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Calcium chloride within carbon dioxide absorbents prevents Compound A production from sevoflurane

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ABSTRACT

Calcium chloride ($CaCl_2$)-containing carbon dioxide (CO_2) absorbers are characterized by their ability to produce almost no pentafluoroisopropenyl fluoromethyl ether (Compound A), a potentially nephrotoxic byproduct of sevoflurane, in vitro. However, the precise role of $CaCl_2$ in this process remains unclear. We aimed to clarify the role of $CaCl_2$ in vitro and determine whether $CaCl_2$-containing CO_2 absorbents produce Compound A during prolonged surgery under low- and minimal-flow sevoflurane anesthesia using Japanese brand Yabashi Lime-f (YL-f). In vitro, a reaction between 1 L of sevoflurane gas (8%) with 5% CO_2 and an absorbent specimen (20 g) with or without water was performed in an artificial closed-circuit system for 15 or 60 min at 45 °C. In vivo, patients scheduled for colorectal resection received 2.0 vol% sevoflurane at fresh gas flows of 2.0, 1.0, or 0.5 L/min (N = 6) with YL-f. Gas samples from the anesthetic circuit were collected 6 h after induction and at the conclusion of surgeries lasting over 7 h. Compound A concentrations were measured using gas chromatography-flame ionization detection. Compound A production was observed in $CaCl_2$-free absorbents but not in those containing $CaCl_2$ in vitro. During 60-min reactions, $CaCl_2$-free YL-f derivatives produced a median 3.5 ppm of Compound A, with higher concentrations (7.1 ppm) observed upon the addition of 3 mL of water. YL-f did not produce Compound A, regardless of the presence of water. Compound A was not detected in in vivo samples. In conclusion, $CaCl_2$ suppresses Compound A production from sevoflurane, likely by trapping water within the anesthetic circuit.

Keywords: calcium chloride, carbon dioxide absorbents, Compound A, deliquescent, sevoflurane

Abbreviations:
AKI: acute kidney injury
$Ca(OH)_2$: calcium hydroxide
$CaCl_2$: calcium chloride
CO_2: carbon dioxide
Compound A: pentafluoroisopropenyl fluoromethyl ether
FGF: fresh gas flow
YL-f: Yabashi Lime-f

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INTRODUCTION

In anesthesiology, the volatile anesthetic sevoflurane can undergo alkaline hydrolysis in the anesthesia circuit when it reacts with carbon dioxide (CO_2) absorbents containing strong alkali hydroxides, producing pentafluoroisopropenyl fluoromethyl ether (Compound A), a potentially nephrotoxic substance that has shown clear nephrotoxicity in rats.[1-3] Due to this risk, when sevoflurane was approved in the United States in 1995, the Food and Drug Administration (FDA) included specific restrictions on fresh gas flow (FGF) during its administration. The FDA labeling recommended that FGF be maintained at no less than 1 L/min for up to 2 minimum alveolar concentration (MAC)-hours and at no less than 2.0 L/min for longer exposure periods.[4] Despite reports of sevoflurane-induced Compound A production and associated renal damage in humans even after approval,[5,6] subsequent findings have demonstrated that Compound A is less likely to cause toxicity in humans due to the low renal β-lyase activity that metabolizes Compound A-cysteine conjugates.[7-9]

Advancements in CO_2 absorbent formulations have reduced the risk of Compound A production,[10,11] and accumulating evidence suggests that even with low- and minimal-flow sevoflurane anesthesia—conditions thought to increase Compound A concentrations—surgeries can be conducted safely without the manifestation of severe nephrotoxicity.[12] As a result, many anesthesiologists no longer regard Compound A toxicity as a significant concern. However, some anesthesiologists remain hesitant to employ low- or minimal-flow sevoflurane anesthesia.[13] This hesitation persists partly because FDA labeling has not changed, and recommendations in drug data sheets or package inserts continue to influence practice in several regions outside the US.[12]

Among the recently developed CO_2 absorbents with calcium hydroxide ($Ca(OH)_2$) as the main component, Drägersorb Free, AMSORB PLUS, and the Japanese brand Yabashi Lime-f (YL-f) contain calcium chloride ($CaCl_2$). Studies evaluating Compound A production both in vitro and in vivo have demonstrated the prevention of Compound A formation from sevoflurane.[14-19] Kobayashi et al suggested that the presence of $CaCl_2$ within these absorbents may contribute to reducing or eliminating Compound A, but the precise role of hygroscopic and deliquescent $CaCl_2$ in this process remains unclear.[17] According to Murray et al, the inclusion of $CaCl_2$ as a humectant in AMSORB helps maintain the dampness of $Ca(OH)_2$.[19] We hypothesized that $CaCl_2$ acts as a humectant and plays a role in trapping water, thereby preventing the water-mediated alkaline hydrolysis of sevoflurane. In the present study, we sought to elucidate the role of $CaCl_2$ in preventing Compound A production in vitro. Furthermore, we evaluated Compound A production in vivo during low- and minimal-flow sevoflurane anesthesia (2%) in surgeries lasting over 6 h using YL-f, a strong base-free CO_2 absorbent containing $CaCl_2$, to determine whether Compound A production was associated with the development of acute kidney injury (AKI) in humans.

MATERIALS AND METHODS

Materials

Sevoflurane purchased from Maruishi Pharmaceutical Co, Ltd (Osaka, Japan) and NIKKO Pharmaceutical Co, Ltd (Hashima, Japan) was used for the in vitro and in vivo studies, respectively. Alkali-free CO_2 absorbent YL-f and its derivative, in which only the amount of $CaCl_2$ was changed to 0, were kindly provided by Yabashi Industries Co, Ltd (Ogaki, Japan). Other strong base-free CO_2 absorbents, such as AMSORB PLUS (Armstrong Medical Inc, Coleraine, UK) and LoFloSorb (Intersurgical Ltd, Wokingham, UK), and sodium hydroxide (NaOH)-containing absorbents, such as Drägersorb 800 Plus and Drägersorb Free (Dräger Medical AG

& Co KG, Lübeck, Germany), were procured commercially. The chemical compositions of the CO_2 absorbent specimens are listed in Table 1. All other reagents and products were purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan) or Sigma-Aldrich Co, LLC (St. Louis, MO, USA).

Table 1 Chemical composition of carbon dioxide absorbents (weight %)

	$Ca(OH)_2$	H_2O	NaOH	Silica	$CaCl_2$	NaCl	$CaSO_4 \cdot 0.5\ H_2O$
Drägersorb 800 Plus	75–83	< 16	1–3				
Drägersorb Free	74–82	14–18	0.5–2		3–5		
LoFloSorb	78	13.5–17.5		6.5			
AMSORB PLUS	77–88	10–18			2.0–3.5		0.6–1.5
Yabashi Lime-f (YL-f)	> 80	12–16			1–2	1–2	
Yabashi Lime-f (YL-f) derivative	> 80	12–16				1–2	

This table was based on information from the respective manufacturers.

In vitro study

An artificial closed-anesthetic circuit system was prepared by connecting two polyvinylidene fluoride (Tedlar) bags to each side of a U-shaped glass tube with silicon hoses, as used in our previous study (Fig. 1A, B).[20] Sevoflurane gas (8 vol%) was prepared using a vaporizer (Tec 7, Datex-Ohmeda Inc, Ohmeda Drive Madison, WI, USA) and a 5% CO_2 gas cylinder. One Tedlar bag was filled with 1 L of sevoflurane, and the other one was left empty. The U-shaped glass tube was filled with 20 g of absorbent specimen with or without water and then placed in a water bath set at 45 °C. The reaction was initiated when the thermometer in the specimen indicated 45 °C. The Tedlar bag containing sevoflurane gas was pressed for 30 s, and the gas moved into the empty bag after passing through a U-shaped glass tube, where it contacted the specimen. Over the next 30 s, the gas-filled bag was pressed, and the gas returned to the original bag after passing through the glass tube. This procedure was repeated for 15 or 60 min, and the temperature of the specimen was monitored simultaneously. After the reaction, 100 mL of the gas sample was collected from the gas-filled Tedlar bag using a gas-tight syringe and transferred to a bottle at 600–760 mmHg. Compound A concentrations in the samples were analyzed within 1 week.

All Compound A analyses were outsourced to Maruishi Pharmaceutical Co, Ltd and conducted according to the method described by Kondoh et al, with minor modifications.[14] The concentrations were measured using a gas chromatograph (model GC-2010; Shimadzu Corporation, Kyoto, Japan) equipped with a flame ionization detector. The chromatograph utilized a 5 m column with an internal diameter of 3.0 mm, packed with 20% dioctyl phthalate and Chromosorb W AW (80/100 mesh) from GL Sciences (Tokyo, Japan). The injection temperature was set to 130 °C and the column temperature was maintained at 110 °C. Nitrogen served as the carrier gas at a flow rate of 23–29 mL/min. Calibration of the gas chromatograph was performed using standard calibration gas prepared from stock solutions of Compound A.

On the day of measurement, a calibration curve was generated with concentrations up to 63.2 ppm. Samples were deemed acceptable for measurement if the correlation coefficient (r) exceeded 0.999. The lower limit of quantification was 3.1 ppm. For concentrations below the

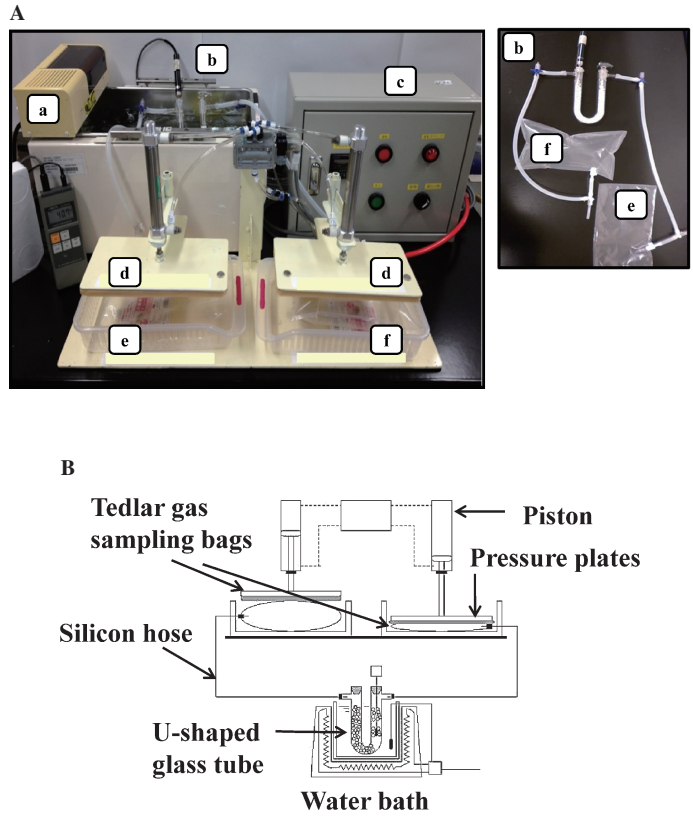

Fig. 1 Overview of the apparatus utilized in the closed-circuit anesthesia system for Compound A production from sevoflurane

Fig. 1A: Photograph of the artificial closed-circuit anesthesia system, showing: (a) constant-temperature water bath set at 45 ºC; (b) hairpin tube containing 20 g of CO_2 absorbent specimen; (c) system control box; (d) pressure plates; (e) empty Tedlar gas sampling bag; and (f) Tedlar gas sampling bag containing 8% sevoflurane (1 L).

Fig. 1B: Schematic representation of the artificial closed-circuit anesthesia system.

quantification limit, the value was officially recorded as 1.55 ppm, which is the median value between 0 and 3.1 ppm.

In vivo clinical study

This prospective study was registered with University Hospital Medical Information Network (UMIN000043925; https://www.umin.ac.jp/ctr/) and approved by the Institutional Review Board of Nagoya University Hospital (Approval number, 2019–0334; August 15, 2019). All procedures adhered to the Declaration of Helsinki, and written informed consent was obtained from all participants.

Patients were recruited between November 2019 and June 2022. Inclusion criteria were as follows: patients with American Society of Anesthesiologists physical status 1 or 2, aged >20 years, and scheduled for elective colorectal resection. Patients with renal dysfunction (estimated glomerular filtration rate <90) or hepatic dysfunction (total bilirubin >1.5 times and <3.0 times the institutional upper limit, and/or aspartate aminotransferase or alanine aminotransferase >2.5

times the upper limit) were excluded. Additional exclusions included patients with preoperative risk factors for perioperative AKI, such as hypertension, diabetes mellitus, congestive heart failure, impaired cardiac function, use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, non-steroidal anti-inflammatory drugs (NSAIDs), antibacterial agents, or diuretics. Pregnant women were also excluded. Patients were randomly assigned to one of three groups based on FGF: 2.0, 1.0, or 0.5 L/min, using computer-generated randomization.

A Perseus A500 (Dräger Medical AG & Co KG) anesthetic machine was used, with a 1,200-mL canister capacity. On the day of surgery, 1 kg of new YL-f was placed in the canister before anesthesia initiation. A data logger was placed in the middle of the canister to monitor internal temperature changes at 1-min intervals. Arterial blood pressure (Edwards Lifesciences Corporation, Irvine, CA, USA), pulse oximetry (Masimo Corporation, Irvine, CA, USA), non-invasive blood pressure, electrocardiography, and capnography (Koninklijke Philips NV, Amsterdam, Netherlands) were continuously monitored. General anesthesia was induced using intravenous propofol, fentanyl, remifentanil, and rocuronium, followed by endotracheal intubation. Maintenance of anesthesia was achieved with air, oxygen, 2.0 vol% sevoflurane at the prescribed FGF, and remifentanil (0.1–0.25 μg/kg/min), with bolus doses of fentanyl and rocuronium administered as needed.

Gas samples were collected from the inspiratory limb of the circle system using a gas-tight syringe at 6 h after anesthesia maintenance and at the end of anesthesia (for surgeries lasting >7 h). A 100-mL gas sample was stored in a vacuum bottle for analysis. If anesthesia concluded before 7 h, only the 6-h sample was collected. The study was terminated early if CO_2 rebreathing was detected by the capnometer, at which point a gas sample was collected, the absorbent was replaced, and surgery continued. Compound A concentrations were measured using the same method as previously described. NSAIDs were avoided postoperatively, and analgesia was managed with acetaminophen or opioids (fentanyl or morphine). Cefmetazole was the sole antimicrobial agent used. Patients with an operative time of <6 h were withdrawn from the study and excluded from evaluation.

To assess renal function, approximately 10 mL of blood was collected immediately after anesthesia induction and on postoperative days (POD) 1, 3, and 7 for serum creatinine analysis using a LABOSPECT 008 α (Hitachi High-Tech Corporation, Tokyo, Japan) and Cygnus Auto CRE (Shino-Test Corporation, Tokyo, Japan). Urine output was measured during and after surgery. Additional data, including blood biochemistry, urinalysis, and surgical records, were transcribed from the patients' medical records.

The primary endpoint was the concentration of Compound A in the anesthetic circuit gas. The secondary endpoint was the evaluation of renal function changes post-surgery. Patients were considered safe if the mean Compound A concentration remained below 20 ppm, as described in the following section, and if they did not meet the criteria for Stage 1 AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

Sample size determination of the in vivo clinical study

This study included three groups: 2% sevoflurane (FGF, 2.0 L/min) + YL-f (N = 6), 2% sevoflurane (FGF, 1.0 L/min) + YL-f (N = 6), and 2% sevoflurane (FGF, 0.5 L/min) + YL-f (N = 6).

The sample size for this clinical trial was calculated based on prior studies reporting nephrotoxic effects of Compound A in humans. Two key studies, one by Eger et al[6] and another by Goldberg et al,[5] demonstrated transient increases in urinary albumin and serum creatinine in healthy volunteers. These studies established toxicity thresholds for Compound A at 80–168 ppm × h and 240 ppm × h, respectively. In contrast, the toxicity threshold range for rats is

150–300 ppm × h.[21]

In our preliminary non-human study using the Flow-i C20 anesthetic machine (Getinge AB, Gothenburg, Sweden), which has a 700-mL canister capacity, YL-f was evaluated under 2% sevoflurane and 0.5 L/min FGF. Compound A concentrations at 0, 3, and 6 h after the reaction were <3.1 ppm. This indicated that the total Compound A exposure at 6 h was 0–18.6 ppm × h, which is approximately one-tenth of the reported human toxicity threshold. Based on these results, we concluded that administering sevoflurane at a minimal-flow rate of 0.5 L/min FGF would be safe.

Bito et al reported Compound A concentrations of 20 ± 7.8 ppm (mean ± SD) during gastrectomy in patients anesthetized with sevoflurane (mean anesthesia time, 6.11 ± 1.77 h; mean MAC-h, 7.13 ± 2.22) at 1.0 L/min FGF using Balalime, a CO_2 absorbent containing NaOH and potassium hydroxide.[22] Despite these levels, no renal dysfunction was observed postoperatively. In a separate preliminary non-human study using the Flow-i C20 anesthetic machine, YL-f demonstrated a mean Compound A concentration of 1.05 ± 2.10 ppm at 6 h under 2% sevoflurane and 2.0 L/min FGF (individual concentrations, 4.2, 0, 0, and 0 ppm; n = 4). Based on these results, the threshold mean value for the study was set at 20 ppm, while the expected mean was set at 1.0 ppm, with a conservatively estimated SD of 7.8 ppm. To account for multiple comparisons across the three groups, the significance level was set at 1.6% (5%/3) using Bonferroni correction. Under these conditions, a one-sample t-test with 80% power indicated that at least five cases per group would be required to detect differences between the expected mean and the threshold mean. To accommodate potential dropouts, the target number of cases increased to six per group, for a total of 18 patients.

Statistical analyses

For the in vitro experiment, Compound A concentrations were compared using the Wilcoxon rank sum test. The maximum reaction temperatures were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's test to examine the differences between absorbents. In the in vivo clinical study, a comparison of the mean Compound A concentrations in each of the three groups with the threshold mean was performed using Student's t-test (one-sample t-test) with Bonferroni correction. The level of significance was set at $P < 0.05$. We also performed one-sample t-test using the data when the six measurements were 0, 0, 0, 3.1, 3.1, and 3.1 as a sensitivity analysis. This data has the highest variance when all measurements are less than 3.1. In other words, this data has the highest p-value for the t-test. All data were analyzed using SPSS software (version 29; IBM Japan Ltd, Tokyo, Japan).

RESULTS

In vitro study

We measured the Compound A concentration produced by several CO_2 absorbent specimens in the 15-min reaction (Fig. 2A). In the comparison among absorbents, although the Compound A concentration in Drägersorb 800 Plus showed a median value of 89.4 ppm, Compound A was not observed in $CaCl_2$-containing Drägersorb Free as well as AMSORB PLUS and YL-f. Compound A concentration of a strong base-free LoFloSorb was 5.0 ppm. At the maximum reaction temperature, ANOVA testing showed a significant difference among the groups ($P < 0.01$). In addition, LoFloSorb and YL-f $CaCl_2$-free derivative showed a significantly lower temperature than those of the other deliquescent substance-containing absorbents, including YL-f (Table 2).

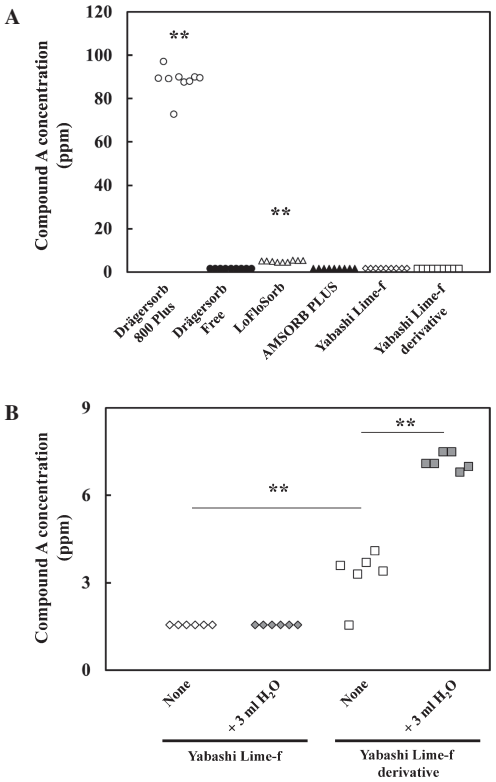

Fig. 2 Compound A production from sevoflurane with CO_2 absorbent specimen
Reaction conditions involving 1 L of 8% sevoflurane (in 5% CO_2) and 20 g of specimens for 15 min (A) or 60 min (B) at 45 °C. The plots represent measured values (A, n = 9; B, n = 6). The values below the quantification limit of 3.1 ppm were set to 1.55 ppm, the median value between 0 and 3.1 ppm. Compound A concentrations of Drägersorb 800 Plus and LoFloSorb were compared with the other deliquescent substance-containing absorbents including Yabashi Lime-f. ** $P < 0.01$ (Wilcoxon rank sum test).

Table 2 Maximum reaction temperatures during the reaction of sevoflurane with several carbon dioxide absorbents

	Maximum temperature (ºC)
Drägersorb 800 Plus	47.5 ± 0.4
Drägersorb Free	47.6 ± 0.2
LoFloSorb	46.9 ± 0.3##
AMSORB PLUS	47.8 ± 0.5
Yabashi Lime-f (YL-f)	47.5 ± 0.4
Yabashi Lime-f (YL-f) derivative	46.7 ± 0.3##

The reactions between 1 L of 8% sevoflurane (in 5% CO_2) and 20 g of CO_2 absorbents started at 45 °C and lasted for 15 min.
Data are expressed as means ± standard deviation (n = 9).
$P < 0.01$ vs the other deliquescent substance-containing absorbents including YL-f (one-way analysis of variance, followed by Tukey's test).

In 60-min reactions using YL-f and its $CaCl_2$-free derivative, the YL-f derivative showed a median Compound A production of 3.5 ppm. Moreover, higher Compound A production (7.1 ppm) was observed in the environment where 3 mL of water was added to the specimen. In contrast, YL-f itself did not produce Compound A in the presence or absence of water (Fig. 2B).

In vivo clinical study

A total of 18 patients completed the study (Fig. 3). The median anesthesia times were 497.0, 549.0, and 696.5 min in the 2.0-, 1.0-, and 0.5-L/min FGF groups, respectively (Table 3). Three patients (1.0 L/min, 1; 0.5 L/min, 2) showed rebreathing of CO_2 in the capnometer and the studies were terminated after the gas sample was collected. Compound A was not observed at all gas sampling points for all participants (Supplemental Table), and they were significantly lower than the threshold average of 20 ppm. A sensitivity analysis was performed, but significance was maintained. There were no differences between the groups in the maximum temperature in the canister (data not shown). Regarding AKI onset, two patients, one each from the 0.5 and 1.0 L/min FGF group, showed a creatinine content 1.5 times higher than the reference value on POD 1 and were diagnosed with Stage 1 disease according to the KDIGO guidelines. These two patients who underwent laparoscopic total pelvic exenteration had significantly longer anesthesia times than those of the others (0.5 L/min FGF, 1,242 min; 1 L/min FGF, 1,201 min; P = 0.025; Supplemental Table).

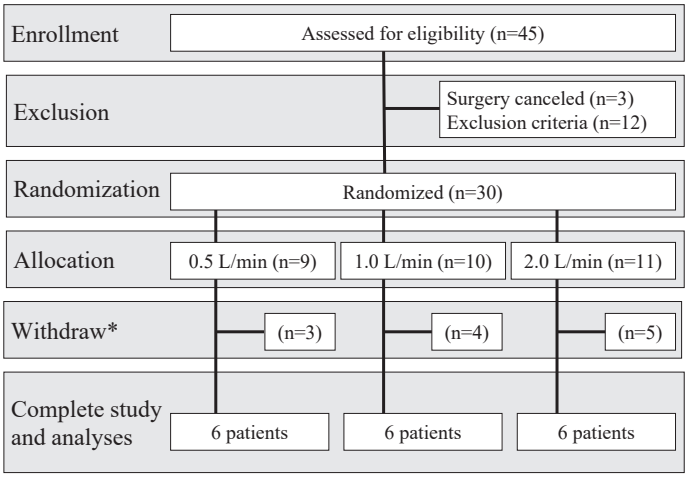

Fig. 3 Consolidated Standards of Reporting Trials (CONSORT) flow diagram

* Withdrawn cases with an operation time of <6 h and one case in the 2.0-L/min group for which data could not be obtained.

Table 3 Demographics of groups

FGF	2.0 L/min n = 6	1.0 L/min n = 6	0.5 L/min n = 6
Age (years)	51 (43, 79)	45 (32, 70)	66 (33, 79)
Male/Female (number of cases)	4/2	2/4	5/1
Body weight (kg)	49.6 (36.3, 61.3)	62.3 (50.6, 77.2)	51.7 (38.0, 69.5)
Body mass index (kg/m^2)	17.5 (15.4, 19.0)	24.4 (19.3, 26.1)	18.7 (15.6, 25.9)
ASA-PS I : II (number of cases)	1 : 5	2 : 4	1 : 5
Operation time (min)	394.5 (268, 522)	460.5 (339, 1110)	603.5 (355, 1136)
Anesthesia time (min)	497.0 (421, 684)	549.0 (436, 1201)	696.5 (459, 1241)

Data are expressed as median (minimum and maximum) or number of patients.
ASA-PS: American Society of Anesthesiologists-Physical Status
FGF: flesh gas flow

DISCUSSION

This study presents several key findings: (1) it confirms that Compound A production from sevoflurane degradation involves the reaction between $Ca(OH)_2$, the main component of CO_2 absorbents, and water in the anesthetic circuit; (2) the inclusion of $CaCl_2$, a hygroscopic agent, in CO_2 absorbents effectively prevents sevoflurane degradation into Compound A, likely by trapping water within the anesthetic circuit; and (3) Compound A production was not detected during low- and minimal-flow sevoflurane anesthesia surgeries lasting at least 6 h when using a $CaCl_2$-containing CO_2 absorbent that was free of strong bases.

Compound A is produced through the alkaline hydrolysis of sevoflurane. In our in vitro study, we evaluated various CO_2 absorbent specimens under conditions that strongly promote Compound A production, based on prior research.[23,24] Using NaOH-containing absorbent Drägersorb 800 Plus, we confirmed that our closed-anesthetic circuit system was effective in collecting Compound A samples from reactions between sevoflurane and the absorbent. In addition to Drägersorb 800 Plus, Compound A production was observed with LoFloSorb, which is free of strong alkalis. This suggests that $Ca(OH)_2$ is involved in the production of Compound A. Several previous studies, both in vitro and in vivo, have similarly demonstrated that even absorbents with reduced strong base content can produce Compound A.[16-18,25] These findings support the hypothesis that $Ca(OH)_2$ dissolves in water, becoming basic and creating an environment conducive to the alkaline hydrolysis of sevoflurane, which leads to Compound A production.

The presence of $CaCl_2$ in absorbent specimens effectively prevented Compound A production, as evidenced by comparisons between Drägersorb Free (containing $CaCl_2$) and Drägersorb 800 Plus (without $CaCl_2$). Compound A production was absent in all $CaCl_2$-containing specimens in the 15-min reactions. Additionally, the higher reaction temperatures observed with $CaCl_2$-containing specimens suggest that $CaCl_2$ interacts with water, generating heat. Interestingly, Compound A was detected in the YL-f $CaCl_2$-free derivative after a 60-min reaction, while YL-f itself (which contains $CaCl_2$) did not produce Compound A even after 60 min. This conclusively

demonstrated that $CaCl_2$ plays a crucial role in preventing Compound A production. Experiments involving the addition of water to these absorbents further clarified this role, showing that the amount of water directly influences Compound A production. When water was added to the YL-f derivative, Compound A concentrations increased, supporting the hypothesis that the hygroscopic properties (its ability to absorb and trap water) of $CaCl_2$ help prevent Compound A formation.

In the in vivo clinical study, no Compound A was detected in any of the 18 patients undergoing surgeries lasting >6 h at normal (2.0 L/min), low (1.0 L/min), or minimal-flow (0.5 L/min) sevoflurane anesthesia using YL-f. This is notable, as previous clinical studies using other $CaCl_2$-containing absorbents, such as AMSORB PLUS and Drägersorb Free, reported surgery durations of 4 and 3 h, respectively. Thus, this study represents the longest clinical evaluation of Compound A production. The absence of Compound A in these extended-duration surgeries suggests that even under conditions where humidity within the anesthetic circuit could rise, the use of $CaCl_2$-containing CO_2 absorbents effectively prevents Compound A formation.

Furthermore, while the CO_2 absorption capacity of YL-f was exceeded in the cases of three patients (two at 0.5 L/min, one at 1.0 L/min), and the further sampling from the patients had to be discontinued due to CO_2 rebreathing, Compound A was not detected immediately before termination. These findings suggest that low- and minimal-flow sevoflurane anesthesia can be performed safely with YL-f, provided that the absorbent is replaced when CO_2 rebreathing occurs.

Although two patients experienced AKI on POD 1, Compound A was ruled out as the cause. This suggests that while AKI may occur during prolonged surgeries, the use of $CaCl_2$-containing absorbents like YL-f can prevent Compound A-related kidney injury, further supporting the efficacy of these absorbents in minimizing sevoflurane degradation risks.

The clinical study had two key limitations. First, the patient selection focused on individuals undergoing colorectal resection, a procedure with minimal impact on renal function. However, this group included patients with Crohn's disease and colorectal cancer, resulting in significant variability in body weight within and between groups. Despite this variation, body weight did not seem to influence Compound A production, and the study was considered complete. The second limitation was the relatively small number of patients. While calculations confirmed that the mean Compound A concentration in all groups was below the safety threshold, larger-scale clinical trials are needed to further evaluate the risk of AKI during low- and minimal-flow sevoflurane anesthesia.

Low- and minimal-flow anesthesia offers multiple benefits beyond economic and environmental advantages. These methods help protect the lungs by humidifying and warming the ventilation gases. The Anesthesia Patient Safety Foundation has recognized the importance of low-flow anesthesia, featuring it in its newsletter and launching educational initiatives in collaboration with the American Society of Anesthesiologists.[13,26] Additionally, growing concerns regarding the environmental impact of desflurane have fueled the momentum toward adopting low-flow sevoflurane anesthesia.[27] To implement such changes, it is crucial to base practices on solid evidence.[10,12]

In conclusion, this study demonstrated that $CaCl_2$ effectively prevents Compound A production during sevoflurane anesthesia by trapping water in the anesthetic circuit. Strong base-free CO_2 absorbents containing $CaCl_2$, such as YL-f, may be particularly useful for low- and minimal-flow sevoflurane anesthesia, improving patient safety. Additionally, the ability of $CaCl_2$-containing absorbents to inhibit carbon monoxide production from the degradation of volatile anesthetics, such as desflurane, further enhances their safety profile.[20]

AUTHOR CONTRIBUTIONS

TA and AM contributed equally as co-first authors to the work. TA conduced study design, obtained written informed consent, collected data, and drafted and revised the manuscript. AM contributed study design, collected and analyzed data, and drafted and revised the manuscript. MN contributed study design and revised the manuscript. KN revised the manuscript and provided study supervision. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

PREVIOUS PRESENTATIONS

Partially presented at the American Society of Anesthesiologists' 114th annual meeting on October 21, 2019, in Orlando, and 118th annual meeting on October 15, 2023, in San Francisco.

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REFERENCES

1 Anders MW. Formation and toxicity of anesthetic degradation products. *Annu Rev Pharmacol Toxicol.* 2005;45:147–176. doi:10.1146/annurev.pharmtox.45.120403.095847

2 Gonsowski CT, Laster MJ, Eger EI 2nd, Ferrell LD, Kerschmann RL. Toxicity of compound A in rats. Effect of increasing duration of administration. *Anesthesiology.* 1994;80(3):566–573. doi:10.1097/00000542-199403000-00013

3 Gonsowski CT, Laster MJ, Eger EI 2nd, Ferrell LD, Kerschmann RL. Toxicity of compound A in rats. Effect of a 3-hour administration. *Anesthesiology.* 1994;80(3):556–565. doi:10.1097/00000542-199403000-00012

4 ULTANE (sevoflurane) volatile liquid for inhalation. Package inset. AbbVie Inc; 2017. Approved June 7, 1995. Revised November 1, 2022. Accessed July 17, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020478s030lbl.pdf

5 Goldberg ME, Cantillo J, Gratz I, et al. Dose of compound A, not sevoflurane, determines changes in the biochemical markers of renal injury in healthy volunteers. *Anesth Analg.* 1999;88(2):437–445. doi:10.1213/00000539-199902000-00040

6 Eger EI 2nd, Gong D, Koblin DD, et al. Dose-related biochemical markers of renal injury after sevoflurane versus desflurane anesthesia in volunteers. *Anesth Analg.* 1997;85(5):1154–1163. doi:10.1097/00000539-

199711000-00036
7 Uttamsingh V, Iyer RA, Baggs RB, Anders MW. Fate and toxicity of 2-(fluoromethoxy)-1,1,3,3,3-pentafluoro-1-propene (compound A)-derived mercapturates in male, Fischer 344 rats. *Anesthesiology.* 1998;89(5):1174–1183. doi:10.1097/00000542-199811000-00018
8 Iyer RA, Frink EJ Jr, Ebert TJ, Anders MW. Cysteine conjugate β-lyase-dependent metabolism of compound A (2-[fluoromethoxy]-1,1,3,3,3-pentafluoro-1-propene) in human subjects anesthetized with sevoflurane and in rats given compound A. *Anesthesiology.* 1998;88(3):611–618. doi:10.1097/00000542-199803000-00009
9 Iyer RA, Anders MW. Cysteine conjugate β-lyase-dependent biotransformation of the cysteine S-conjugates of the sevoflurane degradation product compound A in human, nonhuman primate, and rat kidney cytosol and mitochondria. *Anesthesiology.* 1996;85(6):1454–1461. doi:10.1097/00000542-199612000-00028
10 Feldman JM, Hendrickx J, Kennedy RR. Carbon dioxide absorption during inhalation anesthesia: A modern practice. *Anesth Analg.* 2021;132(4):993–1002. doi:10.1213/ANE.0000000000005137
11 Baum JA, Woehlck HJ. Interaction of inhalational anaesthetics with CO2 absorbents. *Best Pract Res Clin Anaesthesiol.* 2003;17(1):63–76. doi:10.1053/bean.2003.0269
12 Kennedy RR, Hendrickx JF, Feldman JM. There are no dragons: Low-flow anaesthesia with sevoflurane is safe. *Anaesth Intensive Care.* 2019;47(3):223–225. doi:10.1177/0310057X19843304
13 Feldman JM, Lampotang S. Patient safety and low-flow anesthesia. *APSF Newsletter.* 2022;37:54–56. Accessed July 30, 2024. https://www.apsf.org/wp-content/uploads/newsletters/2022/3702/APSF3702-2022-06-a04-SafetyandLow-FlowAnesthesia.pdf
14 Kondoh K, Atiba A, Nagase K, et al. Performance of a new carbon dioxide absorbent, Yabashi lime as compared to conventional carbon dioxide absorbent during sevoflurane anesthesia in dogs. *J Vet Med Sci.* 2015;77(8):961–965. doi:10.1292/jvms.14-0279
15 Yamakage M, Takahashi K, Takahashi M, Satoh JI, Namiki A. Performance of four carbon dioxide absorbents in experimental and clinical settings. *Anaesthesia.* 2009;64(3):287–292. doi:10.1111/j.1365-2044.2008.05759.x
16 Keijzer C, Perez RS, de Lange JJ. Compound A and carbon monoxide production from sevoflurane and seven different types of carbon dioxide absorbent in a patient model. *Acta Anaesthesiol Scand.* 2007;51(1):31–37. doi:10.1111/j.1399-6576.2006.01187.x
17 Kobayashi S, Bito H, Morita K, Katoh T, Sato S. Amsorb Plus and Dragersorb Free, two new-generation carbon dioxide absorbents that produce a low compound A concentration while providing sufficient CO2 absorption capacity in simulated sevoflurane anesthesia. *J Anesth.* 2004;18(4):277–281. doi:10.1007/s00540-004-0253-5
18 Stabernack CR, Brown R, Laster MJ, Dudziak R, Eger EI 2nd. Absorbents differ enormously in their capacity to produce compound A and carbon monoxide. *Anesth Analg.* 2000;90(6):1428–1435. doi:10.1097/00000539-200006000-00033
19 Murray JM, Renfrew CW, Bedi A, McCrystal CB, Jones DS, Fee JP. Amsorb: A new carbon dioxide absorbent for use in anesthetic breathing systems. *Anesthesiology.* 1999;91(5):1342–1348. doi:10.1097/00000542-199911000-00026
20 Ando T, Mori A, Ito R, Nishiwaki K. Important role of calcium chloride in preventing carbon monoxide generation during desflurane degradation with alkali hydroxide-free carbon dioxide absorbents. *J Anesth.* 2017;31(6):911–914. doi:10.1007/s00540-017-2397-0
21 Obata R, Bito H, Ohmura M, et al. The effects of prolonged low-flow sevoflurane anesthesia on renal and hepatic function. *Anesth Analg.* 2000;91(5):1262–1268. doi:10.1213/00000539-200011000-00039
22 Bito H, Ikeuchi Y, Ikeda K. Effects of low-flow sevoflurane anesthesia on renal function: Comparison with high-flow sevoflurane anesthesia and low-flow isoflurane anesthesia. *Anesthesiology.* 1997;86(6):1231–1237. doi:10.1097/00000542-199706000-00003
23 Fang ZX, Kandel L, Laster MJ, Ionescu P, Eger EI. Factors affecting production of compound A from the interaction of sevoflurane with Baralyme and soda lime. *Anesth Analg.* 1996;82(4):775–781. doi:10.1097/00000539-199604000-00018
24 Cunningham DD, Huang S, Webster J, Mayoral J, Grabenkort RW. Sevoflurane degradation to compound A in anaesthesia breathing systems. *Br J Anaesth.* 1996;77(4):537–543. doi:10.1093/bja/77.4.537
25 Struys MM, Bouche MP, Rolly G, et al. Production of compound A and carbon monoxide in circle systems: An in vitro comparison of two carbon dioxide absorbents. *Anaesthesia.* 2004;59(6):584–589. doi:10.1111/j.1365-2044.2004.03704.x
26 Thomas B. Off-label low-flow sevoflurane: Regulatory red herring or liability landmine? *APSF Newsletter.* 2022;372:57–58. Accessed July 30, 2024. https://www.apsf.org/wp-content/uploads/newsletters/2022/3702/APSF3702-2022-06-a05-Off-LabelLow-FlowSevoflurane.pdf

27 Hendrickx JFA, Nielsen OJ, De Hert S, De Wolf AM. The science behind banning desflurane: A narrative review. *Eur J Anaesthesiol.* 2022;39(10):818–824. doi:10.1097/EJA.0000000000001739

SUPPLEMENTARY INFORMATION

Supplemental Table Data for each group

Patient No.	Surgical procedure	Operation time (min)	Anesthesia time (min)	Gas sampling time*	CA conc.** (ppm)	KDIGO criteria*** (urine volume)	KDIGO criteria (creatinine)
2.0 L/min No. 1	Laparoscopic proctocolectomy	522	684	6 h 8 h 35 m	N.D. N.D.	No	No
2.0 L/min No. 2	Laparoscopic colectomy	333	449	6 h	N.D.	No	No
2.0 L/min No. 3	Laparoscopic proctocolectomy	316	421	6 h	N.D.	No	No
2.0 L/min No. 4	Laparoscopic proctocolectomy	493	585	6 h 8 h 30 m	N.D. N.D.	No	No
2.0 L/min No. 5	Total colectomy and ileal pouch-anal anastomosis	456	545	6 h 8 h 10 m	N.D. N.D.	No	No
2.0 L/min No. 6	Laparoscopic colectomy	268	429	6 h	N.D.	No	No
1.0 L/min No. 1	Laparoscopic colectomy	346	436	6 h	N.D.	No	No
1.0 L/min No. 2	Laparoscopic proctocolectomy and laparoscopic colostomy	595	675	6 h 8 h 35 m	N.D. N.D.	No	No
1.0 L/min No. 3	Laparoscopic proctocolectomy	467	566	6 h 8 h 35 m	N.D. N.D.	No	No
1.0 L/min No. 4	Laparoscopic total pelvic exenteration	1110	1201	6 h 9 h 41 m	N.D. N.D.	No	Stage 1 (ΔsCre, POD 1)
1.0 L/min No. 5	Lymph node dissection (Pelvic)	454	532	6 h 7 h 44 m	N.D. N.D.	No	No
1.0 L/min No. 6	Laparoscopic low anterior resection	339	438	6 h	N.D.	No	No

0.5 L/min No. 1	Left hemicolectomy	355	501	6 h	N.D.	No	No
0.5 L/min No. 2	Laparoscopic proctocolectomy	728	809	6 h 10 h 15 m	N.D. N.D.	No	No
0.5 L/min No. 3	Laparoscopic total pelvic exenteration	1136	1241	6 h 10 h 50 m	N.D. N.D.	No	Stage 1 (ΔsCre, POD 1)
0.5 L/min No. 4	Laparoscopic low anterior resection	559	659	6 h 9 h 21 m	N.D. N.D.	No	No
0.5 L/min No. 5	Esophagectomy and right hemicoletomy	648	734	6 h 9 h 22 m	N.D. N.D.	No	No
0.5 L/min No. 6	Right hemicolectomy	364	459	6 h 7 h	N.D. N.D.	No	No

* Gas in the anesthesia circuit was collected 6 h after the start of sevoflurane anesthesia, and at the end of the operation or at the time of carbon dioxide absorbent exchange if the operation lasted longer than 7 h.

** CA conc. Compound A concentration

*** AKI (acute kidney injury) diagnostic criteria and severity classification according to KDIGO (Kidney Disease: Improving Global Outcomes) guidelines. "No" indicates that the diagnostic criteria are not met.

N.D.: Not detected, which indicates less than the quantification limit of 3.1 ppm.

sCre: serum creatinine

POD 1: post-operative day 1

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