Carbon monoxide re-breathing during low-flow anaesthesia in infants and children

V. Nasr1, J. Emmanuel1, N. Deutsch1, M. Slack2, J. Kanter2, K. Ratnayaka2 and R. Levy1*

1 Division of Anesthesiology and Pain Medicine and 2 Division of Cardiology, Children’s National Medical Center, The George Washington University School of Medicine and Health Sciences, 111 Michigan Ave., NW, Washington, DC 20010, USA

*Corresponding author. E-mail: rlevy@cnmc.org

Key points

- Carbon monoxide (CO) is a potentially toxic gas present in anaesthesia breathing systems.
- Low-flow anaesthesia increased inspired and exhaled CO and carboxyhaemoglobin (COHb) in the youngest children.
- High-flow anaesthesia (HFA) reduced inhaled CO and prevented the increase in COHb.
- HFA can minimize CO exposure especially in cases of high endogenous CO production.

Background. Carbon monoxide (CO) has been detected within anaesthesia breathing systems. One potential source in this setting is exhaled endogenous CO. We hypothesized that CO is re-breathed during low-flow anaesthesia (LFA) in infants and children.

Methods. Twenty children (age 2 months–7 yr) undergoing general anaesthesia were evaluated in a prospective observation study. LFA was established for 60 min followed by high-flow anaesthesia (HFA) for the next 60 min. Exhaled and inspired CO were measured every 5 min within the breathing circuit. Carboxyhaemoglobin (COHb%) was measured at baseline, at 60 min, after LFA, and at 120 min, after HFA.

Results. CO concentrations increased during LFA. Inspired CO peaked at 14 ppm. During HFA, exhaled CO levels remained constant whereas inspired CO decreased markedly. Exhaled and inspired CO during HFA differed significantly from LFA. The trajectory of change in exhaled and inspired CO was most closely associated with the fresh-gas flow (FGF):minute ventilation ratio. COHb% significantly increased in children <2 yr of age at 60 min after LFA and remained increased.

Conclusions. LFA increased exhaled and inspired CO and increased COHb% in children <2 yr of age. Thus, LFA resulted in re-breathing of exhaled CO and exposure, especially in the youngest children. Re-breathing exhaled gas during LFA could pose a risk for an acute CO exposure in patients who have elevated COHb and high baseline levels of exhaled CO. If practitioners match or exceed minute ventilation with FGF to avoid LFA, CO re-breathing can be limited.

Keywords: anaesthesia; carbon monoxide; carboxyhaemoglobin; children; closed-circuit; infant; ventilation

Accepted for publication: 30 August 2010

Carbon monoxide (CO) has been detected within anaesthesia breathing systems.1–3 The two potential sources of CO in this setting include CO generated exogenously and exhaled CO arising from endogenous patient sources.4 Exogenous CO formation can occur in circle system breathing circuits when inhalation volatile anaesthetic agents were degraded by certain carbon dioxide absorbents that contain sodium and potassium hydroxides.1,4 Generation of CO is inversely proportional to the water content of the carbon dioxide absorbent and considerable CO formation can occur when inhalation anaesthetics are used with desiccated absorbent.1,4 Endogenous CO is produced as a result of haeme oxygenase-1-mediated haeme catabolism.5 After diffusion into the circulation and formation of carboxyhaemoglobin (COHb), endogenous CO is excreted by the lungs through exhalation.6

Low-flow anaesthesia (LFA) is a commonly used cost-saving technique to permit re-breathing and conservation of volatile anaesthetics.7 Because CO is not scavenged or removed from the breathing circuit, it is possible that during LFA with a closed anaesthesia breathing circuit, patients re-breathe exhaled CO,8 resulting in an active CO exposure.8

We hypothesized that CO is re-breathed during LFA in infants and children. CO re-breathing during LFA has never been evaluated in the paediatric population. Thus, the aim of this study was to quantify the amount of endogenous CO re-breathed during low-flow general tracheal anaesthesia in infants and children and to define the variables associated with change in CO levels within the anaesthesia circuit. This was achieved with the use of fresh carbon dioxide absorbent that lacked sodium and potassium hydroxides to avoid contribution from exogenous CO.9

Methods

This was a prospective observational study and was approved by the institutional review board of Children’s National
Medical Center (Washington, DC, USA). Informed consent was obtained from each patient’s parent or legal guardian.

Patients

Twenty infants and children aged between 2 months and 7 yr and weighing between 2.9 and 25.0 kg undergoing mask induction of anaesthesia followed by general tracheal anaesthesia in the cardiac catheterization laboratory as part of their routine care were studied (Table 1). Patients with known cardiac dysfunction or pulmonary hypertension were excluded because these patients would likely require a non-standard anaesthetic. Cardiac dysfunction was defined as systolic pulmonary artery or right ventricular pressure greater than cardiogram. Pulmonary hypertension was defined as systolic shortening fraction of <30% on the pre-procedure echocardiogram. Cardial dysfunction was defined as systolic pulmonary artery or right ventricular pressure greater than half of the systemic systolic arterial pressure.

Study protocol

Immediately before each procedure, both canisters of carbon dioxide absorbent were replaced in the anaesthesia machine (Aestiva/5, GE Healthcare, Madison, WI, USA) with fresh, out-of-the-package absorbent lacking sodium and potassium hydroxides (Amsorb Plus, Armstrong Medical Limited, Coleraine, Northern Ireland).

Each subject underwent induction of anaesthesia via a mask with sevoflurane (up to 8 vol%, Baxter Healthcare Corporation, Deerfield, IL, USA), 70% nitrous oxide (7 litre min⁻¹), and 30% oxygen (3 litre min⁻¹). An i.v. catheter was placed and venous blood was sampled for ‘baseline’ COHb measurement via 6 wavelength co-oximetry (Radiometer Osm3 Hemoximeter, Copenhagen, Denmark; range 0–100, SD 0.2%). After muscle relaxation with i.v. rocuronium (0.6 mg kg⁻¹), tracheal intubation was performed 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⁻¹) and PCO₂ (5.1 kPa) utilizing peak inspiratory pressures <30 cm H₂O.

For the first 60 min, fresh-gas flow (FGF) (air, 21% oxygen) was fixed at half of the patient Ve (FGF:Ve=0.5). This was defined as the LFA period (Fig. 1A). An FGF:Ve ratio of 0.5 was chosen based on prior work that demonstrated routine CO detection with FGF:Ve<1 and an increase in COHb with FGF:Ve<0.68. Anaesthesia was maintained with either sevoflurane or desflurane (Baxter Healthcare Corporation) based on the anaesthesiologist’s preference. An electrochemical CO sensor (range 0–2000 ppm, resolution 1 ppm) validated in the presence of volatile anaesthetic gases. CO concentration was sampled sequentially from each port (inhaled and inspired) and manually recorded every 5 min.

At the 60 min mark, a post-LFA venous COHb sample was obtained. FGF (air) was then increased to match Ve (FGF:Ve=1). This strategy was continued for the next 60 min and was designated as the high-flow anaesthesia (HFA) period (Fig. 1A). After 60 min of HFA, a post-HFA venous COHb measurement was obtained. Total study time was 120 min (60 min of LFA followed by 60 min of HFA).

Each subject was continuously monitored with pulse oximetry, end-tidal CO₂, non-invasive arterial pressure, electrocardiogram, and temperature measurement. We recorded exhaled volatile anaesthetic agent concentration, age, sex, and body weight. The anaesthesiologist adjusted the concentration of inhaled anaesthetic as necessary.

In vitro control experiment

Both canisters of carbon dioxide absorbent were replaced in the anaesthesia machine (Aestiva/5) with fresh,
was repeated with sevoflurane (3 vol%).

limbs and manually recorded every 5 min. The experiment sampled sequentially from the expiratory and inspiratory limbs. Desflurane was set at 6 vol%, and CO concentration was then increased to 3 litre min$^{-2}$ at 1.5 litre min$^{-1}$.

Repeated-measures ANOVA with post hoc Tukey’s test was used to compare CO concentrations within and between the groups during LFA and HFA. Cross-sectional time series analysis in Stata 10 (Stata Corp LP, College Station, TX, USA) was used to assess change in CO related over time to the following variables: FGF:Ve, sex, age, weight, type, and concentration of volatile anaesthetic. The model-adjusted variance estimates to account for correlation between repeated measurements on the subject. Statistical significance of change in COHb% was assessed with Student’s $t$-test with two-tailed type 1 error set at $P<0.05$. For

### Results

During the LFA period, CO concentrations increased from baseline over time in both inspiratory and expiratory limbs of the breathing circuit (Fig. 2A). During the HFA period, exhaled CO level plateaued, whereas inspired CO decreased dramatically (Fig. 2A). Figure 2A demonstrates the change in inspired CO over time in a representative patient. Mean and range of CO levels during the LFA and HFA periods are listed in Table 1. Inspired CO during LFA peaked at 14 ppm (Table 1). In the majority of subjects, inspired CO during HFA decreased to 0–2 ppm with a maximum of 6 ppm in one subject.

Change in square root of CO during HFA was compared with change in square root of CO during LFA for statistical significance when controlling for differences in baseline levels at the start of each period. CO measured decreased significantly during HFA when compared with concentrations obtained from the corresponding sampling site during LFA ($P<0.0001$, Fig. 2A). During both LFA and HFA, inspired CO concentrations were significantly lower than exhaled levels obtained during the same period ($P<0.0001$, Fig. 2A). In addition, CO concentrations obtained from both sampling sites during HFA differed significantly from measurements taken at the alternative site during LFA (Fig. 2A).

Trajectories of both exhaled and inspired CO differed significantly during HFA when compared with the LFA period ($P<0.001$, $P<0.004$, respectively, Fig. 2B). Furthermore, change in both exhaled and inspired CO trajectories was most significantly associated with FGF:Ve ($P<0.0001$, Table 2). There was no correlation with age or weight (Table 2). Although sex did not correlate with change in inspired CO, male sex was weakly associated with change in exhaled CO ($P<0.03$, Table 2).

In children under 2 yr of age, COHb levels increased significantly from baseline at 60 min after LFA (Fig. 2C). At 120 min, after HFA, these levels remained significantly increased from baseline, but were unchanged from the immediate post-LFA period (Fig. 2C). In children older than 2 yr of age, COHb levels remained unchanged at all time points (Fig. 2C).

In the in vitro control experiment, no CO was detected within the breathing circuit at any time with either desflurane or sevoflurane.
During LFA, CO content within the anaesthesia breathing circuit increased over time in both regions of the system and was associated with an increase in COHb in children, 2 yr of age. Taken together, the presence of CO in the inspiratory limb with an associated increase in COHb indicates CO exposure. Thus, LFA resulted in re-breathing of exhaled CO and exposure, especially in the youngest and smallest children. If FGF does not exceed Ve in a standard anaesthesia machine circle circuit, there will, by definition, be re-breathing, defined as inhalation of gas that has been previously exhaled. Since fresh carbon dioxide absorbent lacking sodium and potassium hydroxides was used and no CO was detected in the control experiments, all CO detected must have originated from endogenous patient sources.

HFA caused the rate of increase in exhaled CO to plateau and inspired CO to significantly decrease. After HFA, COHb remained unchanged from post-LFA levels. It is possible that HFA prevented a further increase in COHb in children, 2 yr as CO was removed from the inspiratory limb. The different responses to LFA with regard to COHb in younger vs older children were likely due to patient size, since CO exposure results in a greater increase in COHb in smaller subjects. The observation that COHb did not decrease after HFA is probably explained by the lack of off-gassing. Off-gassing, the displacement of CO from haemoglobin by oxygen might have been minimized by using air as the fresh gas in the breathing circuit. In addition, CO and COHb continued to be produced endogenously as part of ongoing metabolism during the study period. Thus, during HFA, COHb levels remained constant.

HFA caused a significant change in the trajectories of exhaled and inspired CO. The plateau of exhaled CO and the decrease in inspired CO during HFA correlated most strongly with FGF:Ve. Thus, HFA limited the increase in exhaled CO seen during LFA and dramatically reduced inspired CO content.

### Table 2 Effects of FGF: Ve, sex, age, and weight on change in CO concentration over time

<table>
<thead>
<tr>
<th></th>
<th>Longitudinal coefficient</th>
<th>Z</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhaled CO</td>
<td></td>
<td>Z</td>
<td></td>
</tr>
<tr>
<td>FGF:Ve</td>
<td>−0.923</td>
<td>−5.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>1.348</td>
<td>2.20</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>−0.020</td>
<td>−0.12</td>
<td>0.91</td>
</tr>
<tr>
<td>Weight</td>
<td>−0.055</td>
<td>−0.86</td>
<td>0.39</td>
</tr>
<tr>
<td>Inspired CO</td>
<td></td>
<td>Z</td>
<td></td>
</tr>
<tr>
<td>FGF:Ve</td>
<td>−0.793</td>
<td>−4.88</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.922</td>
<td>1.55</td>
<td>0.12</td>
</tr>
<tr>
<td>Age</td>
<td>0.019</td>
<td>0.12</td>
<td>0.91</td>
</tr>
<tr>
<td>Weight</td>
<td>−0.033</td>
<td>−0.53</td>
<td>0.60</td>
</tr>
</tbody>
</table>
The weak association of sex with change in exhaled CO is likely explained by an unequal distribution of subjects. Of the 20 subjects enrolled, 13 were males and only seven were females. This represents a limitation of the study. Another limitation was study design: LFA followed by HFA. A more scientifically sound approach would have been to randomize patients to undergo either LFA or HFA for the first 60 min followed by the opposite flow strategy for the next 60 min.

With regard to exogenous CO generation within breathing circuits, the consensus among anaesthesiologists is to prevent desiccation of conventional soda lime or to use carbon dioxide absorbents that lack sodium and potassium hydroxides. Exposure to endogenous CO during general anaesthesia is an underappreciated and understudied phenomenon. Here we demonstrate that exhaled CO is re-breathed during LFA in infants and children. It must be stressed, however, that the effect of subclinical CO exposure in human infants and children is unknown. However, the safety of such exposure during prolonged anaesthetics and multiple surgeries must be considered for future study.

Most of what is currently known about overt CO toxicity relates to resultant tissue hypoxia after exposure. Inspired CO diffuses across the alveolar capillary membrane and binds to haemoglobin to form COHb. High levels of COHb interfere with oxygen binding to and dissociation from haemoglobin resulting in impaired tissue oxygen delivery. CO also binds to cellular haeme proteins such as myoglobin and cytochrome oxidase and can circumscribe oxidative phosphorylation. Thus, CO toxicity results from tissue hypoxia; signs and symptoms appear when COHb is >20%.

Nothing is known about the effects of a brief, subclinical exposure to <20 ppm CO resulting in <3% COHb. Therefore, the importance of demonstrating CO re-breathing during LFA in infants and children is yet to be defined. However, there are several clinical situations where re-breathing exhaled CO during general anaesthesia could result in or exacerbate an active CO exposure. These include high haeme turnover states associated with haemolysis (i.e. autoimmune, ABO incompatibility, sickle-cell disease) or conditions that up-regulate haeme oxygenase (sepsis, trauma, shock) which result in elevated COHb levels. In addition, exogenous CO exposure after smoke inhalation or transfusion with banked blood (containing elevated COHb) can increase COHb levels and increase exhaled CO concentrations. It is conceivable that under low-flow general anaesthesia, significant CO levels could be re-breathed. For example, up to 145 ppm CO have been measured in the anaesthesia breathing circuit during LFA in adult smokers. Thus, prolonged re-breathing in such patients could result in an active CO exposure during LFA.

Other implications of CO re-breathing to consider are the effects of nanomolar concentrations of CO on various tissues and organs. Although change in the amount of CO bound to haemoglobin after exposure is readily measurable as COHb, the amount of CO that diffuses into tissues and cells after re-breathing is very difficult to determine. Even small increases in tissue CO concentration can have biological activity. For example, endogenous CO can act as a neurotransmitter and can inhibit haeme proteins such as cytochrome oxidase, catalase, and cytochrome P450. CO also inhibits platelet aggregation, affects heart rate, and causes smooth muscle relaxation via activation of guanylyl cyclase. Re-breathed CO could be synergistic with or causative of the vasodilation seen during LFA. Theoretically, re-breathed CO could interfere with haemostasis, which would also be disadvantageous in the operative setting.

Although future work will focus on identifying the critical COHb and CO levels and duration of exposure necessary to result in tissue and organ toxicity during LFA, avoiding LFA and using a HFA strategy will prevent CO re-breathing. When the mean slopes of the change in square root of CO are plotted against re-breathing fraction (fRB; calculated as 1 – FGF:Ve), a net zero change in CO occurs at an fRB of ~0.4 for inspired CO, and close to an fRB of zero for exhaled CO (Fig. 3). An fRB of zero (zero re-breathing) occurs with HFA at an FGF:Ve of 1. Thus, matching or exceeding Ve with FGF will minimize CO re-breathing and CO exposure during general anaesthesia. Further studies are needed to identify the clinical effects and safety of subclinical CO exposure in infants and children. However, avoidance of LFA in patients with clinical

![Fig 3 Change in CO concentration as a function of re-breathing fraction (fRB). The mean slopes of the trajectory of the square root of CO (sqrtCO) during LFA and HFA are depicted. Values represent mean (SD). fRB was calculated as 1 – FGF:Ve. An fRB of 0.5 represents LFA (50% re-breathing) while an fRB of 0 is HFA (no re-breathing). Lines represent predicted values. Intersection with the zero net change mark in sqrtCO occurs at an fRB of 0.08 (95% confidence interval –0.33 to 0.49) for exhaled CO and 0.39 (95% confidence interval 0.28–0.50) for inspired CO.](https://academic.oup.com/bja/article-abstract/105/6/836/324614)
states that result in elevated COHb levels and exhaled CO will limit potential CO re-breathing.

Acknowledgement

We thank Dr Robert McCarter of the Division of Biostatistics and Informatics at Children’s National Medical Center for assistance with statistical analysis.

Conflict of interest

None declared.

Funding

The Children’s Research Institute Development Funds (R.L.) covered the cost of COHb measurements.

References