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ORIGINAL ARTICLE

Desflurane and sevoflurane concentrations in blood passing through the oxygenator during cardiopulmonary bypass: a randomized prospective pilot study

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Abstract

Purpose Volatile anesthetics (VAs) protect myocardial cells in cardiovascular surgery. A recent clinical trial of cardiopulmonary bypass (CPB) surgery reported no significant difference in mortality rates between the use of VAs and total intravenous anesthetics at 1 year postoperatively. However, oxygenator function may affect the VA pharmacokinetics. Thus, we measured the VA blood concentrations during CPB in patients managed with four different microporous polypropylene hollow fiber membrane oxygenators.

Methods Twenty-four patients scheduled for elective CPB were randomly allocated to one of the two VA groups (desflurane and sevoflurane groups) and, then, randomly divided into one of four oxygenator groups: Terumo, LivaNova, Medtronic, and Senko ($n=3$). Additionally, in each VA group, three patients were randomly selected and redundantly allocated to the human lung group (for control blood VA concentration without oxygenator). Blood samples collected 20 min after starting 6.0 vol% desflurane or 1.7 vol% sevoflurane were analyzed using gas chromatography. Oxygenator-related complications and structural changes in the membrane surface of each oxygenator after surgery were evaluated.

Results The mean (standard deviation) concentrations of desflurane and sevoflurane in the human lung were 182.4 (23.2) and 54.0 (9.6) µg/ml, respectively; not significantly different from those in the four oxygenator groups. No oxygenator-related complications occurred. Structural changes in membrane fibers did not occur after clinical use, except for difficulty in image acquisition with Senko products.

Conclusion Our results demonstrated that the blood concentrations of desflurane and sevoflurane passing through oxygenators used during CPB were similar to those in the human lung control.

Keywords Cardiopulmonary bypass · Concentration · Desflurane · Sevoflurane · Oxygenator

Introduction

The American College of Cardiology/American Heart Association and the European Association for Cardiothoracic Surgery guidelines recommend the use of volatile anesthetics (VAs) in cardiovascular surgery [1, 2]. VAs, such as desflurane and sevoflurane, protect myocardial cells via multiple mechanisms [3–8]. Therefore, their application during cardiopulmonary bypass (CPB) may improve prognosis compared with that of total intravenous anesthesia (TIVA). However, the MYRIAD study disproved the hypothesis that VAs improve clinical outcomes in patients undergoing coronary artery bypass graft compared to TIVA based on the mortality rate in the two groups 1 year after surgery [9]. Although the authors did not use a strict protocol, they argued that their trial was pragmatic and realistic. Indeed, the difficulties of

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conducting large-scale studies under a strict protocol have been recognized, but Zaugg et al. [10] pointed out that the administration protocol determines the success or failure of the study and should be set with stricter criteria in critical studies that verify the protective effect of VAs. Therefore, there is an ample scope for determining the usefulness of VA in CPB, and, hence, the findings of the MYRIAD study must be challenged by strict protocols comparing VA to TIVA in the future.

Besides the administration protocol, we believe that the performance of the oxygenator can also dramatically affect the results, a point that was not addressed in the MYRIAD study. Microporous polypropylene (PP) is often used as the material in the hollow fiber membranes (HFM) of CPB circuit oxygenators. Currently, many manufacturers have introduced PP HFM oxygenators with a biocompatible coating to reduce the adsorption and denaturation of blood cells and plasma proteins, contact reaction of blood with foreign matters, and changes in blood cell components by smoothing the membrane surface. Despite the aforementioned benefits, we believe that these coatings may affect the pharmacokinetics of VA, leading to over- or under-dosage. The effects, including pharmacokinetic effects, of these membranes on isoflurane properties during CPB [11, 12] have been studied, but only a few have considered desflurane or sevoflurane, which are frequently used in CPB general anesthesia [13].

We hypothesized that the blood levels of VAs differed with the use of four different oxygenators. In the present study, we aimed to measure the blood concentrations of desflurane and sevoflurane in patients managed with PP HFM oxygenators from four different manufacturers during CPB.

Methods

Patients and study design

This prospective pilot study was registered with the University Hospital Medical Information Network (UMIN ID: UMIN000033710, Principal investigator: Takahiro Tamura, Date of registration: November 1, 2018) and approved by the Institutional Review Board of the Nagoya University Hospital (IRB #2018–0329), Nagoya, Japan, where this study was conducted. Patients aged 20–90 years who were scheduled for elective cardiac or aortic surgery with CPB between January and August 2019 were recruited. Patients with contraindications for VA use, such as those with malignant hyperthermia and significant renal or hepatic impairment, were excluded. After obtaining written informed consent from the patients, they were randomly assigned via computer-generated simple randomization into one of two VA groups, desflurane or sevoflurane, and, then, into one of four oxygenator groups within each VA group, defined as follows: TE (CAPIOX manufactured by Terumo Co. Ltd., Tokyo, Japan) [14], LI (INSPIRE by LivaNova Japan K.K., Tokyo, Japan) [15], ME (Fusion by Medtronic Japan Co. Ltd., Tokyo, Japan) [16], and SE (EXELUNG by Senko Medical Instrument Mfg. Co. Ltd., Tokyo, Japan) [17]. These four manufacturers supply approximately 80% of the PP HFM oxygenators used in Japan. The allocation sequence was prepared by an independent operator who was blinded to the trial. Assigning of patients was performed by dedicated study personnel in a separate environment, and the patients were randomly assigned to one of the four parallel groups in a 1:1:1:1 ratio ($n=3$). Additionally, in each VA group, three patients were randomly selected and redundantly allocated to the human lung (HL) group (for control blood concentration of VA without an oxygenator before surgical intervention with mechanical ventilation). Only the CPB operator was aware of the patient's allocated oxygenator, but was blinded to the trial participants, anesthesiologists, sample collectors, and sample analysts. The anesthesiologists, sample collectors, and sample analysts were aware of the patients' allocated VA.

The primary outcome of the study was the 20-min arterial blood concentration of desflurane or sevoflurane after administration into each type of oxygenator during CPB. Secondary outcomes included oxygenator-related complications, such as plasma leaks or fissure. In addition, membrane fibers in each oxygenator were assessed using scanning electron microscopy (SEM) before and after VA exposure to determine VA exposure-related changes in membrane surface properties.

General anesthesia procedure

Non-invasive arterial blood pressure monitor, electrocardiography, pulse oximetry, electroencephalography monitor, regional oximetry monitor for the brain, and radial artery cannula for blood pressure monitoring and sampling were employed in all patients. Intravenous (IV) fentanyl and IV midazolam were administered to induce general anesthesia. Remifentanil and rocuronium were used to facilitate tracheal intubation. General anesthesia was maintained using air and oxygen at 3.0 l/min of total flow, 6.0 vol% desflurane or 1.7 vol% sevoflurane, and remifentanil (0.1–0.25 μg/kg/min). Bolus doses of fentanyl (up to 20 μg/kg) and rocuronium were supplemented as required. Porcine heparin (300 U/kg) and additional heparin bolus (50 U/kg) were injected to maintain an activated clotting time of at least 450 s.

The CDI-500 monitoring system (Terumo Co., Ltd.) was used for blood parameter monitoring during CPB (S5, LivaNova Japan K.K.). The circuit was primed with a balanced crystalloid solution. The non-pulsatile pump was maintained at a flow rate of 2.6 l/min/m^2 ± 10%. Alpha-stat blood gas management was used for acid–base control. After

aortic cross-clamping and administration of the cold cardioplegic solution, a stable level of perfusion pressure in mild hypothermia (arterial and rectal temperature, 32–33 °C) was obtained. When reaching the target flow rate, ventilation was stopped, and the delivery of 6.0 vol% desflurane or 1.7 vol% sevoflurane was started through a vaporizer (D-Vaper 3000, Dräger Medical Japan Ltd., Tokyo, Japan) from the oxygenator's gas supply line with a constant gas mixture of oxygen and air (F_IO_2 50–60%) at 0.5–3.0 l/min. The gas was regulated based on the CDI-500 and atrial blood gas readings.

Ventilation and inotropic drug support were started before commencing CPB, and the patients were admitted to the intensive care unit with intubation. The following parameters were subject to the discretion of the individual anesthesiologist: intraoperative ventilator settings other than the vaporizer concentration setting of desflurane or sevoflurane, F_IO_2, total gas flow rate (l/min), fluid infusion volume, anesthesia dosage other than VA, and choice of vasopressor (dopamine, dobutamine, or noradrenaline). Protamine (3 mg/kg) was administered to neutralize the effects of heparin. We used an intraoperative cell salvage device in all cases, and red blood cell concentrates were transfused to maintain a hemoglobin level > 8 mg/dl during CPB. Coagulation function was monitored by TEG 6 s (Haemonetics Japan GK, Tokyo, Japan), and fresh frozen plasma or platelet concentrate was administered where needed.

The anesthetic gas concentration in each oxygenator was monitored using the anesthesia machine (Perseus A500, Dräger Medical Japan Ltd). A drainage system was used to decrease VA leakage during CPB [18, 19]. Gas sampling was performed at the gas inlet of the oxygenator and an outlet port of our VA drainage system where the gas was aspirated at a flow rate of 200 ml/min. The gas analysis monitor was calibrated just prior to starting the study and was adjusted to zero every time before initiating a measurement according to the manufacturer's instruction.

Blood sample collection

Three blood samples were collected in each group via a radial artery cannula system with a closed circuit for blood sampling (Tru Wave with VAMP system, Edwards Lifesciences Co., Ltd., Irvine, CA). To measure desflurane and sevoflurane blood concentrations, blood samples (0.5 ml) were collected in a vial sealed with a rubber cap and aluminum crimp seal containing saline (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). The HL sampling for both anesthetics was undertaken 20 min after starting the delivery of 6.0 vol% desflurane or 1.7 vol% sevoflurane with tracheal intubation and 3.0 l/min total gas flow. To measure the blood concentration of both VAs via oxygenator, blood samples were collected at 20 min after starting the delivery of 6.0 vol% desflurane or 1.7 vol% sevoflurane to the oxygenator with a constant gas mixture of oxygen and air (F_IO_2 50–60%) at 0.5–3.0 l/min. Based on the drug package insert information, it was predicted that the serum concentration of VAs would be sufficiently parallel at 20 min after their delivery to the patient was started. Blood samples were also obtained 40 min after starting the delivery of 1.7 vol% sevoflurane through the oxygenators to investigate changes with time. Several conditions, such as fresh gas flow rate and body temperature at the time of sampling, were transferred from the electronic medical chart.

Gas chromatography

Desflurane, the standard, was obtained from Baxter Limited (Tokyo, Japan), and isoprene, the internal standard, was purchased from Sigma-Aldrich (St. Louis, MO). All other chemicals, including sevoflurane for standard and its internal standard, isoflurane, were purchased from Fujifilm Wako Pure Chemical Industries, Ltd. (Osaka, Japan).

Gas chromatography-tandem mass spectrometry (GC–MS/MS) for desflurane blood concentration was performed on a Shimadzu GCMS-TQ8030 triple quadrupole mass spectrometer (Shimadzu Corp., Kyoto, Japan) with fused-silica capillary column Rtx-5MS (30 m × 0.25 mm internal diameter (i.d.), 0.25 µm film thickness, Restek Corp., Bellefonte, PA). Helium was chosen as the carrier gas at a flow rate of 1 ml/min. The column oven temperature program was as follows: initial temperature of 35 °C held for 2 min, followed by a 10 °C/min linear ramp to a final temperature of 110 °C, with a final hold for 2 min (total run time, 11.5 min). The inlet temperature was set at 150 °C, and the gas sample (500 µl) was injected manually using a gas tight syringe after sample vial incubation for 15 min at 40 °C. MS detector parameters were as follows: interface temperature, 250 °C; ion source temperature, 230 °C. An electron impact (EI) ionization mode with an ionization energy of 70 eV was used. The analysis was performed in the selected ion monitoring (SIM) mode. In the SIM mode, we selected the ions of mass-to-charge ratio (*m/z*) 51 for desflurane and *m/z* 67 for isoprene. Data acquisition, processing, analyte identification, and quantification were conducted using LabSolutions Insight™ software (ver. 4.20, Shimadzu Corp.).

The headspace analysis for sevoflurane blood concentration was performed on a Shimadzu GC-2014AF/SPL 100 V (Shimadzu Corp.) with a flame ionization detector equipped with a capillary column SUPELCOWAX 10 (30 m × 0.25 mm i.d., 0.25 µm film thickness; Sigma-Aldrich). The oven and detector temperatures were 60 °C and 120 °C, respectively. The Shimadzu HS-20 LT headspace (Shimadzu Corp.) was used as an autosampler. The inlet pressure was set at 90 kPa. The carrier gas (helium) flow was 36.5 ml/min. Data acquisition and processing, analyte identification, and quantification were conducted

using LabSolutions Insight™ software (ver. 5.90, Shimadzu Corp.). Further data evaluation was performed using Microsoft Excel (Microsoft Corp., Redmond, WA). Desflurane and sevoflurane concentrations were calculated in μg/ml and corrected for blood sample weight.

Oxygenator membrane and fiber preparation

Of the oxygenators from each manufacturer, the one with the longest VA exposure time in surgeries was selected for this study. The shell of each oxygenator was removed. PP HFMs were randomly selected from near the center of the membrane layer, the middle layer, or near the surface layer and taken out. Membranes from unused oxygenators were prepared as controls.

Scanning electron microscopy settings

The de-cellularized and dried fibers were cut lengthwise to observe the microstructure of the inner surface. The cut fibers were fixed on the sample stage with a carbon tape to observe the inner surface. Then, the fibers were prepared with an osmium coating. The observation was performed using a high-resolution field emission SEM (JSM-7610F, JEOL, Tokyo, Japan).

Statistical analyses

The sample size was calculated as three for each group based on the quality control of gas chromatography ≤ 15%, coefficient of variation ≤ 10%, and sample sizes and variability of blood concentration of desflurane [20] and sevoflurane [21] in drug interview forms. Parametric tests were used for statistical analysis, as the Levene test showed that variances were homogeneous. The groups were compared using one-way analysis of variance, followed by two-tailed Dunnett's or Tukey's test. Non-parametric tests were performed using the Kruskal–Wallis or Mann–Whitney *U* test. *P* values < 0.05 indicated statistical significance and all *P* values were two tailed. All data were analyzed using SPSS software, version 26 (IBM Corp., Armonk, NY).

Results

Between January and August 2019, 24 patients were assessed for eligibility. All 24 were eligible for recruitment and were randomly allocated: 12 to the desflurane and 12 to the sevoflurane administration groups (Fig. 1). The 12 patients in each VA group were further allocated into four groups (TE, LI, ME, and SE) of three individuals. In the sampling for the HL group, three patients were randomly selected in each VA administration group. No patients withdrew from the study. Finally, 30 samples were collected for blood concentration measurement and analyzed. Patient information and surgical characteristics are presented in Table 1.

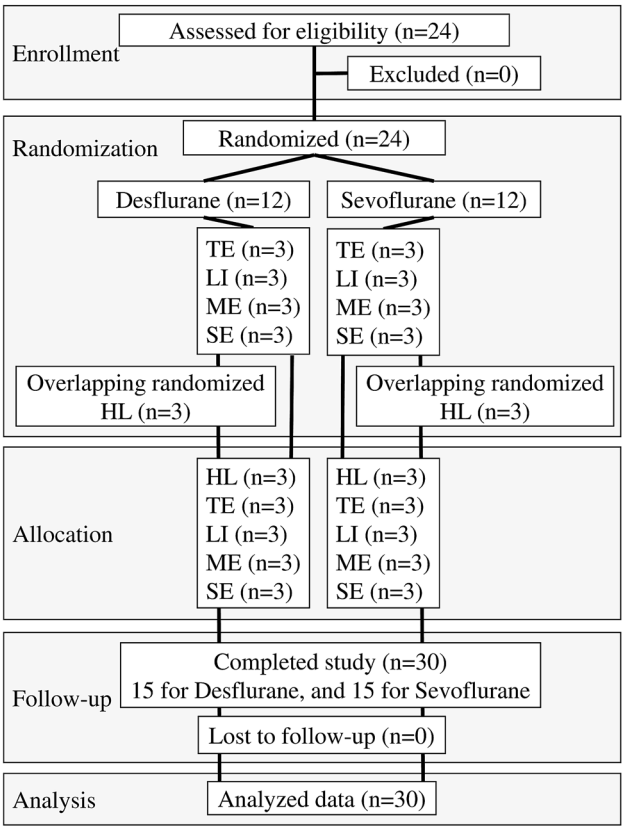

Fig. 1 CONSORT flow diagram. *TE* CAPIOX (Terumo Co. Ltd.), *LI* INSPIRE (LivaNova Japan K.K.), *ME* Fusion (Medtronic Japan Co. Ltd.), *SE* EXELUNG (Senko Medical Instrument Mfg. Co. Ltd.), and *HL* human lung

The mean (standard deviation) concentration of desflurane at 20 min after starting its delivery was 182.4 (23.2) μg/ml in the HL group (Fig. 2a). We did not observe any significant difference for any of the oxygenators (TE: 181.8 (24.3) μg/ml, $P = 1.000$; LI: 163.3 (3.0) μg/ml, $P = 0.613$; ME: 155.8 (9.4) μg/ml, $P = 0.353$; and SE: 162.8 (28.1) μg/ml, $P = 0.595$; Fig. 2a) when compared to the HL group. For sevoflurane, the concentration at 20 min after starting its delivery was 54.0 (9.6) μg/ml in the HL group (Fig. 2b). There was no significant difference in the results from any of the oxygenators (TE: 60.4 (5.9) μg/ml, $P = 0.947$; LI: 63.1 (11.3) μg/ml, $P = 0.773$; ME: 55.4 (5.3) μg/ml, $P = 1.000$; and SE: 60.5 (12.4) μg/ml, $P = 0.943$; Fig. 2b) when compared to the HL group.

Secondary outcomes assessed included complications related to oxygenators, such as plasma leaks, fissure, denaturation, blood clot, hypoxia, and other unexpected complications. No complications were observed in this study.

Table 1 Patients' demographic and surgical characteristics

	Desflurane ($n=12$)	Sevoflurane ($n=12$)
Demographic information		
Age (years)	63.3 (14.6)	59.2 (17.2)
Height (cm)	163.8 (9.5)	165.9 (3.4)
Body weight (kg)	61.0 (10.6)	66.7 (10.4)
Body mass index (kg/m^2)	22.6 (2.5)	24.3 (3.6)
Male:female	11:1	9:3
Surgical information		
Single valve[a]	2	4
Coronary artery[b]	4	1
Aorta[c]	4	3
Congenital[d]	0	1
Complex[e]	2	3

Data are expressed as means (standard deviation) or number of patients. Twenty-four patients scheduled for elective cardiopulmonary bypass were randomly allocated to one of the two VA groups (desflurane and sevoflurane groups) and, then, randomly divided into one of the four groups (TE, LI, ME, and SE) consisted of four individuals within each VA group. The same number of patients was also randomly and redundantly allocated to group HL in each VA group. Therefore, the patients in the HL group are not included in this table to avoid duplication

[a]aortic valve repair, aortic valve replacement, mitral valve repair, or mitral valve replacement

[b]coronary artery bypass grafting

[c]total arch replacement ± elephant trunk, ascending aorta replacement

[d]atrial septal defect

[e]valve + maze procedure, valve + coronary artery bypass grafting

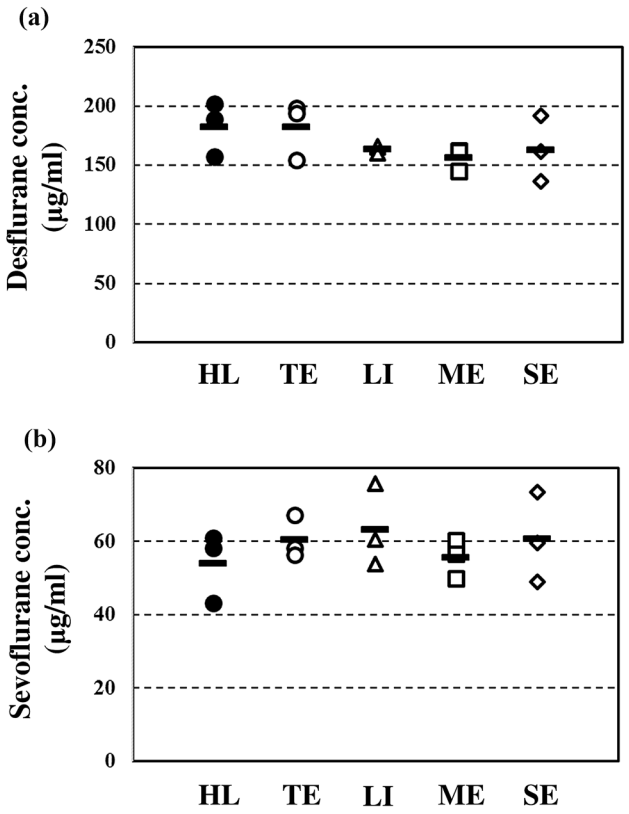

Fig. 2 Blood concentrations of desflurane and sevoflurane via oxygenator. **a** desflurane. **b** sevoflurane. The HL sampling for both anesthetics was taken 20 min after starting the delivery of 6.0 vol% desflurane or 1.7 vol% sevoflurane. Blood samples via each oxygenator were collected 20 min after starting the delivery of 6.0 vol% desflurane or 1.7 vol% sevoflurane to the oxygenator. *Plots* and *horizontal lines* in each group correspond to the measured values ($n=3$) and the mean, respectively. *HL* human lung, *TE* CAPIOX (Terumo Co. Ltd.), *LI* INSPIRE (LivaNova Japan K.K.), *ME* Fusion (Medtronic Japan Co. Ltd.), and *SE* EXELUNG (Senko Medical Instrument Mfg. Co. Ltd.)

Images were acquired for the SEM-based evaluation of fibers in each unused oxygenator HFM, except for SE, in which its unique coating hindered definite image acquisition of the fiber surface. It was apparent that the shape of the fiber surface differed depending on the manufacturer (Fig. 3a). Images of fibers were acquired after clinical use (Fig. 3b). Apparent structural changes were not identified between unused and used fibers of the three oxygenators.

Discussion

The fiber coatings of the different oxygenators used in this study were poly-2-methoxyethyl acrylate coating in TE, phosphorylcholine coating in LI, sulfate and sulfonate groups-polyethylene oxide coating in ME, and polyethylene glycol-silicon-alkyl group coating in SE. They are biocompatible non-biological materials applied to the PP HFM. The results of this study revealed two major findings: First, at 20 min after starting VA administration, there were no significant differences between HL and the four oxygenators tested. Second, no apparent changes were observed in the fiber structures of three PP HFM oxygenators after clinical use.

The selected VA concentrations, 6 vol% desflurane [20] and 1.7 vol% sevoflurane [22, 23], were approximately equal to one minimum alveolar concentration. Moreover, the selected concentrations were close to the concentrations administered in general anesthesia. In the HL group, the mean blood concentration of desflurane with 6 vol% was similar to the value described in the package insert [20]. No data variability between the oxygenator groups and no significant difference from the HL group were noted. Similar results were obtained with 1.7 vol% sevoflurane after 20-min administration. Additionally, the 40-min blood concentration of sevoflurane was almost identical to that at 20 min (Supplemental Fig. 1), demonstrating that the sevoflurane blood concentration is stably maintained after passage through any one of the four types of PP HFM oxygenators. In the

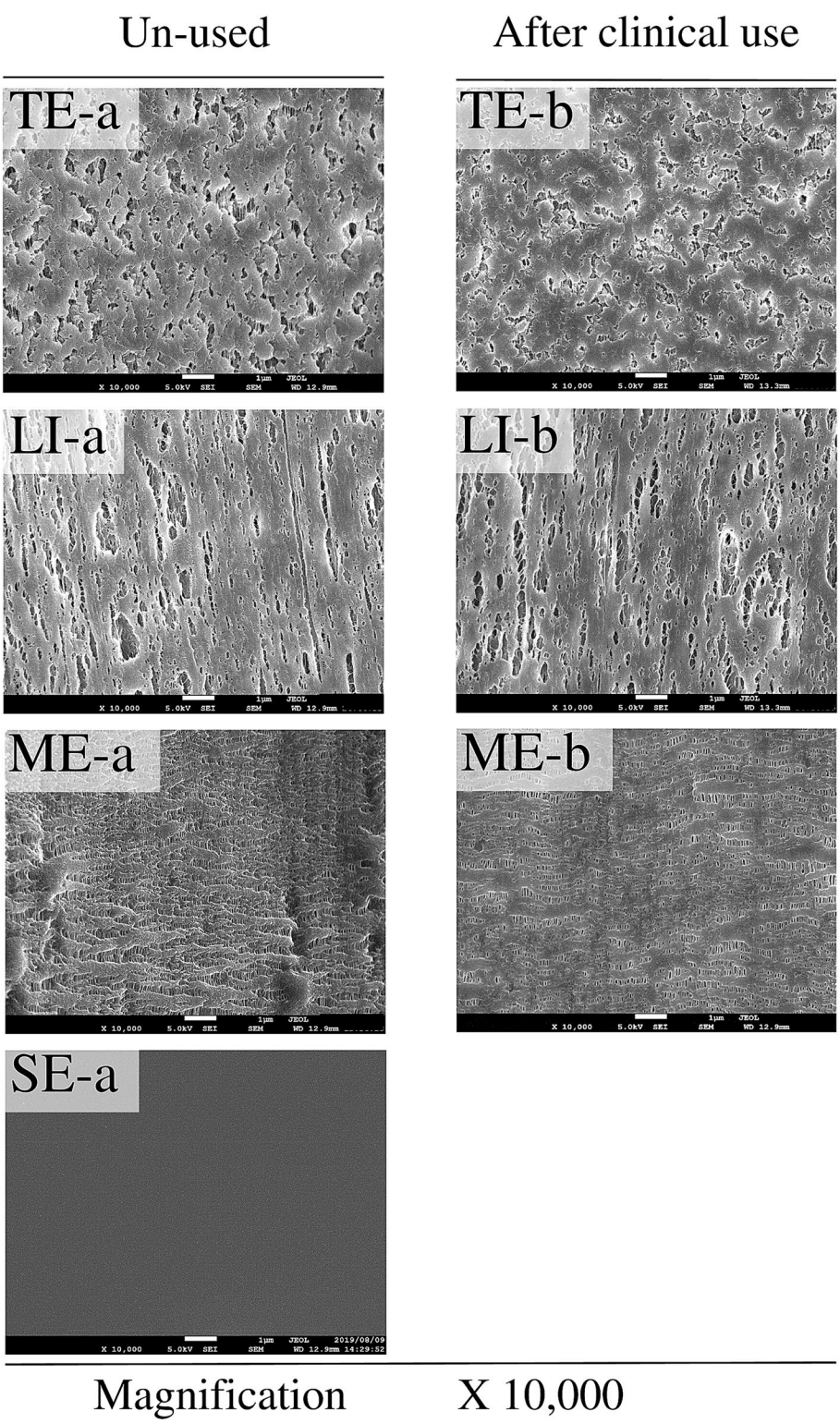

Fig. 3 The microstructure of microporous polypropylene fibers from oxygenators under SEM. Fiber images from both unused (**a**) and clinically used (**b**) oxygenators were captured at 10,000 times magnification. Definite fiber images from unused SE could not be acquired due to its unique coating. Therefore, no further observation was performed. *TE* CAPIOX (Terumo Co. Ltd.); *LI* INSPIRE (LivaNova Japan K.K.), *ME* Fusion (Medtronic Japan Co. Ltd.), and *SE* EXELUNG (Senko Medical Instrument Mfg. Co. Ltd.). *SEM* scanning electron microscopy

previous study conducted by Nitzschke et al. using 1.8 vol% of sevoflurane and types of PP HFM oxygenator different from ours [13], the sevoflurane blood concentration before introduction of the oxygenator was similar to our HL data. In addition, the blood concentrations from 17 to 32 min after introduction of the oxygenator were stable with little variation. These data emphasized that our blood sampling points defined from the package insert and their values were valid. Thus, the uptake and elimination of desflurane or sevoflurane via the tested PP HFM oxygenators are equivalent. In

addition, anesthesiologists could adjust the desflurane or sevoflurane concentrations during cardiac or aortic surgeries with CPB in the same manner as in surgeries without oxygenators.

The fiber structure of the three PP HFM oxygenators did not change with clinical use. The light microscopy results reported by Crosbie et al. [24] confirmed no changes in the structure or integrity of the PP fibers after short-term (3 h) or long-term (1 week) exposure to liquid sevoflurane. We attempted light microscopy, as performed by Crosbie et al., but image acquisition was challenging even with 1000 × magnification. Therefore, we switched to SEM. After cutting the coated PP membrane fiber, we were able to observe the internal structure of the HFM where VAs pass. Considering that the concentrations of desflurane and sevoflurane used in clinical practice are comparable to or lower than those used in this study, the absence of oxygenator-related complications and structural changes in our experiments denotes that an oxygenator can be a safe and reliable option for use in the future. There are no reports of spontaneous oxygenator-related complications occurring during CPB with VA. Nonetheless, there have been multiple reports where liquid VA spillage during vaporizer filling caused the development of cracks in the polycarbonate shell and venous connector of CPB circuit components [25, 26]. In the laboratory setting, we added 10 ml of liquid desflurane or sevoflurane directly to the shell and venous blood reservoir surfaces of each oxygenator and the connector tube. We did not observe any change in these components (data not shown), which might be due to possible improvements in the type of material used based on changes in the process of VA supplementation to vaporizer and the vaporizer placement. Even so, liquid VA spills on peripheral devices, including the oxygenator, should be regarded with caution.

This study had a limitation that should be addressed. We were not able to homogenize the surgical intervention, operator, conditions of the HL, and patient characteristics in each group. Besides fresh gas flow rate and hematocrit values at the time of sampling, the amount of bleeding during surgical intervention, body temperature, and the amount of blood in the CPB reservoir could have influenced the blood concentration of VA because of the volatility of VAs. Actually, in our study, there were significant differences between the HL and LI groups in fresh gas flow rate, between the HL and TE groups in the body temperature, and between the HL and TE, and the HL and LI groups in hematocrit values at the time point of sampling for desflurane measurement. In the sampling for sevoflurane measurement, no group difference was observed in the aforementioned three parameters (Supplemental Table 1). Strictly speaking, regarding sevoflurane, there was no difference between the groups in terms of factors affecting the blood levels. Therefore, it can be stated that there was no problem with the blood concentration values. Conversely, in desflurane, there were some differences. Thus, it may be necessary to conduct detailed examination under the same conditions. However, our results indicated a similar mean blood concentration level and variation among all groups. We believe that our results accurately reflect the clinical settings.

In conclusion, the blood concentrations of desflurane and sevoflurane passing through oxygenators used during CPB were similar to those in the HL control.

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Author contributions All the authors contributed to the study conception and design. Material preparation, and data collection and analysis were performed by TT, AM, and AI. MA and YK are professional statisticians. The first draft of the manuscript was written by TT, and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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