result of the present study is the first depiction of sevoflurane concentration kinetics in exhaled breath of OR personnel. Concentrations of sevoflurane are significantly larger after completion of OR duty as compared with baseline values and control group measurements. A highly significant effect of time on exhaled sevoflurane concentrations was demonstrated.

One notable result was that at all times, OR staff member's sevoflurane concentrations were larger than those of control persons. This may indicate that the time span between cessation of OR duty and commencement of the subsequent work shift may not allow for a complete elimination of inhaled anesthetics

from the circulation of exposed health care workers. This correlates with the biphasic elimination profile of sevoflurane reported in another study (14). During the first rapid exhalation phase the residual sevoflurane volume within the lungs was exhaled. The second slower phase has been described by Kharasch et al. (15,16) with a half time of approximately three hours. This may be of importance because there is conflicting evidence concerning the effects of occupational exposure to volatile anesthetics in the OR and PACU environments on the reproductive and immune system (1,17). Some evidence has implicated the involvement of sevoflurane in the eliciting perioperative leukocytopenia because of apoptosis *in vitro* (4). This effect was achieved at doses exceeding those normally encountered in clinical use. Modern ORs have a large ventilation capacity; therefore, the 24-hour occupational burden by anesthetic gases in the OR is considered to be relatively small (18). Previously reported sevoflurane concentrations of 103 ppbv are 20-fold less than the recommended threshold values (10). Online analysis points toward a rapid exhalation of contaminating anesthetics within the OR and PACU (11).

However, the ability of sevoflurane to induce apoptosis was not only described as dose-dependent, but also as time-dependent comparing incubation times of 12 and 24 hours (4). This emphasizes the importance of the present results that the excretion of sevoflurane lasts for more than 12 hours, and therefore, considerable time-dependent burdens of sevoflurane have to be assumed. The potential impact of long-lasting low-level volatile anesthetic burdens on persons exposed to sevoflurane on a daily basis should be considered in discussions of occupational exposure control.

Accorsi et al. (9) used gas chromatography-mass spectrometry (GC-MS) to detect volatile anesthetics in urine supernatant under different workloads. Results pointed toward the potential of a gross retrospective analysis of volatile anesthetic workload using this method. However, a parallel evaluation of the second important route of volatile anesthetic excretion (via expired air) was deemed essential by the authors in order to complement methods determining occupational exposure. This was considered especially important in new anesthetics such as sevoflurane for which threshold values have not yet been determined by public health authorities. The use of physical and chemical methods in the analysis of VOCs in expired air have become conceivable in the screening for metabolic and neoplastic diseases (12). Detection and real-time determination of sevoflurane in ambient air by PTR-MS have been reported (11). The present study describes a new application of expired air screening by PTR-MS. It highlights the feasibility of detecting increased sevoflurane concentrations in exhaled air of OR personnel. Complementary to urinary measurements, which may offer advantages in retrospective analysis of occupational exposure (9), rapid analysis of volatile anesthetics in exhaled air may serve as a mirror of short-term changes in metabolic pathways. Because one prominent feature of volatile anesthetics with a low molecular weight (i.e., less than 200 Daltons) is a quick traversion of the alveolar membrane, correlations of exhaled anesthetics with corresponding serum levels are conceivable and should be the subject of further investigations.

Some limitations of the present study should be briefly addressed. PTR-MS detects the concentration of specific molecules according to their individual molecular mass. Therefore, interference of molecular species other than the specific molecule in question is a potential source of error. A very small baseline value of mass 181 was noted, even in control groups and, therefore, must represent molecular species other than sevoflurane. For baseline measurements (0.26 ppbv), these levels corresponded to 8% of mass 181, and for the measurements directly after OR duty (0.80 ppbv), these levels corresponded to approximately 2% of the measured concentration for mass 181. Therefore, it may be stated that the gross profile of sevoflurane in exhaled air can be depicted by PTR-MS, even if another molecular species interferes with measurements at small concentrations. More detailed measurements should be performed using exhaled air analysis combining PTR-MS with GC-MS in order to allow accurate exclusion of interfering substances.

Compared with other methods of VOC detection, PTR-MS offers highly sensitive and rapid determinations of VOC profiles and is therefore conceivable as a screening method. Several advantages of PTR-MS should be stated and are as follows: storage of sample bags over brief periods is possible, whereas GC-MS samples, such as those used by other authors (9), have to be measured within minutes. Intertest variability may thus be excluded by measuring different samples of one participant in one session. Furthermore, the possibility of directly mirroring serum concentrations may warrant the conduction of more detailed studies, taking into account physico-chemical properties of volatile anesthetic kinetics across the alveolar membrane. These studies could, in principle, help to determine the excretion of volatile anesthetics sensitively and noninvasively.

It is concluded from the results of the present study that (a) PTR-MS biomonitoring of exhaled sevoflurane is possible as a simple and rapid method to determine volatile anesthetic excretion after occupational exposure, and (b) significant concentrations of sevoflurane may be continuously present in persons who are exposed to daily sevoflurane.

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References

1. Saurel-Cubizolles M, Hays M, Estryn-Behar M. Work in operating rooms and pregnancy outcome among nurses. Int Arch Occup Environ Health 1994;66:235–41.
2. Hoerauf K, Schrögendorfer K, Wiesner G, et al. Sister chromatid exchange in human lymphocytes exposed to isoflurane and nitrous oxide *in vitro*. Br J Anaesth 1999;82:268–70.
3. Hoerauf K, Wiesner G, Schroegendorfer K, et al. Waste anaesthetic gases induce sister chromatid exchanges in lymphocytes of operating room personnel. Br J Anaesth 1999;82:764–6.
4. Matsuoka H, Kurosawa S, Horinouchi T, et al. Inhalation anesthetics induce apoptosis in normal peripheral lymphocytes *in vitro*. Anesthesiology 2001;95:1467–72.
5. Hoerauf KH, Wallner T, Akca O, et al. Exposure to sevoflurane and nitrous oxide during four different methods of anesthetic induction. Anesth Analg 1999;88:925–9.
6. Marx T, Froba G, Koble R, et al. [The effect of anesthetic method on enflurane air pollution in non-air conditioned operating rooms]. Anaesthesist 1996;45:1167–70.
7. Fitzal S, Germann P, Gilly H, et al. [Uptake and elimination of isoflurane and halothane in children and adults]. Anaesthesist 1985;34:571–7.
8. Imbriani M, Ghittori S, Pezzagno G. The biological monitoring of inhalation anesthetics. G Ital Med Lav Ergon 1998;20:44–9.
9. Accorsi A, Barbieri A, Raffi G, Violante F. Biomonitoring of exposure to nitrous oxide, sevoflurane, isoflurane and halothane by automated GC/MS headspace urinalysis. Int Arch Occup Environ Health 2001;74:541–8.
10. Rieder J, Lirk P, Summer G, et al. Exposure to sevoflurane in otorhinolaryngologic operations. Can J Anaesth 2001;48:934.
11. Rieder J, Prazeller P, Boehler M, et al. Online monitoring of air quality at the postanesthetic care unit by proton-transfer-reaction mass spectrometry. Anesth Analg 2001;92:389–92.
12. Rieder J, Lirk P, Ebenbichler C, et al. Analysis of volatile organic compounds: possible applications in metabolic disorders and cancer screening. Wien Klin Wochenschr 2001;113:181–5.
13. Hansel A, Jordan A, Holzinger R, Lindinger W. Proton transfer reaction-mass spectrometry: on-line trace gas analysis at the ppb level. Int J Mass Spectrom Ion Process 1995;149/150:609–19.
14. Dudziak R, Behne M. [Uptake and distribution of sevoflurane]. Anaesthesist 1998;47:S1–6.
15. Kharasch ED, Armstrong AS, Gunn K, et al. Clinical sevoflurane metabolism and disposition. II. The role of cytochrome P450 2E1 in fluoride and hexafluoroisopropanol formation. Anesthesiology 1995;82:1379–88.
16. Kharasch ED, Karol MD, Lanni C, Sawchuk R. Clinical sevoflurane metabolism and disposition. I. Sevoflurane and metabolite pharmacokinetics. Anesthesiology 1995;82:1369–78.
17. Gruber G, Lirk P, Amann A, et al. Neopterin as a marker of immunostimulation: investigations at anesthetic workplaces. Anaesthesia 2002;57:747–50.
18. Sessler D, Badgwell J. Exposure of postoperative nurses to exhaled anesthetic gases. Anesth Analg 1998;87:1083–8.