

Detection of Carbon Monoxide During Routine Anesthetics in Infants and Children

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BACKGROUND: Carbon monoxide (CO) can be produced in the anesthesia circuit when inhaled anesthetics are degraded by dried carbon dioxide absorbent and exhaled CO can potentially be rebreathed during low-flow anesthesia. Exposure to low concentrations of CO (12.5 ppm) can cause neurotoxicity in the developing brain and may lead to neurodevelopmental impairment. In this study, we aimed to quantify the amount of CO present within a circle system breathing circuit during general endotracheal anesthesia in infants and children with fresh strong metal alkali carbon dioxide absorbent and define the variables associated with the levels detected.

METHODS: Fifteen infants and children (aged 4 months to 8 years) undergoing mask induction followed by general endotracheal anesthesia were evaluated in this observational study. CO was measured in real time from the inspiratory limb of the anesthesia circuit every 5 minutes for 1 hour during general anesthesia. Carboxyhemoglobin (COHb) levels were measured at the 1-hour time point and compared with baseline.

RESULTS: CO was detected in all patients older than 2 years (0–18 ppm, mean 3.7 ± 4.8 ppm) and rarely detected in patients younger than 2 years (0–2 ppm, mean 0.2 ± 0.6 ppm). Only the relationship between CO concentration and fresh gas flow to minute ventilation ratio (FGF:V_E) remained significant after adjustment in longitudinal regression analysis ($P < 0.001$). Although not powered to determine such a relationship, CO levels were weakly associated with the use of desflurane and female sex. There was no significant association between CO concentration and anesthetic concentration. Baseline COHb levels were higher in children younger than 2 years and decreased significantly at the 1-hour time point compared with baseline and children older than 2 years. However, COHb levels increased significantly from baseline in a predictable manner consistent with CO exposure in children older than 2 years. FGF:V_E correlated significantly with change in COHb using simple linear regression ($r = 0.62$; $P < 0.02$).

CONCLUSIONS: CO was detected routinely during general anesthesia in infants and children when FGF:V_E was <1 . Peak CO levels measured in the anesthesia breathing circuit were in the range thought to impair the developing brain. Further study is required to identify the source of CO detected (CO produced by degradation of volatile anesthetic versus rebreathing CO from endogenous sources or both). However, these findings suggest that avoidance of low-flow anesthesia will prevent rebreathing of exhaled CO, and use of carbon dioxide absorbents that lack strong metal hydroxide could limit inspired CO if detection was attributable to degradation of volatile anesthetic. (*Anesth Analg* 2010;110:747–53)

Approximately 4 million children undergo general anesthesia each year.¹ Experimental animal studies have demonstrated that anesthetics can cause toxicity and neuronal apoptosis in the developing brain.^{2–4} The exact mechanisms of anesthesia-induced neurotoxicity are unknown and may not necessarily extrapolate to humans. Recent work has suggested that young children exposed to

inhaled anesthetics during inguinal herniorrhaphy were twice as likely to develop behavioral or developmental disorders after exposure compared with controls.⁵ Although developmental outcome in this study may have been influenced by other factors such as prematurity and neonatal hypoxemia, the safety of general anesthesia in infants and children needs to be reexamined and potential mechanisms of neurotoxicity need to be explored.⁵

Carbon monoxide (CO) is a known neurotoxin that is potentially generated within anesthesia breathing systems.⁶ Although CO was not a factor in the anesthesia-induced neurotoxicity in animal studies because of the experimental design, low concentration, subclinical CO exposure has been shown to impair the developing brain.^{7,8} Formation of CO occurs in circle system breathing circuits when inhaled volatile anesthetic drugs are degraded by strong alkali carbon dioxide absorbents.⁸ Degradation is inversely proportional to the water content of the carbon dioxide absorbent, and considerable CO formation occurs when inhaled anesthetics are used with desiccated or dried absorbent.^{8–10} The magnitude of CO generation varies among the different inhaled anesthetics, and CO exposure during anesthesia

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Table 1. Summary of Patients

	0–2 y	2–3 y	3–8 y	All patients
No. of patients	5	5	5	15
M/F	3/2	2/3	3/2	8/7
Age (y)	0.8 ± 0.6	2.7 ± 0.4	5.6 ± 1.9	3.0 ± 2.3 (0.3–8.0)
Weight (kg)	8.0 ± 1.5	14.9 ± 2.1	23.8 ± 6.8	15.5 ± 7.8 (6.5–31.5)
Minute ventilation (L/min)	1.5 ± 0.2	2.3 ± 0.2	2.8 ± 0.7	2.2 ± 0.7 (1.3–3.6)
Sevoflurane anesthetics	3	1	4	8
Desflurane anesthetics	2	4	1	7
Smoker in household	0	1	0	1
Inspired CO (ppm)	0.2 ± 0.6	3.0 ± 4.4	4.1 ± 4.9	2.6 ± 4.3 (0–18)
Diagnosis				
Patent ductus arteriosus				3
Coarctation of the aorta				2
Atrial septal defect				2
Tetralogy of fallot				2
Anomalous coronary artery				1
HLHS				
s/p stage I				1
s/p bidirectional Glenn				2
s/p Fontan				1
Cerebral AVM				1

Values represent means ± sd. Values in parentheses represent ranges.

CO = carbon monoxide; ppm = parts per million; HLHS = hypoplastic left heart syndrome; AVM = arteriovenous malformation; s/p = status post.

is indirectly related to fresh gas flow (FGF) in the breathing circuit.^{9–11}

There are numerous studies and case reports that have demonstrated CO production in the anesthesia circuit related to dried absorbent resulting in clinical signs of CO toxicity and increased carboxyhemoglobin (COHb) levels.^{6,11–13} Although several investigations have shown that fresh, hydrated absorbents produce “little or no” CO, recent work has demonstrated that desflurane can be degraded by fresh, hydrated strong metal alkali absorbent with low FGFs in vitro, producing up to 23 ppm of CO in the breathing circuit.^{9,14}

CO is also produced endogenously as a product of heme catabolism mediated by heme oxygenase-1.¹⁵ Endogenous CO diffuses into the circulation, binds to hemoglobin to form COHb, and is excreted by the lungs via exhalation.¹⁵ It is possible that, during low-flow anesthesia with a closed anesthesia breathing circuit, patients can rebreathe exhaled CO, resulting in an active CO exposure.¹⁶

We hypothesized that CO would be detected routinely during general anesthesia in children and that the level of CO measured would be directly related to FGF relative to patient minute ventilation (\dot{V}_E). In this study, we aimed to quantify the amount of CO present within a circle system breathing circuit during general endotracheal anesthesia in infants and children with fresh strong metal alkali carbon dioxide absorbent and to define the variables associated with the levels detected.

METHODS

This was a prospective observational study and was approved by the IRB of Children’s National Medical Center. Informed consent was obtained from each patient’s parent or legal guardian.

Patients

Fifteen pediatric patients aged 4 months to 8 years, weighing between 6.5 and 31.5 kg, undergoing mask induction of

anesthesia followed by general endotracheal anesthesia in the cardiac catheterization laboratory as part of their routine care were studied (Table 1). We prospectively enrolled patients based on age to evenly distribute across 3 subgroups: 0 to 2 years, 2 to 3 years, and 3 to 8 years. Groups were defined based on anticipated \dot{V}_E (because prior work suggested a relationship with FGF): 0 to 2 years (up to 2 L/min), 2 to 3 years (approximately 2–3 L/min), and 3 to 8 years (>3 L/min).^{11,17} Patients were excluded if they had known cardiac dysfunction or pulmonary hypertension because these patients would likely require a nontraditional anesthetic. Cardiac dysfunction was defined as a left ventricle shortening fraction of <30% on the preprocedure echocardiogram. Pulmonary hypertension was defined as systolic pulmonary artery or right ventricular blood pressure more than half of the systemic systolic blood pressure.

Study Protocol

Immediately before each procedure, both canisters of carbon dioxide soda lime absorbent were replaced in the anesthesia machine (Aestiva/5, GE Healthcare, Madison, WI) with fresh, out-of-the-package strong metal hydroxide absorbent (Medisorb, GE Healthcare, Helsinki, Finland).

Each patient underwent induction of anesthesia via mask with sevoflurane (up to 8%, Baxter Healthcare, Deerfield, IL), 70% nitrous oxide (7 L/min), and 30% oxygen (3 L/min). An IV catheter was placed and venous blood was sampled for “baseline” COHb measurement via 6-wavelength CO-oximetry (range 0%–100% ± 0.2%, Radiometer OSM3 Hemoximeter, Copenhagen, Denmark). After muscle relaxation with IV rocuronium (0.6 mg/kg), patients’ tracheas were intubated with either a cuffed or uncuffed tracheal tube such that there was no audible airway leak at <30 cm H₂O. Mechanical ventilation was titrated to prospectively designated standard target ranges for tidal volume (10 mL/kg) and Pco₂ (40 mm Hg) using peak inspiratory pressures ≤30 cm H₂O. FGF was fixed at

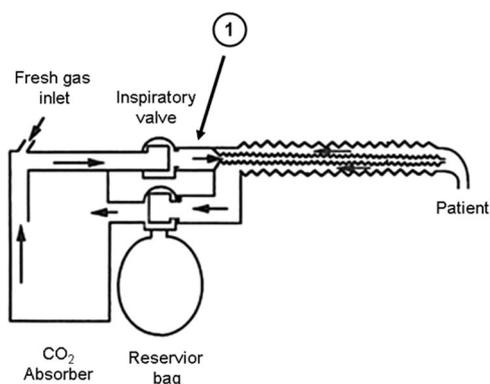


Figure 1. Carbon monoxide sampled in the anesthesia breathing circuit. An electrochemical carbon monoxide sensor was connected to a sampling port (indicated by the number 1) in the inspiratory limb of the breathing circuit (just distal to the anesthesia machine).

1.5 L/min (air, 0.21% oxygen), and anesthesia was maintained with either sevoflurane (up to 3.6%) or desflurane (up to 6%, Baxter Healthcare) (based on the anesthesiologist's preference). Because the minimal FGF of oxygen with this machine was 25 mL/min, the inspired oxygen concentration for all patients was 23% to 24%. An electrochemical CO sensor (range 0–2000 ppm, resolution 1 ± 2 ppm, Monoxor III, Bacharach, Anderson, CA) underwent 2-point calibration (zero [ambient air] and 25 ppm [stock gas]) and was connected to a sampling port in the inspiratory limb of the breathing circuit (just distal to the anesthesia machine, Fig. 1). The device uses the electrochemical oxidation principle and draws 150 mL/min with a 40-second response time. Sampled gas was not returned to the circuit. This technology has been validated in the presence of volatile anesthetic gases.¹⁸ Each patient was continuously monitored with pulse oximetry, end-tidal CO₂, noninvasive arterial blood pressure, electrocardiogram, and temperature measurement.

We manually recorded inspired CO concentration (ppm), \dot{V}_E , and exhaled volatile anesthetic drug concentration every 5 minutes for 1 hour and recorded patient age, sex, and body weight. The anesthesiologist was permitted to adjust the concentration of inhaled anesthetic and \dot{V}_E as clinically necessary. However, the FGF remained fixed at 1.5 L/min. At the 1-hour time point, venous blood was again sampled for COHb measurement.

Statistical Analysis

A sample size of 15 was chosen based on the number of patients required to detect a 2 ppm change in inspired CO with a power of 80 based on an α of 0.05. Data were assessed for normality by examining histograms and box plots and underwent square root transformation. Linear correlations were calculated and correlation coefficients determined for continuous variables. Longitudinal regression models were applied to determine the independent effect of different variables on CO concentration and to adjust for covariates.¹⁹ Cramér's V coefficients were used to assess correlation of CO concentration with discrete variables.

COHb levels at the 1-hour time point were compared with baseline values within and between groups. Statistical

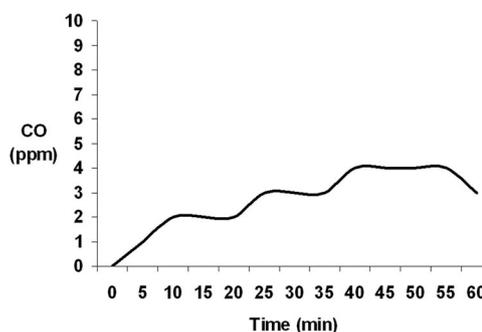


Figure 2. Carbon monoxide (CO) detected in the anesthesia breathing circuit. Inspired CO concentration was tracked over 1 hour during general anesthesia. A representative plot is depicted. CO concentration is expressed in parts per million (ppm).

Table 2. Correlation Coefficients Between Inspired CO Concentration and Pertinent Variables

	Sevoflurane concentration	Desflurane concentration	Age	Weight	FGF: \dot{V}_E
Age	0.199*	0.155			
Weight	0.147	0.151	0.971†		
FGF: \dot{V}_E	0.208	0.108	0.826†	0.851†	
CO	0.018	0.163	0.511†	0.515†	0.613†

FGF: \dot{V}_E = fresh gas flow ratio-to-minute ventilation.

* $P < 0.05$, † $P < 0.001$.

analysis of mean values was performed with paired t test. Change in COHb was correlated with FGF to \dot{V}_E ratio (FGF: \dot{V}_E) using linear regression, and correlation coefficient was determined. Significance was set at $P < 0.05$.

RESULTS

CO was detected within the anesthesia breathing circuit in all patients older than 2 years and in 2 of 5 patients younger than 2 years. Initial inspired CO was 0 ppm in all cases and, when detected, appeared at the 5- to 15-minute mark after induction of anesthesia (Fig. 2). Mean inspired CO concentrations measured during 1 hour are listed in Table 1.

Relationships Between CO Detected and Patient Variables

Inspired CO concentrations were tested for correlation with patient age, weight, and sex. Statistically significant correlations were found for CO concentration with age ($r = 0.511$; $P < 0.001$) and with body weight ($r = 0.515$; $P < 0.001$) (Table 2). Cramér's V yielded a weak, but significant, association between CO level and female sex (Table 3). Post hoc analysis revealed a significant correlation between body weight and female sex ($P < 0.01$). Thus, weight and sex were covariates, and association of CO with female sex was simply attributable to heavier body weight.

Relationships Between CO Detected and Anesthesia Management-Related Variables

When inspired CO concentrations were tested for simple linear correlation with anesthesia management-related variables (FGF: \dot{V}_E), only correlation with FGF: \dot{V}_E ($r = 0.613$; $P < 0.001$; Fig. 3, Table 2) was found to be statistically

Table 3. Cramér's V Between Inspired CO Concentration and Discrete Variables

	Sex	Type of anesthetic
Sex	—	—
Type of anesthetic	0.3393*	—
CO	0.3993*	0.2997*

CO = carbon monoxide.

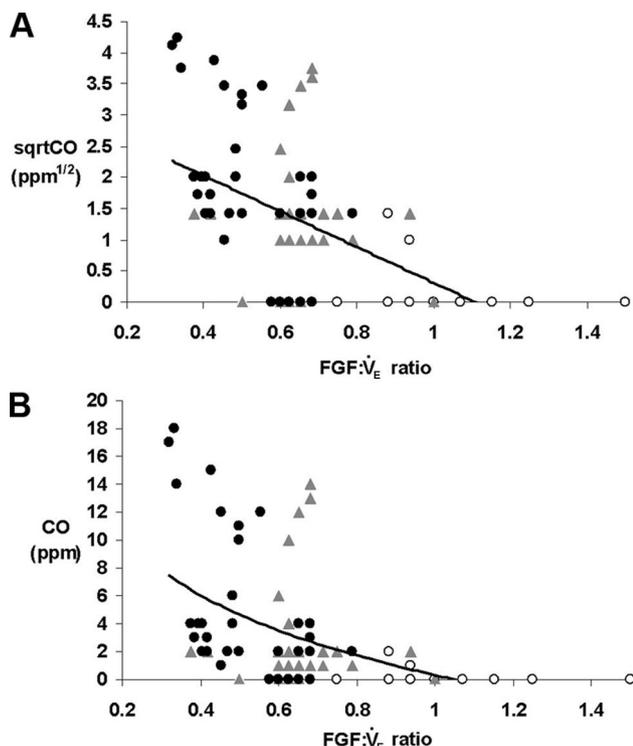
* $P < 0.001$.

Figure 3. A, Correlation between the square root of carbon monoxide concentration (sqrtCO) and fresh gas flow to minute ventilation ratio (FGF:VE). Observed measurements made every 5 minutes for 1 hour are depicted. Line represents predicted value. SqrtCO concentration is expressed in square root of parts per million ($\text{ppm}^{1/2}$). $r = 0.613$, $P < 0.001$. B, Relationship between CO and FGF:VE. Observed measurements made every 5 minutes for 1 hour are depicted. Line represents predicted value. CO concentration is expressed in parts per million (ppm). Open circles represent children aged 0 to 2 years, shaded triangles represent those aged 2 to 3 years, and closed circles represent those 3 to 8 years.

significant. Type of anesthetic (desflurane) was significantly but weakly associated with CO concentration using Cramér's V correlation (Table 3).

Regression Analysis to Assess Independent Effect on CO Detection

Longitudinal regression analyses were performed to assess the independent effects of patient age, weight, and FGF:VE on inspired CO concentration (Table 4). Because a strong intercorrelation was seen between age and body weight ($r = 0.971$), 3 independent models were tested for correlation with CO (Table 4). Each model yielded a statistically significant correlation between CO concentration and FGF:VE (Table 4).

Table 4. Independent Effects of Age, Weight, and FGF:VE on Inspired CO Concentration

	Longitudinal regression coefficient	Z	P
Model 1			
FGF:VE	0.914	5.42	<0.001
Model 2			
Weight	0.027	0.88	0.379
FGF:VE	0.866	4.92	<0.001
Model 3			
Age	0.090	0.88	0.379
FGF:VE	0.868	4.94	<0.001

FGF:VE = fresh gas flow-to-minute ventilation ratio; CO = carbon monoxide.

Effect of CO Exposure on COHb Level

CO binds avidly to hemoglobin to form COHb.¹⁸ After exposure of a known quantity of CO, COHb increases in a predictable manner.²⁰ Thus, we measured venous COHb during induction of anesthesia as an approximation of endogenous COHb and characterized this value as "baseline." We again measured venous COHb at the 1-hour time point to assess for CO exposure and compared the mean values with baseline levels.

Baseline COHb was significantly higher in patients younger than 2 years compared with older children (Fig. 4). There was no difference in baseline values between patients aged 2 to 3 years and those older than 3 years (Fig. 4). At the 1-hour time point, COHb significantly decreased in the youngest age group compared with baseline and compared with the other groups (Fig. 4). However, 1-hour COHb significantly increased in those aged 2 to 3 years and 3 to 8 years compared with baseline values (Fig. 4).

Relationship Between Change in COHb and FGF:VE

Change in COHb was tested for correlation with FGF:VE using simple linear regression. A statistically significant correlation was found ($r = 0.62$; $P < 0.02$; Fig. 5). Using this relationship, we determined that FGF:VE of 0.68 (95% confidence interval 0.47–0.90) would yield a zero net change in COHb.

DISCUSSION

In this study, we demonstrated that CO is detected within the anesthesia breathing circuit during routine general anesthetics in infants and children. FGF:VE had the strongest correlation with inspired CO concentration in univariate analysis and was the only variable to correlate significantly with measured CO in longitudinal analyses. Furthermore, the quantity of CO detected was proportional to FGF:VE. Importantly, CO measured in the inspiratory limb in this study occurred with use of fresh carbon dioxide absorbent and was weakly associated with desflurane use (versus sevoflurane) but was not affected by anesthetic concentration. However, based on the study design, it is impossible to determine the source of the CO. One possibility is that fresh conventional absorbent degraded volatile anesthetic drugs leading to CO generation. This is supported by the association between CO concentration and the use of desflurane.⁶ The other potential source of CO within the breathing circuit was exhaled patient gas.

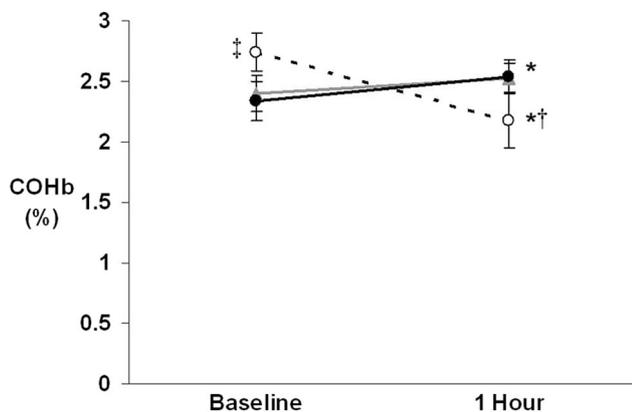


Figure 4. Carboxyhemoglobin (COHb) levels during induction (baseline) and after 1 hour of anesthesia. Venous levels were measured via CO-oximetry and are expressed as COHb%. Open circles represent children aged 0 to 2 years, shaded triangles represent those aged 2 to 3 years, and closed circles represent those aged 3 to 8 years. Values are means \pm SE. * $P < 0.05$ versus baseline, † $P < 0.05$ versus 2 to 8 year olds at 1 hour, ‡ $P < 0.05$ versus 2 to 8 year olds baseline.

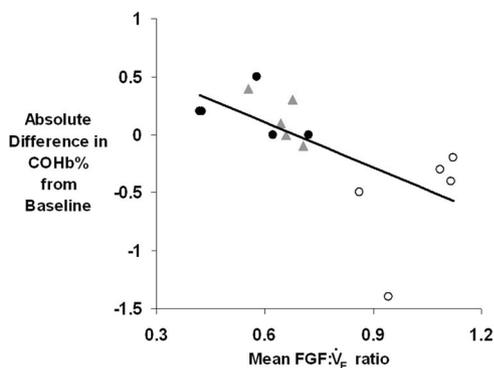


Figure 5. Correlation between difference in carboxyhemoglobin level (COHb%) from baseline and fresh gas flow to minute ventilation ratio (FGF:VE). Open circles represent children aged 0 to 2 years, shaded triangles represent those aged 2 to 3 years, and closed circles represent those aged 3 to 8 years. Absolute differences with directionality of change in 1-hour COHb% level from baseline are depicted against mean FGF:VE values for each patient. $r = 0.62$, $P < 0.02$. Zero change in COHb% correlates with an FGF:VE of 0.68.

Because endogenously formed CO is eliminated via exhalation, it is possible that during low-flow anesthesia (FGF:VE < 0.68), exhaled CO was rebreathed, leading to CO exposure.¹⁶

Lack of detection of CO initially does not necessarily indicate that zero CO was present within the circuit. It is possible that exhaled CO within the circuit was not detectable because of the limits of the CO sensor after induction with high FGFs. The consistent detection of CO at the 5- to 15-minute mark, however, could be consistent with the time constant for exhaled CO to appear in the inspiratory limb given FGF of 1.5 L/min and could also represent the time delay for chemical degradation of volatile anesthetic. Thus, inspired CO may arise from degradation of volatile anesthetics by fresh conventional soda lime or rebreathing of exhaled CO or both.

Because CO binds 240 times more avidly to hemoglobin than oxygen, COHb levels can reflect endogenous CO

binding or indicate exogenous exposure.²⁰ Endogenous CO is produced routinely as a breakdown product of heme catabolism.²¹ High heme turnover states yield more CO and higher COHb levels and may explain why the infants younger than 2 years had significantly higher “baseline” COHb.^{22,23} However, there is no way to determine exactly why, in this study, the younger infants had higher baseline COHb levels. It should be noted that, as a limitation of this work, baseline COHb, although representative of the pre-exposure state, may not truly characterize pure endogenous levels. The reason is that these measurements were taken during induction of anesthesia and not before (as is the limitation with working with children).

In light of this, a number of observations regarding COHb should be made. First, 1 child (aged 2–3 years) lived in a home with a smoker. Despite this, there was no difference in baseline COHb compared with her cohorts. In children older than 2 years, COHb levels significantly increased after 1 hour of general anesthesia and significantly decreased in those younger than 2 years. The increases, although incremental, are consistent with predicted values based on known time-weighted CO exposure.²⁰ The importance and relevance of increased COHb levels is that they represent evidence of CO exposure. Exposure, in this work, simply means the presence of CO in inspired gas regardless of source. However, decreased COHb levels at 1 hour in the youngest cohort are interesting and deserve some discussion.

FGF:VE correlated significantly with change in COHb from baseline. Importantly, the calculated FGF:VE that would have no net effect on COHb level was 0.68 (95% confidence interval 0.47–0.90). This relationship suggests that FGF:VE set > 0.68 (with a lower limit of FGF set to about half of VE) would result in little or no CO exposure during anesthesia and a decrease in 1-hour COHb and FGF:VE set < 0.68 (with an upper limit of FGF set to just below VE) would lead to inspiration of CO and an increase in 1-hour COHb. Examination of the analyses of CO concentration and FGF:VE supports this (Fig. 3). When FGF:VE was > 0.68 , CO was detected between 0 and 2 ppm (Fig. 3). Furthermore, CO was never detected when the FGF:VE was ≥ 1 (Fig. 3). The importance of FGF:VE is that it can be applied to all patients regardless of size because it is a ratio. Thus, one would expect that when FGF is set to meet or exceed VE, CO will not be inspired by any patient. It should be noted, however, that these relationships may not exactly translate when using other types of anesthesia machines.

The effects of FGF and VE on inspiratory CO concentration have been reported.^{11,24} It is likely that these relationships are solely attributable to the amount of CO rebreathing (rebreathing fraction [f_{RB}]) regardless of source. f_{RB} is defined as $1 - (FGF/VE)$.²⁴ When we plot inspired CO concentration versus f_{RB} , we find a statistically significant association between sqrtCO and f_{RB} ($r = 0.612$; $P < 0.001$) that is essentially the inverse of the relationship with FGF:VE (Fig. 6). However, when the change in COHb% is plotted versus a f_{RB} , a stronger correlation is identified ($r = 0.71$; $P < 0.01$) compared with the association with FGF:VE (Fig. 7). This further supports the notion that CO will not be inspired when FGF exceeds VE.

In this study, decreased COHb levels at 1 hour in the youngest cohort were likely attributable to a combination of trivial amounts of inspired CO, negligible rebreathing,

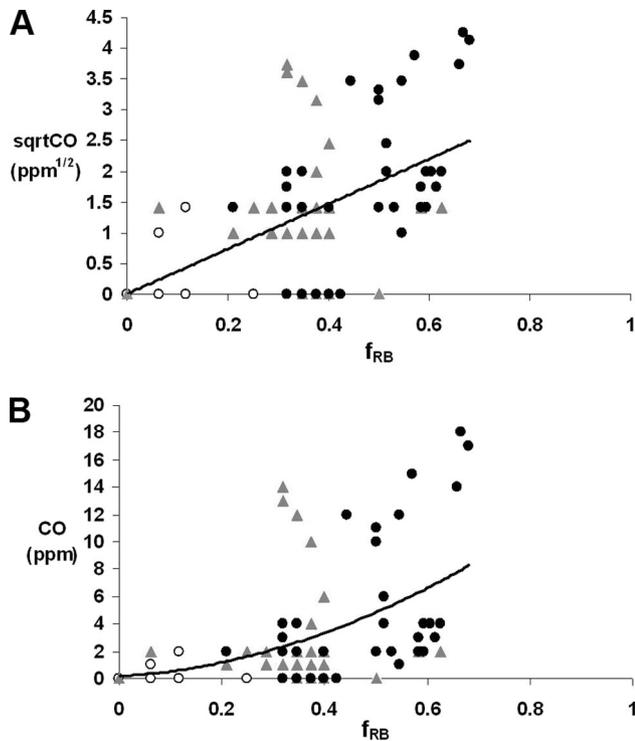


Figure 6. A, Correlation between the square root of carbon monoxide concentration (sqrtCO) and rebreathing fraction (f_{RB}). Observed measurements made every 5 minutes for 1 hour are depicted. Line represents predicted value. sqrtCO concentration is expressed in square root of parts per million ($\text{ppm}^{1/2}$). $r = 0.612$, $P < 0.001$. B, Relationship between CO and f_{RB} . Observed measurements made every 5 minutes for 1 hour are depicted. Line represents predicted value. CO concentration is expressed in parts per million ($\text{ppm}^{1/2}$). Open circles represent children aged 0 to 2 years, shaded triangles represent those aged 2 to 3 years, and closed circles represent those 3 to 8 years.

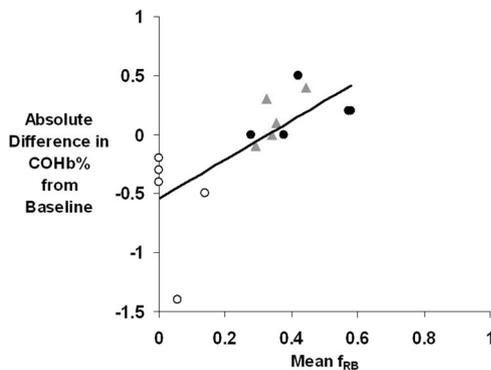


Figure 7. Correlation between difference in carboxyhemoglobin level ($\text{COHb}\%$) from baseline and rebreathing fraction (f_{RB}). Open circles represent children aged 0 to 2 years, shaded triangles represent those aged 2 to 3 years, and closed circles represent those 3 to 8 years. Absolute differences with directionality of change in 1-hour $\text{COHb}\%$ level from baseline are depicted against mean f_{RB} values for each patient. $r = 0.71$, $P < 0.01$. Zero change in $\text{COHb}\%$ correlates with an f_{RB} of 0.33.

and 23% to 24% inspired oxygen. Because oxygen competes with CO and can displace it from hemoglobin (offgassing), exposure to oxygen concentrations above ambient levels reduce $\text{COHb}\%$ leading to increased CO exhalation.^{25,26} With high FGF and minimal rebreathing, this offgassing

effect would result in CO removal (into the scavenger) and decreased $\text{COHb}\%$. The obvious limitation with this explanation is that we did not measure exhaled CO in the circuit and did not sample the scavenger gas.

The means by which low-dose CO induces neurotoxicity in the developing brain are unknown. There is evidence that mild postnatal CO exposure (12.5 ppm) impairs the developing auditory system and defects persist into adulthood.⁷ Furthermore, maternal exhaled concentrations of CO >5 ppm during pregnancy are associated with significantly decreased birth weight and small infant head circumference.²⁷ Thus, detecting CO with up to 18 ppm within the anesthesia breathing circuit during routine anesthesia in infants and children could be important. From an exposure standpoint, time-weighted average is probably a more meaningful unit of measure, accounting for the concentration of CO exposed to over time. It is unknown whether exposure to subclinical CO as a result of low-flow anesthesia has any effect on the developing human brain. However, if infants and children are at unique risk, then longer exposure times during prolonged anesthetics could pose a major safety concern.

In 2005, the Anesthesia Patient Safety Foundation (APSF) addressed potential CO production in the setting of desiccated conventional carbon dioxide absorbents.²⁸ The APSF consensus statement, aimed to “reduce the risk of adverse interactions with volatile anesthetic drugs,” recommended the use of absorbents that lack strong metal hydroxides and do not degrade inhaled anesthetics.^{28,29} For institutions that choose to use conventional absorbents, the APSF provided several recommendations targeted to prevent desiccation.²⁸

Although further investigation is required to identify the source(s) of CO detected within the anesthesia breathing circuit in this study and to determine whether such an exposure affects the developing brain, it is likely that using absorbents lacking strong metal alkali may reduce, but not necessarily eliminate, the possibility of CO exposure (caused by rebreathing). However, given the uncertainty and variability of the source of CO, avoidance of low-flow anesthesia in infants and children would likely prevent CO exposure during general anesthesia. It is important to note that using one or both of these preventative approaches may cause an increased financial burden, the extent of which would be related to the relative cost of absorbents lacking strong metal alkali versus conventional absorbents and the relative increase in FGF versus current practice patterns. In addition, these findings suggest a potential role for real-time CO monitoring within the inspiratory limb of the breathing circuit. Although such monitoring may enhance safety, there are inherent logistical concerns and cost-benefit ratios to consider. In the end, the safest approach may be to simply avoid low-flow anesthesia.

Future studies will aim to quantify the amount of CO produced by fresh soda lime in vivo and to determine the magnitude of endogenous CO rebreathed using absorbents that do not degrade volatile anesthetics during low-flow anesthesia in infants and children. Such investigation may help us better define best practice with regard to FGF relative to \dot{V}_E and rebreathing fraction. Ultimately, complete prevention of potential CO formation and rebreathing may enhance

the safety of delivering general anesthesia to infants and children. ■■

AUTHOR CONTRIBUTIONS

RJL, RFK, OR, and FXM were involved in study concept and design. RJL, VGN, RR, OR, MS, KR, and JPK helped in acquisition of data. RJL and FXM helped in analysis and interpretation of data. RJL was involved in manuscript preparation and FXM in critical revision of the manuscript for important intellectual content. RJL and VGN supervised the study and helped in statistical analysis.

REFERENCES

1. Sun LS, Li G, Dimaggio C, Byrne M, Rauh V, Brooks-Gunn J, Kakavouli A, Wood A; Coinvestigators of the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) Research Network. Anesthesia and neurodevelopment in children: time for an answer? *Anesthesiology* 2008;109:757–61
2. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci* 2003;23:876–82
3. Fredriksson A, Ponten E, Gordh T, Eriksson P. Neonatal exposure to a combination of N-methyl-D-aspartate and γ -aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. *Anesthesiology* 2007;107:427–36
4. Nikizad H, Yon JH, Carter LB, Jevtovic-Todorovic V. Early exposure to general anesthesia causes significant neuronal deletion in the developing rat brain. *Ann N Y Acad Sci* 2007;1122:69–82
5. DiMaggio CJ, Sun LS, Kakavouli A, Guohua L. Exposure to anesthesia and the risk of developmental and behavioral disorders in young children. *Anesthesiology* 2008;109:A1415
6. Coppens MJ, Versichelen LF, Rolly G, Mortier EP, Struys MM. The mechanisms of carbon monoxide production by inhalational agents. *Anaesthesia* 2006;61:462–8
7. Webber DS, Korsak RA, Sininger LK, Sampogna SL, Edmond J. Mild carbon monoxide exposure impairs the developing auditory system of the rat. *J Neurosci Res* 2003;74:655–65
8. Lopez I, Acuna D, Webber DS, Korsak RA, Edmond J. Mild carbon monoxide exposure diminishes selectively the integrity of the cochlea of the developing rat. *J Neurosci Res* 2003;74:666–75
9. Fang ZX, Eger EI II, Laster MJ, Chortkoff BS, Kandel L, Ionescu P. Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and baralyme. *Anesth Analg* 1995;80:1187–93
10. Wissing H, Kuhn I, Warnken U, Dudziak R. Carbon monoxide production from desflurane, enflurane, halothane, isoflurane, and sevoflurane with dry soda lime. *Anesthesiology* 2001;95:1205–12
11. Tang CS, Fan SZ, Chan CC. Smoking status and body size increase carbon monoxide concentrations in the breathing circuit during low-flow anesthesia. *Anesth Analg* 2001;92:542–7
12. Frink EJ, Nogami WN, Morgan SE, Salmon RC. High carboxyhemoglobin concentrations occur in swine during desflurane anesthesia in the presence of partially dried carbon dioxide absorbents. *Anesthesiology* 1997;87:308–16
13. Bonome C, Belda J, Alvarez-Refojo F, Soro M, Fernández-Goti C, Cortés A. Low-flow anesthesia and reduced animal size increase carboxyhemoglobin levels in swine during desflurane and isoflurane breakdown in dried soda lime. *Anesth Analg* 1999;89:909–16
14. Fan SZ, Lin YW, Chang WS, Tang CS. An evaluation of the contributions by fresh gas flow rate, carbon dioxide concentration and desflurane partial pressure to carbon monoxide concentration during low fresh gas flows to a circle anaesthetic breathing system. *Eur J Anaesthesiol* 2008;25:620–6
15. Hayashi M, Takahashi T, Morimatsu H, Fujii H, Taga N, Mizobuchi S, Matsumi M, Katayama H, Yokoyama M, Taniguchi M, Morita K. Increased carbon monoxide concentration in exhaled air after surgery and anesthesia. *Anesth Analg* 2004;99:444–8
16. Woehlck HJ. Carbon monoxide rebreathing during low flow anesthesia. *Anesth Analg* 2001;93:516–7
17. Stahl WR. Scaling of respiratory variables in mammals. *J Appl Physiol* 1967;22:453–60
18. Bermudez JA. Investigation of electrochemical carbon monoxide sensor monitoring of anesthetic gas mixtures. *Anesthesiology* 2003;99:1233–5
19. Schildcrout JS, Heagerty PJ. On outcome-dependent sampling designs for longitudinal binary response data with time-varying covariates. *Biostatistics* 2008;9:735–49
20. Hauck H, Neuberger M. Carbon monoxide uptake and the resulting carboxyhemoglobin in man. *Eur J Appl Physiol Occup Physiol* 1984;53:186–90
21. Piantadosi CA. Carbon monoxide, reactive oxygen signaling, and oxidative stress. *Free Radic Biol Med* 2008;45:562–9
22. Marks GS, Vreman HJ, McLaughlin BE, Brien JF, Nakatsu K. Measurement of endogenous carbon monoxide formation in biological systems. *Antioxid Redox Signal* 2002;4:271–7
23. Stark MJ, Clifton VL, Wright IM. Carbon monoxide is a significant mediator of cardiovascular status following preterm birth. *Pediatrics* 2009;124:277–84
24. Woehlck HJ, Dunning M III, Raza T, Ruiz F, Bolla B, Zink W. Physical factors affecting the production of carbon monoxide from anesthetic breakdown. *Anesthesiology* 2001;94:453–6
25. Woehlck HJ, Mei D, Dunning MB III, Ruiz F. Mathematical modeling of carbon monoxide exposures from anesthetic breakdown: effect of subject size, hematocrit, fraction of inspired oxygen, and quantity of carbon monoxide. *Anesthesiology* 2001;94:457–60
26. Adachi T, Hirota K, Hara Y, Sasaki Y, Hara Y. Exhaled carbon monoxide levels change in relation to inspired oxygen fraction during general anesthesia. *Anesth Analg* 2007;105:696–9
27. Gomez C, Berlin I, Marquis P, Delcroix M. Expired air carbon monoxide concentration in mothers and their spouses above 5 ppm is associated with decreased fetal growth. *Prev Med* 2005;40:10–5
28. Carbon Dioxide Absorbent Desiccation Safety Conference Convened by APSF. Available at: http://www.apsf.org/resource_center/newsletter/2005/summer/01co2.htm. Accessed January 2, 2009
29. 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;91:1342–8