

## Long-duration, Low-flow Sevoflurane Anesthesia Using Two Carbon Dioxide Absorbents

### Quantification of Degradation Products in the Circuit

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**Background:** Sevoflurane reacts with soda lime, generating degradation products. The concentrations of sevoflurane degradation products in a low-flow circuit have been reported for anesthesia times of less than 5 h. In this study, sevoflurane degradation products generated during low-flow anesthesia exceeding 10 h were examined.

**Methods:** Sixteen patients received sevoflurane anesthesia with a fresh gas flow rate of 1 l/min. In eight patients, soda lime was used as the CO<sub>2</sub> absorbent; in the other eight patients, Baralyme was used. During anesthesia, the concentrations of degradation products in the circuit, the temperature of the CO<sub>2</sub> absorbent, inspired and end-tidal sevoflurane concentrations, and the volume of CO<sub>2</sub> eliminated by the patient were measured. Gas was sampled from the inspiratory limb of the circuit and analyzed by gas chromatography.

**Results:** Two degradation products, CF<sub>2</sub>=C(CF<sub>3</sub>)-O-CH<sub>2</sub>F (compound A) and CH<sub>3</sub>OCF<sub>2</sub>CH(CF<sub>3</sub>)OCH<sub>2</sub>F (compound B), were detected. In the soda lime group, the individual maximum concentration of compound A was 23.6 ± 2.9 (12.0-37.4) ppm. In the Baralyme group, the concentration was 32.0 ± 2.3 (23.5-41.3) ppm. The individual maximum concentration of compound A in the Baralyme group was significantly higher than that in the soda lime group. Compound B was detected in two patients, reaching a maximum concentration of 0.2 ppm. The end-tidal sevoflurane concentration, temperature of the CO<sub>2</sub> absorbent, and volume of CO<sub>2</sub> eliminated by the patient were the same in both groups.

**Conclusions:** The degradation products detected were at low concentrations in long-duration, low-flow anesthesia with sevoflurane. Baralyme produced higher concentrations of degradation products than soda lime. (Key words: Anesthetic system; low-flow circuit. Anesthetics, volatile: sevoflurane. Carbon dioxide, absorption: Baralyme; soda lime.)

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SEVOFLURANE reacts with soda lime,<sup>1</sup> resulting in the generation of several degradation products.<sup>2</sup> Five degradation products of sevoflurane have been identified *in vitro*.<sup>3</sup> Among these degradation products, CF<sub>2</sub>=C(CF<sub>3</sub>)-O-CH<sub>2</sub>F (compound A) has been reported to be a possible cause of organ toxicity.<sup>4</sup> The concentration of compound A is higher in low-flow or closed-circuit sevoflurane anesthesia than in relatively high-flow anesthesia at a flow rate of 6 l/min,<sup>3</sup> and therefore there has been debate regarding the safety of low-flow or closed-circuit sevoflurane anesthesia.<sup>5,6</sup> Frink *et al.*<sup>5</sup> measured the concentrations of degradation products and evaluated patients for hepatic or renal dysfunction after low-flow anesthesia using soda lime or Baralyme as the CO<sub>2</sub> absorbent. However, in their study, the anesthesia time was limited to 5 h. Moreover, fentanyl was administered concomitantly with sevoflurane, and thus the sevoflurane concentration was relatively low, approximately 1%. The purpose of this study was to carry out low-flow sevoflurane anesthesia exceeding 10 h duration using soda lime or Baralyme (Allied Healthcare Products, Inc., St. Louis, MO) as the CO<sub>2</sub> absorbent and to measure the concentrations of degradation products in the circuit.

In the study of Frink *et al.*,<sup>5</sup> one point that required clarification was the observed temperature difference between soda lime and Baralyme. *In vitro* studies have shown that, when the same volume of CO<sub>2</sub> is added to either of these two CO<sub>2</sub> absorbents, the resulting temperatures are almost the same.<sup>7</sup> Therefore, it is possible that some other difference in the conditions of anesthesia with soda lime and with Baralyme may have been responsible for the observed temperature difference between the two CO<sub>2</sub> absorbents in their study, presumably differences in CO<sub>2</sub> elimination from the patient, differences in fresh-gas flow, or differences in heat produced by the exothermic reaction between sevoflurane and CO<sub>2</sub> absorbent. It is known that the

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production of degradation products increases as the temperature of the CO<sub>2</sub> absorbent increases.<sup>8</sup> The objective of the study of Frink *et al.*<sup>5</sup> was not to compare soda lime and Baralyme, and so other variables were not eliminated. In the current study, to permit the accurate comparison of degradation products when soda lime or Baralyme was used as the CO<sub>2</sub> absorbent, the temperature of the CO<sub>2</sub> absorbent and the volume of CO<sub>2</sub> eliminated by the patient were measured.

### Materials and Methods

This study was approved by the institution's Committee on Human Research, and informed consent was obtained from all patients. The subjects in this study were 16 patients of ASA physical status class 1 or 2 with tumors of the head and neck who were scheduled to undergo tumor resection and for whom prolonged surgery of 10 h or longer duration was planned. Patients in whom the medical history, physical examination, or laboratory tests showed evidence of abnormal hepatic or renal function or severe cardiovascular disorders were excluded from the study.

Fifty milligrams hydroxyzine and 0.5 mg atropine sulfate were injected intramuscularly 45 min before induction of anesthesia. Anesthesia was induced with 4–5 mg/kg thiopental and 0.12–0.15 mg/kg vecuronium. After tracheal intubation, the flow rates of O<sub>2</sub> and N<sub>2</sub>O were set to 300 and 700 ml/min, respectively. The ratio of the O<sub>2</sub> and N<sub>2</sub>O flow rates was adjusted to maintain the O<sub>2</sub> concentration in the inspiratory limb greater than 30%. The sevoflurane concentration was adjusted to maintain systemic blood pressure within  $\pm 20\%$  of baseline. The lungs were ventilated mechanically with a tidal volume of 10–12 ml/kg, with the ventilatory rate adjusted to maintain an end-tidal CO<sub>2</sub> partial pressure of 30–40 mmHg.

For the first eight patients, soda lime (Sodasorb, W.G. Grace and Co., Lexington, MA) was used as the CO<sub>2</sub> absorbent, and for the other eight patients, Baralyme was used. The CO<sub>2</sub> absorbent was changed before the administration of anesthetics in each patient. The anesthesia machine was a Modulas II Anesthesia System (Ohmeda, Madison, WI).

Two temperature probes were inserted, one into the upper part of the upper absorbent canister and the other into the middle of the lower canister, and soda lime or Baralyme temperatures were recorded at 15-min intervals.

Table 1. Maximum Compound A Concentration, Anesthesia Time, and MAC-hour in Individual Patients

	Soda Lime Group								Baralyme Group							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Compound A maximum concentration (ppm)	27.6	20.7	37.4	15.4	12.0	31.5	21.9	22.6	23.5	37.8	33.5	24.8	37.8	41.3	27.8	29.8
Anesthesia time (h)	16.75	12.27	14.80	14.38	10.40	10.55	13.20	13.58	18.55	11.73	10.00	15.50	10.25	13.63	13.30	14.28
MAC-h	13.41	8.45	18.23	10.09	6.46	11.24	11.30	12.35	11.40	9.85	9.64	11.02	10.51	11.92	10.70	10.52

Compound A maximum concentration = maximum concentration of compound A measured in the anesthesia circuit; MAC-h = sevoflurane MAC-h exposure for each patient.

**Table 2. Hourly Compound A Concentration, End-tidal Sevoflurane Concentration, and Amount of Carbon Dioxide Eliminated**

	1 h	2 h	3 h	4 h	5 h	6 h	7 h
Compound A concentration (ppm)	16.0 ± 1.9	19.5 ± 2.1	19.6 ± 2.8	22.0 ± 3.5	17.8 ± 2.0	18.7 ± 2.4	18.6 ± 2.4
End-tidal sevoflurane concentration (%)	1.4 ± 0.1	1.5 ± 0.2	1.8 ± 0.2	1.7 ± 0.2	1.5 ± 0.1	1.6 ± 0.2	1.6 ± 0.2
Amount of CO <sub>2</sub> eliminated as an hourly average (ml/min)	129.5 ± 7.2	142.6 ± 9.4	138.0 ± 9.2	140.8 ± 8.8	142.5 ± 9.9	148.5 ± 12.2	157.7 ± 12.3
No. of patients	8	8	8	8	8	8	8

Values are mean ± SE.

During anesthesia, end-tidal CO<sub>2</sub> concentrations and inspired and end-tidal sevoflurane concentrations were monitored by mass spectrometry (Medical Gas Analyzer 1100, Perkin Elmer, Pomona CA), and the volume of CO<sub>2</sub> eliminated by the patient was monitored using a system described previously,<sup>9</sup> with the mean hourly volume calculated based on measurements obtained every 1 min. The mass spectrometer was calibrated against a known concentration of sevoflurane that was verified by calibration with a gas chromatograph (GC-9A, Shimadzu, Kyoto, Japan).

Gas in the circuit was collected from the inspiratory limb using a glass syringe (20 ml). Silicone grease was applied to ensure that the syringe was airtight. The concentrations of degradation products in the circuit were measured using a gas chromatograph (GC-9A, Shimadzu) equipped with a gas sampler (MGS-5, Shimadzu) at 1-h intervals. A glass column with a length of 5 m and an internal diameter of 3 mm packed with 20% dioctyl phthalate on a Chromosorb WAW (Technolab S. C., Osaka, Japan) 80/100 mesh was maintained at 100°C in the gas chromatograph. The injection port was maintained at 140°C. A carrier stream of nitrogen

flowing at 50 ml/min was delivered through the column to a hydrogen flame ionization detector. Stock calibration standards of compound A and CH<sub>3</sub>OCF<sub>2</sub>CH(CF<sub>3</sub>)OCH<sub>2</sub>F (compound B) were obtained from Maruishi Pharmaceutical (Osaka, Japan). Gas standards were prepared by injecting 20 μl (compound A) or 5 μl (compound B) stock solution into a 150-ml glass vial sealed with a Teflon stopper. Gas then was extracted using a gas-tight syringe and injected into a 2.7-l flask. The amount of gas injected into the 2.7-l flask was 1–5 ml for the 10–50-ppm standard calibration gas (compound A) or 0.1–0.5 ml for the 0.2–1.0-ppm standard calibration gas (compound B). Standard calibration gas was extracted using a 20-ml glass syringe and injected into a gas sampler (MGS-5, Shimadzu).

Measured values are expressed as mean ± SE. Repeated-measures analysis of variance was used (when appropriate) with the Student's *t* test for comparison of soda lime and Baralyme with regard to the individual maximum compound A concentration, hourly compound A concentrations, hourly ratio of compound A concentration to end-tidal sevoflurane concentration, the peak temperature of CO<sub>2</sub> absorbent, the end-tidal

**Table 3. Hourly Compound A Concentration, End-tidal Sevoflurane Concentration, and Amount of Carbon Dioxide Eliminated**

	1 h	2 h	3 h	4 h	5 h	6 h	7 h
Compound A concentration (ppm)	19.7 ± 2.1	27.9 ± 2.4	23.7 ± 1.5	27.5 ± 1.4	24.2 ± 2.2	25.6 ± 3.3	22.6 ± 1.9
End-tidal sevoflurane concentration (%)	1.4 ± 0.1	1.9 ± 0.2	1.4 ± 0.1	1.6 ± 0.1	1.5 ± 0.2	1.7 ± 0.2	1.6 ± 0.1
Amount of CO <sub>2</sub> eliminated as an hourly average (ml/min)	128.1 ± 6.7	130.0 ± 5.9	129.4 ± 7.3	137.3 ± 12.8	135.3 ± 8.9	140.4 ± 10.3	145.4 ± 9.5
No. of patients	8	8	8	8	8	8	8

Values are mean ± SE.

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## as an Hourly Average in the Soda Lime Group

8 h	9 h	10 h	11 h	12 h	13 h	14 h	15 h	16 h
18.9 ± 2.3	20.6 ± 2.5	19.1 ± 1.9	12.8 ± 0.6	12.4 ± 1.2	12.2 ± 0.5	10.8 ± 1.0	9.6	7.8
1.7 ± 0.2	1.9 ± 0.2	1.7 ± 0.2	1.4 ± 0.1	1.4 ± 0.2	1.5 ± 0.1	1.6 ± 0.3	1.2	1.2
163.7 ± 14.1 8	153.5 ± 7.5 8	158.9 ± 7.8 8	170.8 ± 5.9 6	169.0 ± 4.5 6	165.9 ± 6.5 5	164.7 ± 11.0 3	166 1	164.8 1

sevoflurane concentration, the volume of CO<sub>2</sub> eliminated by the patient, the anesthesia time and the MAC-hours of anesthesia. *P* values less than 0.05 were considered statistically significant.

## Results

Among the potential degradation products of sevoflurane, compound A [CF<sub>2</sub>=C(CF<sub>3</sub>)—O—CH<sub>2</sub>F] and compound B [CH<sub>3</sub>OCF<sub>2</sub>CH(CF<sub>3</sub>)OCH<sub>2</sub>F] were detected. When soda lime was used as the CO<sub>2</sub> absorbent, the individual maximum concentration of compound A was 23.6 ± 2.9 ppm (12.0–37.4 ppm) (table 1). On the other hand, when Baralyme was used, the concentration was 32.0 ± 2.3 ppm (23.5–41.3 ppm) (*P* < 0.05) (table 1). In the soda lime group, the concentration of compound A measured at 1-h intervals reached 19.5 ± 2.1 ppm (12.0–30.0 ppm) at 2 h after anesthesia, remained at a similar level until 10 h, and decreased thereafter (table 2 and fig. 1). In the Baralyme group, the concentration of compound A measured at 1-h intervals reached 27.9 ± 2.4 ppm (18.3–37.8 ppm) at 2 h, remained at a similar level until 10 h, and decreased thereafter, as was the case with soda lime (table 3 and fig. 1). A comparison of the concentration of

compound A measured at 1-h intervals in the soda lime and Baralyme groups did not show a statistically significant difference (fig. 1). At 3–10 h of anesthesia, the ratio of compound A concentration to end-tidal sevoflurane concentration measured at 1-h intervals was significantly higher in the Baralyme group than in the soda lime group (fig. 2). There was a positive correlation between the concentration of compound A and the end-tidal sevoflurane concentration during 10 h of anesthesia in both groups (fig. 3). Compound B was detected in the anesthetic circuit in only two patients in the Baralyme group, with a highest measured concentration of 0.2 ppm.

The peak temperature of soda lime was 45.6 ± 0.6°C, and that of Baralyme was 46.9 ± 0.6°C (*P* > 0.05). The anesthesia time was 13.2 ± 0.8 in the soda lime group and 13.4 ± 1.0 in the Baralyme group (*P* > 0.05) (table 1). MAC-hour was 11.44 ± 1.24 in the soda lime group and 10.69 ± 0.27 in the Baralyme group (*P* > 0.05) (table 1).

End-tidal sevoflurane concentration ranged between 0.8% and 2.8% for both groups, with no significant difference between the groups. The mean volume of CO<sub>2</sub> eliminated by the patient at 1-h intervals was 83.3–245.8 ml/min for both groups; this difference was not statistically significant.

## as an Hourly Average in the Baralyme Group

8 h	9 h	10 h	11 h	12 h	13 h	14 h	15 h	16 h	17 h	18 h
22.8 ± 2.2	24.6 ± 2.1	21.1 ± 1.8	19.6 ± 1.0	17.6 ± 1.7	13.7 ± 1.4	12.7 ± 1.3	8.9 ± 3.3	7.0	7.0	6.5
1.5 ± 0.1	1.6 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	1.4 ± 0.0	1.1 ± 0.1	0.9	1.3	1.2
146.8 ± 8.8 8	150.9 ± 8.7 8	155.1 ± 8.6 8	161.7 ± 9.5 6	150.4 ± 0.8 5	152.7 ± 3.6 5	149.9 ± 2.9 3	149.2 ± 8.8 2	162.5 1	160.5 1	157.3 1

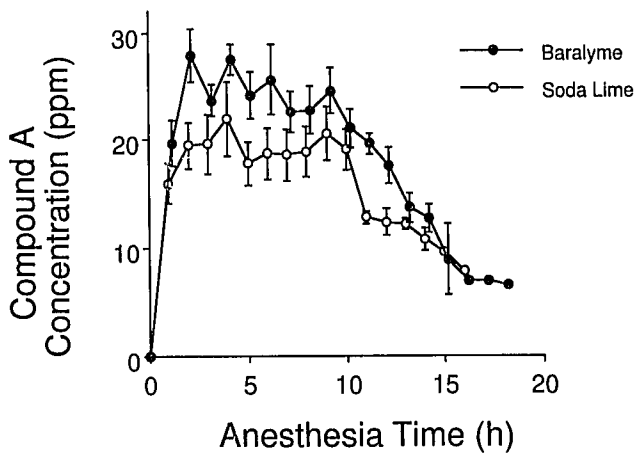


Fig. 1. Comparison of compound A concentrations in the anesthesia circuit with soda lime and Baralyme. Values are mean  $\pm$  SE.

## Discussion

To analyze the degradation products resulting from the reaction of sevoflurane with two different CO<sub>2</sub> absorbents, we administered sevoflurane to surgical patients using a low-flow circuit with fresh gas flow at 1 l/min. The degradation products of sevoflurane accumulate during anesthesia using a low-flow circuit,<sup>5</sup> and the potential toxicity of these degradation products has led to questions regarding the safety of sevoflurane administration.<sup>6</sup> Frink *et al.*<sup>5</sup> studied sevoflurane anesthesia in a low-flow circuit with anesthesia times of less than 5 h and a sevoflurane concentration of approximately 1% and evaluated the levels of the degradation products and their organ toxicity. In the current study, we examined the concentrations of degradation products in a low-flow circuit with sevoflurane anesthesia exceeding 10-h duration.

In the report by Frink *et al.*,<sup>5</sup> compound A levels increased over time, whereas our results showed that the concentration of compound A remained at the same level during 10 h of anesthesia. Reasons for this discrepancy may include differences in end-tidal sevoflurane concentration or patient-to-patient variability. Our results show that the concentration of compound A tended to decrease after 10 h. In our previous report, using a closed circuit,<sup>10</sup> the level of compound A decreased in a similar manner after 5 h. The study of Frink *et al.*<sup>5</sup> also reported a decrease after 5 h when Baralyme was used. Another report<sup>11</sup> has suggested that the generation of degradation products decreases be-

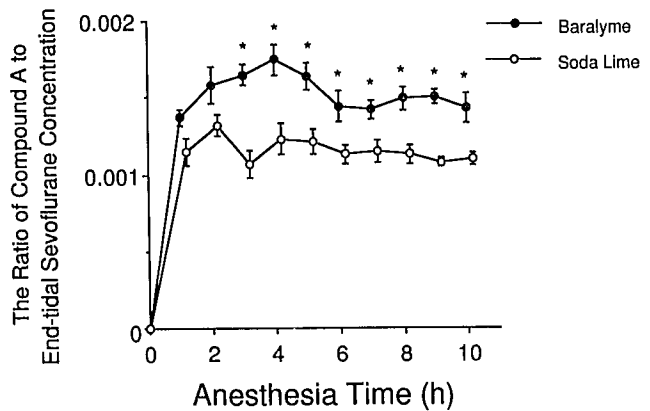


Fig. 2. Comparison of the ratio of compound A concentration to end-tidal sevoflurane concentration with soda lime and Baralyme. \* $P < 0.05$  versus the soda lime group. Values are mean  $\pm$  SE.

cause of exhaustion of the CO<sub>2</sub> absorbent or an increase in the humidity of the CO<sub>2</sub> absorbent. Compound B was detected in only two patients in the Baralyme group, and the highest measured concentration was 0.2 ppm. Such a low concentration should have no effect on humans, as compound B is reportedly less toxic than compound A.<sup>4</sup>

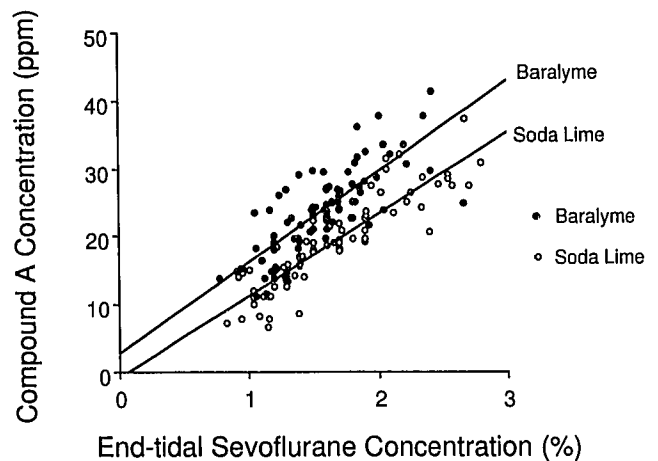


Fig. 3. Relation between compound A concentration and end-tidal sevoflurane concentration in the soda lime group ( $r = 0.80$ ,  $P < 0.01$ ) and the Baralyme group ( $r = 0.61$ ,  $P < 0.01$ ). The range of values obtained for compound A concentration was 6.7–37.4 ppm in soda lime group, 11.3–41.3 ppm in Baralyme group. The range of values obtained for end-tidal sevoflurane concentration 0.8–2.8% in soda lime group, 0.8–2.7% in Baralyme group.

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The factors that tend to increase the concentrations of degradation products in the circuit include use of the low-flow or closed-circuit anesthetic technique,<sup>5</sup> a higher concentration of sevoflurane,<sup>5</sup> higher temperature of the CO<sub>2</sub> absorbent,<sup>8</sup> use of Baralyme rather than soda lime,<sup>5,7</sup> and use of fresh CO<sub>2</sub> absorbent.<sup>5,11</sup> Thus, to clarify the differences in the concentrations of degradation products due to the composition of the CO<sub>2</sub> absorbent used in the circuit, it is necessary for the other factors to be controlled. Although Frink *et al.*<sup>5</sup> compared two CO<sub>2</sub> absorbents, the temperature of the soda lime was higher than that of the Baralyme. *In vitro* experiments have demonstrated that, when the same volume of CO<sub>2</sub> gas contacts soda lime or Baralyme, the resulting temperature of the two absorbents is almost the same.<sup>7</sup> Therefore, there must have been some other reason for the observed temperature difference in the CO<sub>2</sub> absorbents in the study of Frink *et al.*<sup>5</sup> Because one factor affecting the temperature of the CO<sub>2</sub> absorbent is the total volume of CO<sub>2</sub> in contact with the CO<sub>2</sub> absorbent, in clinical practice both the CO<sub>2</sub> eliminated by the patient and fresh gas flow are related to the increase in temperature. Another factor is the heat produced by the exothermic reaction between sevoflurane and CO<sub>2</sub> absorbent. Because the fresh gas flow did not vary significantly among patients in the study by Frink *et al.*,<sup>5</sup> it is speculated that the temperature difference was due to differences in the volume of CO<sub>2</sub> eliminated by the patient or differences in heat produced by the exothermic reaction between sevoflurane and CO<sub>2</sub> absorbent. In this study, there was no difference in CO<sub>2</sub> elimination between the two groups and no temperature difference in the CO<sub>2</sub> absorbents. Moreover, there was no difference in end-tidal sevoflurane concentrations between the two groups. It can be said that the results of our study comparing the concentrations of the degradation products using these two CO<sub>2</sub> absorbents reflected only differences in absorbent composition. In this study, the individual maximum concentration of compound A was significant higher for Baralyme than for soda lime ( $P < 0.05$ ). The ratio of compound A concentration to end-tidal sevoflurane concentration at 3–10 h of anesthesia was 1.2–1.5 times higher for Baralyme than for soda lime ( $P < 0.05$ ).

In a closed circuit, there is complete rebreathing, and thus the temperature of the soda lime should be

higher and the gas washout in the circuit should be lower than in a low-flow circuit. Therefore, closed-circuit anesthesia should produce higher concentrations of degradation products than a low-flow circuit. However, the concentration of compound A reported in a previous study using a closed circuit<sup>10</sup> was the same as that observed in the current study using a low-flow circuit with soda lime. Because the amount of water expired by the patient and generated by the conversion of CO<sub>2</sub> to CaCO<sub>2</sub> is greater in a closed circuit than in a low-flow circuit, water accumulates in the CO<sub>2</sub> absorbent. Moist CO<sub>2</sub> absorbent may be less effective in the degradation of sevoflurane.<sup>11</sup>

A higher concentration of sevoflurane results in a higher concentration of compound A in the circuit *in vitro*.<sup>5</sup> Our results show a positive correlation between the end-tidal sevoflurane concentration and the concentration of compound A. Values after 11 h were excluded from the statistical analysis because the decrease in the observed concentration of compound A was less than would be expected for the sevoflurane concentration.

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