High Carboxyhemoglobin Concentrations Occur in Swine during Desflurane Anesthesia in the Presence of Partially Dried Carbon Dioxide Absorbsents

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Background: Increased carboxyhemoglobin concentrations in patients receiving inhalation anesthetics (desflurane, enflurane, and isoflurane) have been reported. Recent in vitro studies suggest that dry carbon dioxide absorbents may allow the production of carbon monoxide.

Methods: The authors used high fresh oxygen flow (5 or 10 L/min) through a conventional circle breathing system of an anesthesia machine for 24 or 48 h to produce absorbent drying. Initial studies used 10 L/min oxygen flow with the reservoir bag removed or with the reservoir bag left in place during absorbent drying (this increases resistance to gas flow through the canister). A third investigation evaluated a lower flow rate (5 L/min) for absorbent drying. Water content of the absorbent and temperature were measured. Pigs received a 1.0 (human) minimum alveolar concentration desflurane anesthetic (7.5%) for 240 min using a 1 L/min oxygen flow rate with dried absorbent. Carbon monoxide concentrations in the circuit and carboxyhemoglobin concentrations in the pigs were measured.

Results: Pigs anesthetized with desflurane using Baralyme exposed to 48 h of 10 L/min oxygen flow (reservoir bag removed) had extremely high carboxyhemoglobin concentrations (more than 80%). Circuit carbon monoxide concentrations during desflurane anesthetics using absorbents exposed to 10 L/min oxygen flow (reservoir bag removed, 24 h) reached peak values of 8,800 to 13,600 ppm, depending on the absorbent used. Carboxyhemoglobin concentrations reached peak values of 73% (Baralyme) and 53% (soda lime). The water content of Baralyme decreased from 12.1 ± 0.3% (mean ± SEM) to as low as 1.9 ± 0.4% at the bottom of the lower canister (oxygen flow direction during drying was from bottom to top). Absorbent temperatures in the bottom canister increased to temperatures as high as 50°C. With the reservoir bag in place during drying (10 L/min oxygen flow), water removal from Baralyme was insufficient to produce carbon monoxide (lowest water content = 5.5%). Use of 5 L/min oxygen flow (reservoir bag removed) for 24 h did not reduce water content sufficiently to produce carbon dioxide with desflurane.

Conclusions: An oxygen flow rate of 10 L/min for 24 h in a conventional anesthesia circuit can dry carbon dioxide absorbents sufficiently to produce extremely high levels of carbon monoxide with high carboxyhemoglobin concentrations in desflurane-anesthetized pigs. When the reservoir bag is in place on the anesthesia machine or when a lower oxygen flow rate (5 L/min) is used, carbon dioxide absorbent drying still occurs, but 24–48 h exposure time is insufficient to allow for carbon monoxide production with desflurane. (Key words: Anesthetic, volatile: desflurane; Blood, hemoglobin: carboxyhemoglobin, saturation; Gases, nonanesthetic: carbon monoxide.)

A recent study suggests that desflurane, enflurane, and isoflurane may degrade in carbon dioxide absorbents to release carbon monoxide if the water content of the absorbent is reduced.¹ A recent report by Lentz¡ cites a case of increased carboxyhemoglobin concentrations (31.5%) when a desflurane anesthetic was used. Available data from these clinical cases and in vitro investigation suggest that several hours (or days) of drying of carbon dioxide absorbent (such as during a weekend) may produce increased carbon monoxide when a desflurane anesthetic is delivered. However, the time, circuit configuration, and oxygen flow rates required to produce sufficient carbon dioxide absorbent drying are unknown. In addition, it is unknown what carboxyhemoglobin concentrations might result from this potential carbon monoxide exposure. Therefore, we designed a study to determine whether a high fresh gas flow of several hours duration through a

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Fig. 1. Diagram showing oxygen flow direction through the absorbent canister to produce drying of the carbon dioxide absorbent. If the reservoir bag (RB) is in place on the circuit, greater resistance to flow through the absorbent is present, which reduces absorbent drying. E = exhalation valve; I = inhalation valve; BV = bag/ventilator switch; FGF = fresh gas flow; APL = adjustable pressure limiting valve (pop-off valve); upper = upper carbon dioxide absorbent canister; lower = lower carbon dioxide absorbent canister. Dashed lines in absorbent canisters indicate the location of mesh screens.

circle breathing system could produce sufficient carbon dioxide absorbent drying for carbon monoxide production with desflurane and to determine what carboxyhemoglobin concentrations might result from carbon monoxide exposure during desflurane anesthesia in pigs. In this study, we exposed carbon dioxide absorbents to a 5 or 10 l/min fresh oxygen flow for 24 or 48 h through a North American Dräger anesthesia delivery system. Subsequently we anesthetized pigs using desflurane and evaluated absorbent water content and temperature of the absorbent, as well as circuit carbon monoxide concentrations and carboxyhemoglobin concentrations in the pigs.

Materials and Methods

Baralyme and Soda Lime Drying
Fresh Baralyme (Chemetron Medical Division, Allied Health Care Products, St. Louis, MO) or soda lime (Sodasorb; W.R. Grace and Co., Lexington, MA) was placed in both upper and lower carbon dioxide absorbent canisters of a Narkomed 2 model anesthesia machine (North American Dräger, Telford, PA). Oxygen flow was initially delivered at 10 l/min through the circuit without the disposable circle breathing system or reservoir bag in place and with the adjustable pressure-limiting valve (pop-off valve) completely open (fig. 1). The absorbent was exposed to the 10 l/min gas flow for a total of 24 or 48 h. In a second set of studies, the reservoir bag was left in place on the machine and drying was performed using a 10 l/min gas flow for 24 or 48 h. In a third set of studies, the effect of a lower oxygen flow rate on carbon dioxide absorbent drying was studied using a 5 l/min oxygen flow rate for 24 h (with the reservoir bag removed). Absorbent samples (approximately 10 g) for water content analysis were removed from the carbon dioxide absorbents before and after oxygen exposure for drying. Samples were obtained from the upper, middle, and lower one-third sections of both the upper and lower carbon dioxide canisters for all 24-h drying studies. For the 48-h drying time investigation, Baralyme samples were obtained only from the upper one-third of the upper and lower canisters. The absorbent was separated into three regions within each canister using circular mesh screens. This allowed absorbent samples to be obtained from specific regions in the carbon dioxide absorbent canister.

Anesthetic Exposures
After we received approval from the University of Arizona Animal Care and Use Committee, we used domestic swine (20-30 kg) for the study. Animals received inhalation induction via mask with halothane using an anesthetic machine different from that containing the dried Baralyme. After inhalation induction, an intravenous catheter was inserted and the trachea was intubated using pancuronium (0.1-0.15 mg/kg) for muscle relaxation. A femoral arterial catheter was inserted for pressure monitoring and to obtain blood for blood gas measurements. The animals' lungs were ventilated via the anesthesia circuit containing the dried Baralyme or soda lime, and anesthesia was administered using desflurane (7.5% end tidal, equivalent to 1.0 minimum alveolar concentration [MAC] in humans) with a total fresh gas flow of 1 l/min using an air and oxygen mixture to deliver an inspired oxygen concentration of 40%. The animals' lungs were mechanically ventilated using a tidal volume of 12-15 ml/kg with the ventilatory rate adjusted to maintain an end-tidal carbon dioxide concentration of 35-40 mmHg.

Studies Using 24- or 48-Hour Drying Time (Reservoir Bag Removed)
Nine animals were included in the studies using 48-h absorbent drying (which were performed with the reservoir bag removed) and Baralyme as the carbon dioxide absorbent. Of these nine animals, three died of cardiac arrest within 20 min of initiation of desflurane.
anesthesia and six were resuscitated with administration of intravenous epinephrine and discontinuation of the desflurane anesthetic. For this reason, further evaluation of 48-h drying times was discontinued.

Studies using 24-h drying time were performed in 19 pigs (Baralyme, n = 10; soda lime, n = 9). During these investigations, the carbon dioxide absorbent temperature was monitored by placing temperature probes of a digital thermometer (Fischer Scientific, Tustin, CA) in the center of the absorbent in the upper, middle, and lower one-third sections of each canister. Temperature was recorded every 10 min for the first 60 min and then every 30 min for the rest of the study.

End-tidal desflurane, oxygen, and carbon dioxide were measured using a Datex Capnomac Monitor (Datex Instrument Corp., Helsinki, Finland). Arterial pressure and heart rate were monitored using a Datascpe 2000A (Datascpe Corp., Paramus, NJ). Arterial blood was sampled before administration of desflurane anesthesia and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 150, 180, 210, and 240 min during anesthesia, provided anesthesia could be continued for the 4-h period. Blood samples were analyzed for percentage of carboxyhemoglobin using an Instrumentation Laboratory (Waltham, MA) model 482 co-oximeter.

Water content for Baralyme or soda lime was determined by removing 10 g of the carbon dioxide absorbent, which was subsequently lyophilized for 24 h using a Lyph-lock lyophilizer (Labonco, Kansas City, MO). The carbon dioxide absorbent was reweighed and the change in weight was reported as a percentage of water content. Circuit gas samples were obtained for carbon monoxide concentration determination at 5, 10, 15, 20, and 30 min, and every 30 min thereafter to a total of 240 min. Samples were obtained using a 10-ml locking gas-tight syringe (Supelco, Bellefonte, PA).

Studies Using 24- or 48-Hour Drying Time (Reservoir Bag in Place on the Circuit during Drying)

Eight pigs were studied using 24-h Baralyme drying time (n = 4) or 48-h Baralyme drying time (n = 4) with the reservoir bag left in place on the anesthetic circuit. After 24- or 48-h drying of Baralyme, pigs were anesthetized using desflurane exactly as outlined in the previously described studies in which the reservoir bag was absent. End-tidal desflurane, oxygen and carbon dioxide were determined as described previously and arterial blood sampling for carboxyhemoglobin levels was performed as previously outlined. The water content of Baralyme was determined as outlined in the previous set of investigations.

Studies Using 24-Hour Drying Time and 5 l/min Oxygen Flow Rate (Reservoir Bag Removed)

Four pigs were studied for carbon monoxide exposure using Baralyme exposed to 5 l/min oxygen flow rate for 24 h. In this portion of the study, the reservoir bag was removed during absorbent drying. Pigs were anesthetized with 1.0 MAC desflurane and sampling procedures were identical to the studies described before.

Carbon Monoxide Analytical Technique

Carbon monoxide samples were analyzed using a Varion Aerograph (Palo Alto, CA) series 1-400 gas chromatograph equipped with a thermal conductivity detector (200 mA × 4) and a Hewlett-Packard 3396 Series II Integrator (Palo Alto, CA). Typical calibration curves of carbon monoxide resulted in a linear relation between the thermal conductivity detector response to the concentration of carbon monoxide. The correlation coefficients were routinely greater than 0.99.

All data are shown as means ± SEM. Comparison between groups used repeated measures analysis of variance. Probability values less than 0.05 were considered to be significant.

Results

-48-Hour Drying Studies (Reservoir Bag Removed)

Exposure of Baralyme to 10 l/min oxygen flow for 48 h resulted in a decrease in water content from 11.9 ± 0.4% (fresh) to a water content of 3.9 ± 0.8% at the top of the upper canister and 1.2 ± 0.2% water content in the upper portion of the lower canister. This concentration of drying resulted in extremely high circuit carbon monoxide concentrations (mean peak concentration, 37,000 ± 3,500 ppm) occurring within 10 to 15 min of initiation of desflurane anesthesia. All animals had carboxyhemoglobin concentrations greater than 80%, with seven of nine animals achieving concentrations of 90% or more. Three pigs died during anesthetic administration. The remaining six animals were successfully resuscitated by discontinuing anesthetic and administering 100% oxygen and epinephrine intravenously (dose range, 0.25-2.0 mg given intravenously). None of the animals tolerated anesthesia with desflurane beyond 30 min due to hypotension (systolic blood pressure < 60 mmHg) from carbon monoxide exposure.
24-Hour Drying Studies (Reservoir Bag Removed)

Exposure of carbon dioxide absorbents to 24 h of oxygen flow (10 l/min) resulted in lower carboxyhemoglobin concentrations and a lower incidence of cardiovascular instability (hypotension) with desflurane than had occurred during the studies using 48 h dried absorbent. This allowed evaluation of effects for the 240-min study period. In addition, both Baralyme and soda lime carbon dioxide absorbents were evaluated. The water content of Baralyme (fresh = 12.1 ± 0.3%) decreased to 8.9 ± 0.4%, 6.7 ± 0.2%, and 6.0 ± 0.5% in the upper, middle, and lower one-third regions, respectively, of the upper canister with 24-h exposure to 10 l/min oxygen. In the bottom canister, water contents for Baralyme in the upper, middle, and lower one-third regions were 4.8 ± 0.5%, 3.0 ± 0.2%, and 1.9 ± 0.4%, respectively. Water contents for soda lime were slightly...
higher than that of Baralyme but followed a similar distribution pattern for canister regions (fig. 2).

Circuit carbon monoxide concentrations reached a maximum concentration of 13,600 ± 3,000 ppm (means ± SEM) at the 10-min time point when Baralyme was used. As can be seen in figure 3, carbon monoxide concentration increased rapidly, peaking at 10 min and decreasing to half this value by the 20-min time point. Dry soda lime produced lower carbon monoxide concentrations, with the peak value being 8,800 ± 4,100 ppm at 10 min.

As shown in figure 4, exposure to carbon monoxide within the anesthesia circuit during desflurane anesthesia resulted in high concentrations of carboxyhemoglobin in the pigs. Peak concentrations developed rapidly, reaching a maximum concentration of 72.6 ± 2.8% (20-min time point) with Baralyme present and 52.5 ± 5.8% (25 min) with soda lime present. Carboxyhemoglobin concentrations gradually decreased to concentrations of 23.7 ± 1.3% (Baralyme) and 15.7 ± 1.1% (soda lime) by 240 min of desflurane anesthesia.

Figures 5 and 6 show the changes in carbon dioxide absorbent temperature. For all canister regions (upper and lower canisters), absorbent temperatures were slightly higher with Baralyme than with soda lime. However, with both absorbents the pattern of temperature change for a given region of the canister was similar. Absorbent temperatures in the top canister increased over time, reaching a maximum of 43-45°C with Baralyme and 35.1-40.4°C with soda lime. The increase in temperature occurred most rapidly in the upper, followed by the middle and then the lower one-third sections of the upper canister. Absorbent temperature in the bottom canister followed an unusual pattern that appeared to be related to the degree of absorbent dryness, with higher temperatures occurring in regions with the driest absorbent. In the top one third of the bottom canister, absorbent temperature increased gradually, reaching 40°C by 120 min with Baralyme. In contrast, the temperature in the middle third of the bottom canister increased rapidly during the first 30 min, decreased until the 90-min time point (most notable with Baralyme), and again gradually increased until the study ended. This pattern was more accentuated in the bottom one third of the bottom canister, with temperatures exceeding 50°C at 20 min, and then decreasing by the 120-min time point to 33.6°C when Baralyme was present. A similar pattern occurred with soda lime, but temperatures were lower.

24-Hour Drying Studies (Reservoir Bag on Circuit)

Exposure of carbon dioxide absorbent to 10 l/min oxygen flow for 24 h with the reservoir bag present on the circuit reduced the water content of Baralyme to 5.5 ± 0.1% in the bottom portion of the lower canister. The eight pigs anesthetized with desflurane and 24- or 48-h dried Baralyme using this circuit configuration did not show an increase from baseline values in carboxyhemoglobin concentration, and there was no detectable carbon monoxide present within the circuit, indicating that although absorbent drying had occurred, a 48-h exposure did not produce sufficient absorbent drying to produce carbon monoxide.
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24-Hour Drying Studies with 5 l/min Oxygen Flow Rate (Reservoir Bag Removed)

Drying of Baralyme for 24 h using an oxygen flow rate of 5 l/min reduced the absorbent water content at the bottom of the lower canister to 6.8 ± 0.2%. A 1.0 MAC desflurane anesthesia with this absorbent did not produce carbon monoxide within the anesthesia circuit and did not change carboxyhemoglobin concentrations in the pigs.

Discussion

Isolated cases of increased carboxyhemoglobin concentrations in patients have occurred with isoflurane, sevoflurane, and most recently with desflurane anesthesia.
The work of Fang et al.\textsuperscript{1} has suggested that dry absorbent can produce carbon monoxide when exposed to isoflurane, enfurane, and desflurane. Results of this \textit{in vitro} study show that the highest concentrations of carbon monoxide appear to be produced by desflurane, followed by enfurane and then isoflurane, with greater concentrations occurring in the presence of Baralyme compared with soda lime. With these data in mind, we determined what oxygen flow rates and circuit conditions through an anesthesia circle system could produce significant drying of Baralyme or soda lime to produce carbon monoxide with desflurane anesthesia. We also evaluated the level of carboxyhemoglobin occurring in pigs anesthetized under these conditions. Our results show the following:

1. With circuit conditions as used in this study (\textit{i.e.}, reservoir bag removed), high oxygen flow (10 l/min) for 24 h can decrease the water content of Baralyme...
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or soda lime, and there is a gradient from top to bottom that depends on where oxygen flow is greatest (i.e., in our system oxygen flow was from bottom to top, so the lowest water content was observed in the lower portion of the bottom canister). High gas flows through the anesthetic machine are required to produce sufficient drying within 24 h. Flows of 5 l/min for 24 h did not produce sufficient absorbent drying, whereas flows of 10 l/min did produce enough drying for carbon monoxide production with desflurane anesthesia.

2. Circuit configuration during drying appears important. If the reservoir bag remains in place, some degree of carbon dioxide absorbent drying will still occur. However, water content of the absorbent was not reduced sufficiently even at high gas flows (10 l/min) for 48 h to produce carbon monoxide with desflurane exposure. Removal of the reservoir bag during high fresh gas flow (10 l/min) allows an increase in flow through the absorbent canister, producing greater absorbent drying.

3. Delivery of a 1.0 MAC desflurane anesthetic (human MAC age, 18–30 yr = 7.3%) with a total fresh gas flow rate of 1 l/min through sufficiently dried absorbent results in high concentrations of circuit carbon monoxide, which peak within 10 min and then decrease rapidly.

4. The concentrations of carbon monoxide produced with sufficiently dried absorbent can result in high and potentially lethal concentrations of carboxyhemoglobin in pigs receiving desflurane anesthesia.

5. The production of CO from desflurane appears to be an exothermic reaction, because areas of the carbon dioxide canister containing the driest absorbent had the greatest increase in temperature with desflurane exposure.

Our anesthesia equipment included a North American Dräger machine that could be used for clinical anesthesia in humans. We did not evaluate other anesthesia delivery systems (e.g., Ohmeda), and different results could occur using different types of anesthesia delivery systems. In addition, the circuit configuration and fresh gas flow rate during carbon dioxide absorbent drying appears critical. If the reservoir bag is absent from the machine during 10 l/min oxygen exposure, then significant absorbent drying occurs, and high levels of carbon monoxide are produced with exposure to desflurane. If, however, the reservoir bag was on the anesthesia circuit during exposure to 10 l/min circuit gas flow for as long as 48 h, carbon dioxide absorbent drying was insufficient to produce carbon monoxide. We evaluated an oxygen flow rate of 5 l/min for 24 h with the reservoir bag removed and found that it was insufficient to produce enough Baralyme drying to allow carbon monoxide production with desflurane anesthesia.

Some of the limitations of our study include the use of only 1.0 MAC of desflurane. To maximize carbon monoxide concentrations, we delivered desflurane at a reasonably high concentration (1.0 MAC) and used a low flow (1 l/min) system. Use of higher flow rates or lower desflurane concentration could result in lower carbon monoxide concentrations. In addition, in this investigation, an inspired oxygen fraction of 0.40 was used. Use of a higher inspired oxygen fraction (e.g., 100%) would have resulted in lower carboxyhemoglobin concentrations than were observed in our study due to competitive binding between oxygen and carbon monoxide for hemoglobin. Use of a lower inspired oxygen fraction (e.g., 21%) would produce higher carboxyhemoglobin concentrations than observed in our study.

We used a Datex Capnomac Ultima to monitor end tidal desflurane concentrations in this study. Previous investigations by Wochlick et al.² suggest that trifluoromethane is produced when desflurane or enfurane degrade to produce carbon monoxide. This trifluoromethane may be indicated incorrectly as desflurane by the Datex infrared monitor used in our study, which could result in an end-tidal desflurane concentration that is actually lower than that measured by the monitor.³ Therefore, it is possible that our end-tidal desflurane concentration of 7.5% desflurane was not achieved during the initial phases of anesthetic delivery due to degradation and monitor interference. However, a practitioner using desflurane in a similar clinical scenario with this agent monitor may have made anesthetic administration adjustments similar to ours.

Another limitation of our investigations was the use of pigs that weighed 20–30 kg. Use of a larger animal (more comparable to the size of a human) may have resulted in lower carboxyhemoglobin concentrations for exposure to a given concentration of carbon monoxide. A fourth limitation was the method used to evaluate water content of the carbon dioxide absorbent. We analyzed samples from the canister sectioned into thirds. Therefore, the water contents (e.g., 1.9% for the bottom of the lower canister) represent a mean value for the lower region. The water content of the absorbent at the very bottom was likely lower than this value. Given these limitations, we still believe that our results
indicate that high carboxyhemoglobin levels can develop if desflurane is administered with partially dried carbon dioxide absorbent to humans.

An unusual observation in our study was that carbon dioxide absorbent temperatures increased during the first 20 min in the middle and bottom one-third sections of the lower absorbent canister. The temperature increase was high (> 50°C) with Baralyme and appears to be related to the low degree of water content in the absorbent. An interesting possibility is that the generation of carbon monoxide from desflurane may be an exothermic reaction, but further work with other anesthetics will be needed to evaluate this possibility. These changes are in contrast to those commonly observed when a low-flow anesthetic is delivered and temperatures more generally parallel those observed in the upper canister during our studies, with absorbent temperatures gradually increasing as a result of exposure to carbon dioxide. There is typically no rapid increase in temperature in the bottom canister, as we observed in this study.

Our results are consistent with those of Fang et al. in that the appearance of carbon monoxide with desflurane produces a rapid peak, which then quickly declines. The reason for the rapid decrease in carbon monoxide production is unclear, but we hypothesize that carbon monoxide generation with desflurane occurs at a reactive surface area of only the very dry absorbent at the lowest part of the bottom canister. The reactive component of this readily available surface is likely used rapidly and carbon monoxide production then decreases to much lower levels.

Carbon monoxide is not readily detected by conventional end-tidal agent monitors. Pulse oximetry does not reliably change with the presence of carboxyhemoglobin, because the absorbance spectrum of carboxyhemoglobin is similar to that of oxyhemoglobin at 660 nm. It has been observed that in dogs, even with carboxyhemoglobin concentrations of 70%, the pulse oximetry monitor will record a saturation rate of 90% or more. In adults, unless a co-oximetry blood analysis is performed, the presence of carboxyhemoglobin will not be detected reliably. An additional concern is the inability of the anesthetist to recognize that absorbents in the circle system may be of low water content. Unless the anesthetist detects that absorbent may have been dried due to the presence of a high gas flow, the absorbent may not be replaced.

Clearly, given the correct circuit conditions, the potential exists for reduced water content in carbon dioxide absorbents to develop, and, with a subsequent desflurane anesthetic, for carbon monoxide exposure to occur. Why have more cases of carbon monoxide exposure with anesthetics containing a CHF$_3$O (difluoromethoxy) moiety (i.e., desflurane, enfurane, and isoflurane) not been reported? It is possible that some concentrations of carbon monoxide exposure go unrecognized because our routine monitoring modalities will not detect such exposure. Prolonged exposure to high fresh gas flows appears to be required for absorbent drying to be sufficient to produce carbon monoxide. The requirement that several factors occur simultaneously may prevent carbon monoxide exposure from happening more frequently. Cautionary measures, such as changing the absorbent when this condition may be present, are required to prevent potential carbon monoxide exposure. In addition, results of this study indicate that carbon dioxide absorbent drying is reduced if the reservoir bag of the anesthesia circuit is left in place on the anesthesia machine or if high oxygen flow rates (e.g., 10 l/min) across absorbents are not allowed to be present for an extended period of time. Both the 5 l/min oxygen flow rate with the reservoir bag absent and the 10 l/min flow rate with the reservoir bag in place still allowed absorbent drying to occur (6.8% and 5.5% water content, respectively). However, the duration of drying (for as long as 48 h) did not produce absorbent that was dry enough to create carbon monoxide with desflurane. It is possible that longer exposure time with these two conditions could allow absorbent drying sufficient for carbon monoxide production with desflurane, and caution should be exercised.

References