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Anesthesia-related Carbon Monoxide Exposure: Toxicity and Potential Therapy

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Abstract

Exposure to carbon monoxide (CO) during general anesthesia can result from volatile anesthetic degradation by carbon dioxide absorbents as well as re-breathing of endogenously produced CO. Although adherence to the Anesthesia Patient Safety Foundation guidelines reduces the risk of CO poisoning, patients may still experience a sub-toxic CO exposure during low-flow anesthesia. The consequences of such exposures are relatively unknown. In contrast to the widely recognized toxicity of high CO concentrations, the biological activity of low concentration CO has recently been shown be cytoprotective. As such, low dose CO is being explored as a novel treatment for a variety of different diseases. Here we review the concept of anesthesia-related CO exposure, identify the sources of production, detail the mechanisms of overt CO toxicity, highlight the cellular effects of low dose CO, and discuss the potential therapeutic role for CO as a part of routine anesthetic management.

Keywords

carbon monoxide; exposure; low-flow anesthesia; general anesthesia; toxicity; cytoprotection; therapy; exogenous; endogenous

Introduction

Carbon monoxide (CO) is a colorless, odorless, and tasteless gas that exerts a number of biologic effects in a variety of different tissues and organs.[1,2] Historically, CO was regarded as a poison due to the well-characterized tissue hypoxia and overt toxicity that result following exposure to high concentrations.[2] Classification of CO as a life-threatening toxin is certainly warranted given that it continues to be the major cause of poison-related death in the United States.[1,2] However, CO also has biological activity at sub-toxic levels, affecting several cellular pathways in a more complex manner. Such CO-mediated effects can be either cytoprotective or pathologic, depending on the context, duration, and concentration of exposure. Anesthesiologists should be aware of CO and its effects given that CO exposure can occur during general endotracheal anesthesia.[3–6] Although the consequences of such anesthesia-related exposures are relatively unknown and investigative efforts to understand

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them are just beginning, low dose CO is being developed more generally to treat a variety of conditions. Here we review the concept of CO exposure in the setting of an anesthetic and identify the sources of production, detail the mechanisms of overt CO toxicity, highlight the cellular effects of low dose CO, and discuss the potential therapeutic role for CO as a part of routine anesthetic management.

CO Exposure During General Endotracheal Anesthesia

The first report of CO detection within a closed circuit anesthesia system was published in 1965.[7] In this study, the authors documented levels of CO as high as 810 parts per million (ppm) within the breathing circuit and concluded that “complete closure of the anesthetic system [allowed] build up” of CO.[7] Although **it is** over 50 years **old, this work** insightfully **identified** the patient's own alveolar gas as a potential **source** of CO.[7]

In the early to mid-1990s, generation of CO within the anesthesia breathing circuit and patient exposure became more widely recognized.[8] **Several** studies and anecdotal case reports during that period described high CO concentrations within the anesthesia circuit along with clinical signs of CO toxicity and elevated carboxyhemoglobin (COHb) levels.[9–11] The earliest case report of such toxicity described a rise in COHb in a 76 year old, non-smoking woman undergoing general endotracheal anesthesia for thyroid resection.[10] An arterial blood gas measured 25 minutes following anesthesia induction and 1 hour later demonstrated COHb levels of 9.1% and 28%, respectively.[10] These findings were somewhat serendipitous given that co-oximetry **measurement was performed** on all blood gas samples **as a standard** and the anesthesiology care providers did not intend to assess such values as part of routine clinical care.[10] The patient experienced a headache postoperatively **which resolved** with hyperbaric oxygen therapy.[10] Fresh gas contamination was suspected, **but** was ruled out by **the absence** of CO in the oxygen and nitrous oxide supply lines.[10]

Several weeks later, a second case of intraoperative CO exposure was identified at the same institution.[10] In this case, a COHb level of 24.7% was measured in a patient undergoing total hip replacement **under** general anesthesia.[10] Although initial investigation failed to locate an exogenous source of CO, thorough assessment of the anesthesia circuit identified CO concentrations in excess of 500 ppm in the gas exiting the carbon dioxide absorbent canister.[10] Eight cases of anesthetic-related CO exposure were subsequently reported in 1990 **and, in** all, a total of 31 cases were reported.[3,12] In some instances, CO concentrations within the breathing circuit exceeded 1000 ppm and patient COHb levels reached 30% or greater.[3]

At the annual meeting of the American Society of Anesthesiologists in 1990, a review of these cases revealed one shared characteristic: most occurred on a Monday morning as the first anesthetic of the day or with an anesthesia machine that had been idle for at least two days previously.[10] This finding raised the possibility of a chemical reaction between the conventional carbon dioxide absorbent and volatile anesthetic agents.[10] **Subsequent** investigation demonstrated definitively that CO is generated when volatile anesthetics are degraded by conventional carbon dioxide absorbents.[8,11,13–15] Importantly, the magnitude of CO production inversely **correlated with** the water content of the absorbent.[8]

In 2003, Abbott Laboratories, in collaboration with the Food and Drug Administration, **released** a “Dear Health Care Professional” letter to notify practitioners of the risk of adverse events when sevoflurane interacts with desiccated absorbent.[16,17] This letter focused mostly on the risk of fire due to the exothermic reaction, **but** the reader was **also** alerted to the risk of CO production. In 2005, the Anesthesia Patient Safety Foundation (APSF) convened a meeting of medical experts and industry representatives to address the risk of fire within the anesthesia breathing circuit and the potential for CO exposure as a result of the chemical reaction.[18] This safety conference focused mostly on formation of toxic products via the chemical breakdown of volatile anesthetics.[18] As a result of **the** meeting, the APSF made two recommendations: first, they suggested the use of absorbents that lack strong alkali hydroxides and do not degrade inhalation anesthetics.[18,19] Second, they provided several recommendations aimed at preventing conventional absorbent desiccation.[18] Although adherence to these guidelines reduces the risk of overt CO poisoning, limiting volatile agent degradation by using hydrated absorbent does not necessarily prevent sub-toxic anesthesia-related CO exposure.

Exogenous Sources

Exogenous CO is generated within the anesthesia breathing circuit when volatile anesthetic agents are degraded by conventional carbon dioxide absorbents.[3,20] One mechanism believed to contribute to CO production is proton abstraction of the difluoromethyl ether moiety of halogenated agents (such as desflurane and isoflurane), catalyzed by the base of the absorbent to yield a carbanion intermediate (figure 1).[20] In the absence of adequate water, the carbanion **decomposes** and subsequently **interacts** with hydroxide or residual water, generating CO.[20] Sevoflurane and halothane can also generate CO, yet lack a difluoromethyl ether group, suggesting that other, less well defined mechanisms **may be** involved.[21] Importantly, CO production via degradation by conventional absorbents has been demonstrated with all of the volatile anesthetic agents currently in use today.[13,21,22]

As mentioned earlier, water content is a key factor in determining the magnitude of anesthetic degradation and exogenous CO production within the anesthesia breathing circuit.[8,13] Specifically, the amount of CO generated is inversely proportional to the amount of water in the absorbent.[13] Completely dried absorbent produces the greatest amount of CO compared to partially hydrated absorbent.[8,13] Reducing the water content in barium hydroxide lime from 13% (fully hydrated) to 8–10% by drying overnight for up to 14 hours with a fresh gas flow of 10 liters per minute, for example, leads to only minimal amounts of CO generation.[23] On the other hand, reducing the water content of the absorbent to 5% or less by drying for 24 hours or more results in the production of significant concentrations of CO.[23] This property likely explains the severe CO exposures seen on Monday mornings following use of anesthesia machines that **were** idle over the weekend with fresh gas flowing.[23]

Desiccated Baralyme® (Chemetron Medical Division, Allied Healthcare Products, St. Louis, MO), now obsolete and no longer commercially available, was shown to generate up to 20,000 ppm CO **during a desflurane anesthetic** while Baralyme® containing 1.6% or 3.2% water **produced** lower concentrations of CO (peak concentrations of 15,000 ppm or

less) (table).[13] With soda lime, fully desiccated absorbent generates approximately 2500 ppm CO from desflurane and ~500 ppm from isoflurane while partially hydrated absorbent produces only ~60 ppm CO and ~100 ppm with each agent, respectively.[13] Rehydrating desiccated barium hydroxide lime **prevented** CO formation from desflurane which suggested that fully hydrated conventional absorbents **would be completely safe.**[8,13] However, *in vitro* experimentation demonstrated that fully hydrated soda lime **could**, indeed, degrade desflurane during a 2-hour exposure and generates up to 23 ppm CO.[24] Although the magnitude of CO produced from hydrated absorbent is markedly less than that generated by desiccated absorbent, CO formation still occurs and fresh gas flow (FGF) inversely correlates with CO concentration.[24] A potential explanation is that fresh gas dilutes the CO that is formed during anesthetic degradation and lower FGFs may limit this dilutional effect within the breathing circuit, resulting in higher concentrations.[24]

In addition to the water content within the absorbent, other important variables that affect the degree of CO production include type of volatile agent used, anesthetic concentration, absorbent temperature, patient carbon dioxide production, and the chemical composition of the specific carbon dioxide absorbent in use.[13,24] The amount of CO generated at equipotent anesthetic concentrations for the different volatile agents **is** generally described **as**: desflurane ≥ enflurane > isoflurane ≥ halothane = sevoflurane, with higher volatile agent concentrations producing higher peak concentrations of CO for each anesthetic.[3,13,20,24] However, this relationship is not absolute given that the CO generating capacity of each agent depends on a number of variables and specific conditions. For example CO production from sevoflurane was shown to be exponential, reaching levels greater than 11,000 ppm when the temperature of desiccated Baralyme® rose to 80 °C.[25] Such levels of CO exceed those produced by equipotent enflurane and isoflurane at temperatures of 45 °C with the same absorbent.[13] Thus, comparisons made between anesthetic agents should be interpreted cautiously with regard to CO generation.

With regard to temperature, degradation of anesthetics **and** CO production **are accelerated by heat**.[13] This attribute is particularly important because volatile agent degradation is an exothermic process.[25,26] Thus, heat resulting from anesthetic breakdown raises the temperature of the absorbent, leading to further anesthetic degradation and greater CO formation.[13,25,26] This **effect** is **magnified** when desiccated or partially dried absorbent is used.[13] For example, sevoflurane undergoes 13% degradation over 1 hour at 40 °C while 56% is degraded over the same period of time when the temperature of the absorbent is increased to 60 °C.[27]

Carbon dioxide absorption is also exothermic and can reduce the water content in absorbent within the upstream canister over time.[28] The combined effects of heating and drying the absorbent may indirectly increase the amount of CO produced and may explain why patients who produce more carbon dioxide may **encounter** higher concentrations of CO during an anesthetic.[24,28] Although absorbent temperature is an important variable, the lack of a rise in soda lime temperature does not predict the amount of CO that is formed.[21]

Chemical composition of the carbon dioxide absorbent is another critical factor that influences volatile anesthetic breakdown and CO formation. Specifically, strong alkali

hydroxides, such as potassium hydroxide and sodium hydroxide, are key components within conventional carbon dioxide absorbents responsible for anesthetic degradation.[29] Since base-catalyzed proton abstraction occurs to a greater degree with potassium versus sodium hydroxide, dried barium hydroxide lime will produce more CO than desiccated soda lime.[3,20] This is because Baralyme® contained 4.6% potassium hydroxide while conventional soda lime is composed of 2.6% potassium hydroxide and ~1.5% sodium hydroxide (table).[20] Of note, Baralyme® was voluntarily removed from the United States market in 2004 by the manufacturer due to "concerns regarding [it's] use…in conjunction with…newer inhalation anesthetics when Baralyme® [was]…allowed, contrary to recommended practice, to become desiccated".[30]

More modern carbon dioxide absorbents lack potassium and sodium hydroxide (table).[31] These newer absorbents are composed of calcium or lithium hydroxide and generate approximately one tenth as much CO as conventional absorbents.[3] However, CO production may still occur and **clinical** reports **suggest** significant CO generation with some of the calcium containing absorbents when they become desiccated.[31] On the other hand, lithium hydroxide based absorbents appear to lack CO-generating capability, even when completely desiccated.[31]

Endogenous Sources

In addition to exogenous formation within the anesthesia breathing circuit, CO can also arise from endogenous patient sources.[32] CO is produced naturally within the liver, spleen, and kidney and in tissues within the central nervous system and reticuloendothelial system during heme catabolism (figure 2).[33] Following formation, CO diffuses into the circulation, binds to hemoglobin to form COHb, and is ultimately excreted by the lungs via exhalation.[33].

Low-flow anesthesia (LFA) is a commonly used, cost-saving paradigm to permit re-breathing and conservation of volatile anesthetics.[34] Because exhaled CO is not scavenged or removed from the breathing circuit, patients may re-breathe exhaled CO **during LFA**.[9] Children inspire up to 20 ppm CO with a concomitant rise in COHb during general endotracheal anesthesia when FGF is set below the rate of minute ventilation.[5,6] CO re-breathing has also been demonstrated in adults during LFA and concentrations within the circuit may reach levels as high as 145 ppm CO in smokers.[4] CO exposure inversely correlates with FGF rates such that higher CO levels result from lower FGFs.[4,5] Importantly, little or no CO is re-breathed by children when FGFs exceed patient minute ventilation rates and CO has been predicted to decrease within the circuit by an average of 5.9 ppm for each 1 liter per minute increase in FGF in adults.[4,5]

Endogenously produced CO is thought to yield about 0.5% COHb and levels of up to 3% COHb in non-smoking city dwellers are considered normal.[35] **Increased endogenous CO production can occur in** several clinical scenarios, leading to elevated COHb levels. **This is seen with** high heme turnover **diseases** such as autoimmune-mediated hemolysis, sickle cell **anemia, and** conditions that upregulate heme oxygenase activity and **with** heme breakdown **states** such as trauma, sepsis, and shock.[36–39] Furthermore, environmental CO exposure, as occurs with smoke inhalation and with exposure to air pollution or tobacco smoke (including

recreational water pipe smoking), also increases circulating COHb.[40] In addition, patient COHb levels rise following transfusion with homologous packed red blood cells that have an elevated COHb content.[41] The increase in COHb in these disease processes and following such exogenous exposures leads to greater CO concentrations in exhaled breath. As a result, these patients may experience an even more profound CO exposure when re-breathing is permitted during LFA.

Biologic effects of CO

Policy

In 1971, the United States Environmental Protection Agency established the National Ambient Air Quality Standard for CO which set the limit for a time-weighted average exposure at 9 ppm for 8 hours and 35 ppm for 1 hour in outdoor environments.[42] This limit was based on research that demonstrated a correlation between an acute CO exposure and a rise in COHb with a concomitant reduction in time to the onset of angina in adults with coronary artery disease during exercise.[43–50] There are currently no established limits for anesthesia-related CO exposure, **in part** because **of** a paucity of research assessing the risk of such exposures. **However,** one prior investigation demonstrated that preoperative exposure to tobacco smoke was a cardiac risk factor in patients undergoing general endotracheal anesthesia.[51] In this work, acute smoking prior to surgery **resulted** in a mean exhaled CO concentration of 52.4 ppm (versus 9.4 ppm CO in non-smokers) and these concentrations along with rate pressure product were significant predictors of intraoperative ST segment depression when simultaneously considered.[51] CO exposure during a general endotracheal anesthetic, **thus,** has the potential to interrupt myocardial tissue oxygenation.[51] Such findings raise the question of whether safety limits for anesthesia-related CO exposure should be investigated and considered.

With regard to indoor ambient levels of CO, no legal regulations **currently exist**. However, several US agencies have put forward guidelines regarding the upper limits of exposure. For example, the Occupational Safety and Health Administration (OSHA) suggests limiting CO exposure to 50 ppm for 8 hours, The National Institute for Occupational Safety and Health (NIOSH) recommends a time-weighted limit of 35 ppm over 8 hours with an upper ceiling of 200 ppm, and The American Conference of Governmental Industrial Hygienists (ACGIH) recommends limiting CO exposure to 25 ppm for 8 hours.[42]

It should be noted that CO concentrations produced by completely desiccated and partially dehydrated conventional soda lime **may** exceed these recommended concentration limits.[13,31] However, with strict adherence to the APSF guidelines, the risk of anesthesia-related CO poisoning can be reduced. With regard to LFA, the amount of CO inspired (from either exogenous or endogenous sources) can also meet or exceed these time-weighted limits depending on the concentration of CO in the circuit, the duration of the anesthetic, and the length of exposure.[4–6,24] Unfortunately, anesthesia-related CO exposure has been poorly studied, so the consequences of such exposures remain relatively unknown.

Overt toxicity

Following inspiration, CO diffuses across the alveolar capillary membrane and rapidly binds to hemoglobin to form COHb.[52] The affinity of hemoglobin for CO is about 240 times greater than that for oxygen, and formation of COHb can interfere with the ability of oxygen to bind to and dissociate from hemoglobin.[53,54] High levels of COHb shift the oxygen-hemoglobin dissociation curve to the left and impair tissue oxygen delivery (figure 3).[54] Furthermore, CO can bind to hemoproteins such as myoglobin within the cytosol and cytochrome oxidase within the electron transport chain of mitochondria and high concentrations interrupt aerobic cellular energy production (figure 3).[55,56] Thus, overt CO toxicity manifests as a result of tissue and cellular hypoxia and causes clinically detectable signs and symptoms when COHb is greater than 10-20%.[2] In addition to tissue hypoxia, a number of other mechanisms of overt CO toxicity have recently been elucidated. These include CO-induced oxidative stress, peroxynitrite formation, inflammation, apoptosis, and immune-mediated injury.[57] Thus, clinically relevant CO toxicity results from both tissue hypoxia and direct cellular effects.[57]

Organs with the greatest aerobic activity, such as the brain and the heart, are most vulnerable to overt CO toxicity.[2] Cardiovascular effects of acute CO poisoning include hypotension due to vasodilation, arrhythmias, ischemia, infarction, and cardiac arrest while neurologic manifestations include headache, dizziness, impaired judgment, confusion, altered mental status, seizures, syncope, stroke, and coma.[2,58] Such physiologic derangements occur regardless of the source of CO and can be seen in patients following toxic exposure to indoor or outdoor pollution as well as in burn-injured patients following smoke inhalation.[2] Symptoms of CO toxicity in children may include nausea, vomiting, and lethargy.[59,60] Interestingly, many of these symptoms mimic the adverse effects of a variety of anesthetic agents as well as clinical signs seen during routine emergence from general anesthesia. Thus, without monitoring inspired CO concentrations, determining CO content in exhaled breath, or measuring COHb levels, toxic anesthesia-related CO exposure **can** easily be overlooked. It should be noted that anesthesia-related CO exposure due to desiccated carbon dioxide absorbent reported in the 1990s often resulted in COHb levels that exceeded the 10-20% threshold and was associated with clinical signs of overt CO toxicity.[8–10,12] In at least one of these cases, hyperbaric oxygen therapy led to resolution of the patient's symptoms.[10]

The magnitude of COHb formed and the manifestation of toxic effects depend on the concentration of CO that is inhaled and the duration of exposure.[58,61] This time-weighted relationship is critical in determining the degree of toxicity following exposure to CO.[58] Environmental exposure to less than 120 ppm CO for up to 4 hours, for example, is usually asymptomatic, does not result in tissue hypoxia, and is not life threatening.[58,62,63] Lack of clinically detectable signs and symptoms defines such an exposure as sub-clinical and sub-toxic.[58] On the other hand, exposure to an environment containing concentrations of CO that exceed 200 ppm readily elicits symptoms of overt toxicity and inspiring greater than 800 ppm CO leads to COHb levels that exceed 60% and can rapidly result in death.[58]

With regard to anesthesia-related CO exposure, the magnitude of COHb formation has previously been determined **using** a validated mathematical model **that accounts** for clinically relevant conditions during a general anesthetic with isoflurane or desflurane in the context of desiccated barium hydroxide lime.[22] Calculated COHb levels were found to be **higher in patients who were** smaller, **had** anemia, and **were breathing** lower inspired oxygen concentrations.[22] For example, with 7.5% desflurane and partially desiccated barium hydroxide lime, COHb levels exceeded 60% within 20 minutes of exposure in a 25 kg patient, but only reached 30% in a 100 kg patient during the same time period.[22]

Because anesthesia-related CO exposure was not commonly recognized in the era of routine Baralyme® use and prior to the institution of guidelines aimed at preventing desiccation of conventional soda lime, the role of such toxic CO exposures in causing perioperative morbidity and mortality is, historically, unknown. Importantly, removal of Baralyme® from the market and strict adherence to the APSF guidelines greatly reduces the risk of anesthesia-related overt CO toxicity. However, institutions continue to use conventional carbon dioxide absorbents and complete and partial desiccation can still occur. Therefore, exposure to high concentrations of CO during an anesthetic remains plausible and a potential risk. Nevertheless, the current rate of toxic anesthesia-related CO exposure is unknown, **partly** because monitoring for CO exposure is not a standard of care during anesthetic management.

As mentioned earlier, because the signs and symptoms of a toxic CO exposure can mimic those seen following a routine general anesthetic, CO poisoning can easily go undetected. **From** a safety standpoint, it seems logical that CO measurement technology should be incorporated into the anesthesia breathing system to monitor for and detect CO levels within the circuit. Devices that use an electrochemical oxidation principle to quantify CO concentrations currently exist and have been validated with the use of volatile anesthetic agents.[64] **Such** monitoring is, **thus,** feasible. Furthermore, technology that measures COHb levels via non-invasive pulse co-oximetry has also been developed.[65] Although COHb levels determined with this device compare favorably to those obtained via standard co-oximetry with acceptable limits of bias and precision, some studies suggest that the non-invasive technology is less accurate and limited to states of normoxia.[65–70]

Although evaluating COHb (invasively or non-invasively) may not be as useful in providing timely information regarding instantaneous exposure, monitoring gaseous CO levels within the circuit would certainly protect patients from a known anesthesia-related toxin by providing real-time data to the anesthesiologist (for example, elevated inspired CO levels could indicate use of desiccated soda lime and anesthetic degradation, prompting a change in absorbent). The primary goal of monitoring for CO within the anesthesia breathing circuit would be to prevent a toxic exposure.

With regard to sub-toxic CO exposures, inspiring low concentrations of CO commonly occurs during low-flow endotracheal anesthesia due to exogenous CO generation, re-breathing of endogenously produced exhaled CO, or both. The impact of such an exposure during an anesthetic is not known and has been poorly studied. Unlike toxic CO concentrations, however, low dose CO acts as a signaling molecule and can exert a range of

diverse and complex **cytoprotective** effects.[71] As such, low dose CO is currently being investigated and developed as a novel therapy for use in a variety of disease processes. Because patients often inspire low concentrations of CO during LFA, the beneficial effects of CO may be clinically relevant in the perioperative setting and could carry therapeutic potential. However, future study is necessary to determine if CO represents a common anesthesia-related pollutant with deleterious effects or if sub-toxic exposure during an anesthetic influences and improves patient outcomes.

A suggestion of a biologic effect of low-flow anesthesia

Despite the lack of rigorous scientific investigation of the effect of low dose CO exposure during LFA, **several** publications suggest a potential clinical impact of LFA, itself. For example, **when compared with a high-flow approach**, LFA with desflurane preserved pulmonary function and mucociliary clearance in adults undergoing tympanomastoidectomy.[72] **Such potential** effects of LFA on respiratory function are consistent with known protective effects of low dose CO in the context of lung inflammation and oxidative injury.[73] In **another observational** study evaluating the effect of fresh gas flow rates, LFA with sevoflurane was associated with lower plasma viscosity and prolonged activated partial thromboplastin times compared with high-flow anesthesia.[74] In other work, LFA with desflurane in adults undergoing thyroidectomy was associated with a relative preservation of and significant increase in plasma nitric oxide (NO) levels 24 hours after surgery compared with a high-flow anesthesia approach.[75] Although CO can cause a rapid release of NO from the hemoproteins that bind it, the relative increase in circulating NO seen postoperatively with LFA could be consistent with CO-mediated activation of nitric oxide synthase (NOS).[76–81]

Effects of low concentration CO

Although CO was once believed to be an insignificant toxic byproduct of endogenous heme catabolism, it is now evident that nanomolar concentrations can exert important biological activity in a variety of cells and tissues.[82] CO was first identified as a signaling molecule following discovery of its ability to weakly stimulate soluble guanylate cyclase (sGC) to produce cyclic guanosine 3′,5′-monophosphate (cGMP).[83–85] CO binds directly to the heme iron of the enzyme to stimulate cGMP generation in a manner similar to the well-known sGC agonist, NO.[86] However, the process of CO binding is more simplistic than that of NO and CO-mediated activation of sGC is less potent than NO-mediated activation by approximately 100 fold.[86,87] In addition, indirect and dynamic interactions between the two molecules exist. For example, in the presence of low concentrations of NO, CO modestly activates sGC, but with high concentrations of NO, CO acts a partial antagonist.[87] Thus, although there are similarities between CO and NO, the biologic effects of each are complex and may differ when there is interaction between the two gaseous mediators.[87]

Since its identification as a gasotransmitter, CO has also been shown to modulate a number of p38 mitogen-activated protein kinase (MAPK)-related signaling pathways via both cGMP-dependent and independent processes, directly activate calcium-dependent potassium channels, induce protein kinase B (Akt) phosphorylation via the phosphatidylinositol 3-kinase/Akt pathway, and regulate the activity of a number of hemoproteins by binding to the

iron center within their heme prosthetic groups.[71, 88] Examples of CO-mediated cGMP-dependent signaling include inhibition of smooth muscle cell proliferation, inhibition of platelet aggregation, neurotransmission, and vasodilation, while CO-mediated cGMP-independent effects include anti-inflammation, anti-apoptosis, and anti-proliferation (figure 4).[89–91] In addition, low dose CO **promotes** host and cell survival by stimulating mitochondrial biogenesis, inducing autophagy via mitochondrial reactive oxygen species generation, and accelerating the resolution of inflammation via a proresolving mechanism (figure 4).[92–94]

Potential therapeutic role of CO

Interpretation of studies evaluating the potential therapeutic effect of CO should be carried out cautiously given the importance of oxygen tension and oxyhemoglobin saturation in determining the tissue delivery of CO.[95,96] Drawing definitive conclusions about the effects of specific CO concentrations becomes difficult without explicit measurement of such variables. Furthermore, the lack of hemoglobin and its impact on CO binding and diffusion with *in vitro* experimentation must be taken into account when interpreting the effect of CO exposure of cells and tissue in culture. As such, *in vitro* exposure to specific concentrations of CO may not exactly reflect similar time-weighted exposures *in vivo*. In addition, many of the experiments studying low dose exposure used CO concentrations in excess of those inspired during routine LFA. Although technically sub-toxic, such CO exposures may not be directly translatable to the setting of an anesthetic. In lieu of these limitations, preclinical investigation using various animal models of injury and disease **suggests** that inhaled exogenous CO confers cytoprotection in many different tissues and organ systems.[89,97,98] The clinical scenarios that have been experimentally modeled represent human disease states that are commonly encountered in the perioperative setting. Thus, the therapeutic potential of CO may prove to be clinically relevant to anesthesiologists in the near future.

In a rat model of hyperoxia-induced lung injury, for example, inhaled CO (250 ppm) attenuated neutrophil accumulation and apoptosis in the lungs following exposure and significantly improved survival.[97] In a **rodent** model of ventilator-induced lung injury, various concentrations of exogenous CO (up to 250 ppm) reduced tumor necrosis factor-α (TNF- α) and total cell count in bronchoalveolar lavage fluid while increasing levels of the anti-inflammatory cytokine, interleukin (IL)-10.[99] The mechanisms of CO-mediated protection from ventilator-induced lung injury appear to involve p38 MAPK signaling, differential regulation of anti- and pro-inflammatory transcription factors such as the proliferator-activated receptor (PPAR)-gamma and early growth response (Egr)-1, and increased caveolin-1 expression.[99–101]

In mechanically ventilated baboons with pneumococcal pneumonia, inhaled CO (100–300 ppm) given along with antibiotics **accelerated** the resolution of acute lung injury.[102] **In** a mouse model of aspiration, inhalation of 500 ppm CO for 6 hours significantly reduced the number of neutrophils in the lavage fluid and decreased the degree of lung injury following intratracheal injection of an acidic solution.[103] Furthermore, in an aeroallergen model of asthma, inhaled CO (250 ppm) markedly reduced the amount of eosinophils and IL-5 in the

bronchoalveolar lavage fluid and reduced airway reactivity via a cGMP-dependent mechanism.[104,105]

In addition, inhaled low dose CO **protects** the lungs following ischemia and reperfusion by attenuating the inflammatory response and by preventing apoptosis.[106–111] These pro-survival effects have been demonstrated in clinically relevant animal models of lung transplantation, cardiopulmonary bypass (CPB), and secondary lung injury due to remote ischemia/reperfusion.[108,110,112,113] The mechanisms of such cytoprotection involve the p38 MAPK pathway, the phosphatidylinositol 3-kinase/Akt pathway, and Egr-1 expression.[107,109–111] The CO-mediated effects could potentially benefit mechanically ventilated patients routinely cared for by anesthesiologists in the operating room environment and in the intensive care unit (ICU).

In humans, the anti-inflammatory effects of inhaled CO have been preliminarily tested in patients with chronic obstructive pulmonary disease.[114] In a recent pilot study, for instance, inspiring 100–125 ppm CO for 2 hours a day for 4 consecutive days resulted in a trend toward reduced eosinophils within the sputum and improved airway responsiveness to methacholine.[114] In other work, a Phase I trial is currently assessing the safety of inhaled CO (100–200 ppm) in intubated ICU patients with sepsis-induced Acute Respiratory Distress Syndrome.[115]

The cardiovascular system **is another** successful therapeutic target of low dose CO. In a rat model of left anterior descending coronary artery occlusion, for example, pre-occlusion exposure to CO reduced the infarct area size, suppressed macrophage and monocyte migration into the area at risk, and decreased the expression of TNF- α.[116] CO-mediated protection was related to cGMP and endothelial NOS and activation of the p38 MAPK and Akt pathways within myocardium.[116] In a CPB model in pigs that included 2 hours of cardiac arrest, exposure to 250 ppm CO for 2 hours prior to application of the aortic cross clamp **and** administration of CO-saturated cardioplegia solution resulted in enhanced myocardial bioenergetics, less interstitial edema and cardiomyocyte apoptosis, and fewer number of electrical cardioversions required post reperfusion.[117] Thus, exogenous CO may prevent injury to the heart following ischemia and reperfusion.

As with the lungs, low dose CO also **protects** the heart in the setting of organ transplantation. In a model of mouse-to-rat cardiac transplantation, exposure of the donor and recipient to 250–400 ppm CO prior to and following transplant, respectively, suppressed rejection and promoted long-term graft survival via inhibition of platelet aggregation, thrombosis, myocardial infarction, and cardiomyocyte apoptosis.[118] In related work, exposing rat donors to 400 ppm CO prior to transplantation and placing the explanted heart in storage solution containing 1000 ppm CO protected the graft from ischemia/reperfusion injury via an anti-apoptotic mechanism.[119] Furthermore, exposing rat heterotopic heart transplant recipients to 20 ppm CO for up to 100 days post-transplant, markedly prolonged allograft survival.[120] In this model, exogenous CO reduced the amount of vascular inflammation, fibrosis, and cellular infiltration in the donated heart, and inhibited the expression of pro-inflammatory cytokines and mediators.[120] Thus, CO **may** be developed in

the near future as a novel therapeutic adjunct to standard myocardial protective strategies in the setting of cardiac surgery and cardiac transplantation.

Pulmonary arterial hypertension (PAH), a pathologic state that manifests from a wide range of etiologies and disease processes, carries significant perioperative risk.[121] In a rat model of PAH, chronic exposure to 50 ppm CO attenuated hypoxia-induced PAH via activation of calcium-activated potassium channels within pulmonary artery smooth muscle cells.[122] In other work, exposure to 250 ppm CO for 1 hour per day reversed PAH and right ventricle hypertrophy and restored pulmonary vascular architecture to near normal in a variety of rat PAH models.[123] CO-mediated reversal of PAH in these studies involved endothelial NOS and was associated with an increase in smooth muscle apoptosis and a decrease in cellular proliferation.[123]

With regard to clinical studies, two ongoing trials are currently evaluating CO as a potential therapy for PAH.[124,125] The first, a Phase I/Phase II trial in adults with severe PAH, is evaluating the safety and efficacy of inspiring 150 ppm CO for 3 hours at variable frequencies over a 16 week study period.[124] The second study is a Phase I trial in neonates with PAH evaluating for adverse events associated with inspiring exogenous CO.[125] Depending upon **trial outcomes**, it is possible that inhaled CO could be developed as a therapeutic intervention for patients with PAH.

The brain is another potential target of low concentration CO. Exposure to 250 ppm CO, for example, preconditioned mouse neurons cultured *in vitro* and provided protection from experimentally-induced cell death via an anti-apoptotic manner.[126] The pro-survival mechanism in this work involved activation of GC and NOS and was dependent on CO-mediated generation of reactive oxygen species.[126] Preconditioning with low dose CO *in vivo* also **protects** neuronal tissue in a variety of animal models. For instance, in a piglet model of cardiopulmonary bypass, exposure to 250 ppm CO for 3 hours, 1 day prior to surgery, completely prevented cell death in the neocortex and hippocampus following deep hypothermic circulatory arrest.[127] In other work, preconditioning with 250 ppm CO prevented hypoxia- and ischemia-induced apoptosis in the hippocampus of newborn mice.[128] Post-conditioning with CO also **provides** some degree of neuroprotection in models of permanent brain ischemia. For example, exposing mice to 250 ppm CO for 18 hours following complete occlusion of the middle cerebral artery reduced infarct size by about 30%.[129] Thus, low concentration CO has potential **as a** future therapy to protect the brain from injury.

In contrast, however, low concentration CO **can** pathologically disrupt proliferation, differentiation, myelination, and natural apoptosis in the brain and neuronal tissue during development.[130–134] Low dose CO exposure in the postnatal period, for example, permanently impaired the developing rodent auditory system and CO-mediated inhibition of natural programmed cell death in the newborn mouse brain resulted in excess number of neurons and long-lasting cognitive and behavioral defects.[134–137] These disruptive effects of CO exposure are likely due to the **unique sensitivity and vulnerability of** the developing brain to a variety of biologically active agents **that can interrupt** the critical processes involved in neurodevelopment.[138,139]

Juxtaposed **with** the deleterious effect on natural cell death, however, is the **ability of** low dose CO to protect the developing brain against certain neurotoxic pro-apoptotic stimuli.[140,141] For example, in a mouse model of anesthesia-induced neurodegeneration, postnatal exposure to 100 ppm CO limited and prevented isoflurane-induced neurotoxicity via an anti-apoptotic mechanism and modulated lipid peroxidation within forebrain mitochondria.[140,141] Thus, the pro-survival effects of low concentration CO may have differential effects in the developing brain depending on the context of exposure. As such, further work will be necessary to determine the neurodevelopmental consequences of CO exposure during states of health and disease before low concentration CO can be adopted as a therapeutic agent for infants and children.

Conclusions

Because patients can be exposed to CO during the administration of a general endotracheal anesthetic, anesthesiologist should appreciate the history of anesthesia-related CO exposure, understand the conditions for exposure, and be aware of the sources of CO within the anesthesia breathing system. Although the risk of anesthesia-related overt CO toxicity can be reduced by strict adherence to APSF guidelines, generation of high concentrations of CO within the circuit can still occur with the use of certain carbon dioxide absorbents when they become desiccated. Thus, anesthesia care providers should know the type of carbon dioxide absorbent they are using, understand their institutional and departmental practice with regard to changing the absorbent, and maintain vigilance to ensure that policies are followed to prevent conventional absorbent desiccation. Furthermore, CO monitoring and detection technology within the anesthesia breathing circuit **should be considered** as a standard safety measure to prevent toxic exposures.

Anesthesiologists should **also** understand that the practice of low-flow general endotracheal anesthesia may result in low concentration CO exposure. Although the effects of such sub-toxic exposures are not well understood, animal studies indicate that inspiring low dose CO might be beneficial from a cytoprotective standpoint, **but** might also have pathologic consequences depending on the context of exposure. Because of the lack of clinical information and formal study regarding such anesthesia-related CO exposures in patients, further investigation is necessary and anesthesiologists should not change their practice. Instead, they should be aware of ongoing clinical trials and await the results of studies aimed at determining the safety and therapeutic efficacy of low concentration CO. Furthermore, anesthesiologists should recognize that the phenomenon of anesthesia-related CO exposure provides us with the opportunity to be at the forefront of translational investigation **evaluating** the effect of such exposures in our patient populations and unique clinical settings.

The preclinical evidence demonstrating the potential pro-survival benefits of low dose CO is certainly intriguing. However, because sub-toxic CO exposure has the potential for both beneficial and deleterious consequences, further understanding of the biologic effects is necessary. In order for CO to be developed as a novel perioperative therapeutic agent, ideal patient populations and clinical contexts will need to be identified and the benefits of exposure will need to outweigh the risks. If successful, CO could be seamlessly incorporated

into to the armamentarium of gaseous agents that we routinely administer and titrate to effect each day. Intended CO exposure, whether achieved by a LFA technique or by exogenous CO administration, could be guided by real-time monitoring within the anesthesia breathing circuit to permit exact dosing and precise time-weighted exposures. With future investigation and better understanding, we may find that perioperative CO exposure has the potential to impact our patients by improving their recovery from various disease processes, preventing perioperative-related injury, and enhancing outcome and survival.

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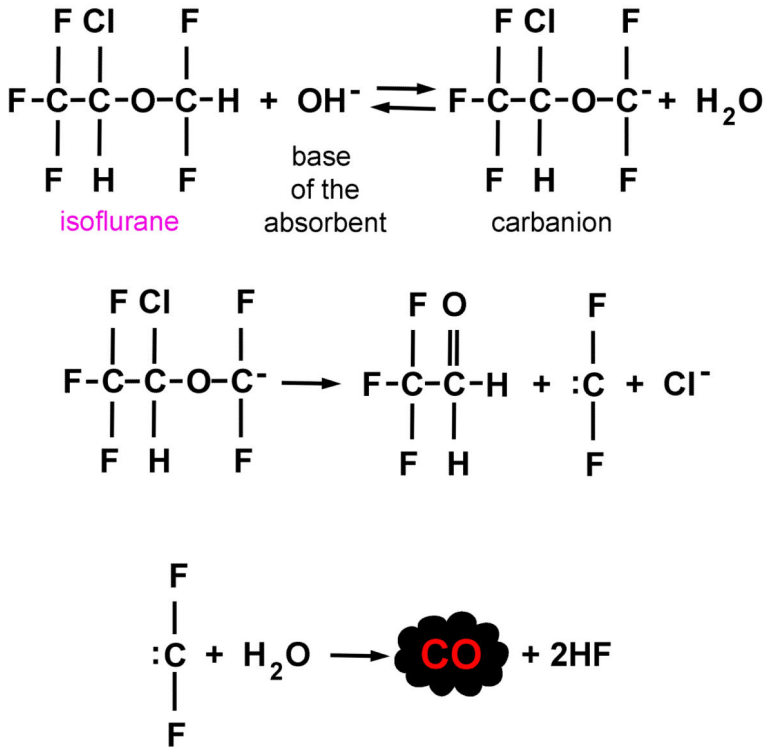

Figure 1. A proposed mechanism of carbon monoxide (CO) generation from isoflurane

Proton (H^+) abstraction is catalyzed by the base (OH^-) of the carbon dioxide absorbent. In the absence of adequate water, the carbanion decomposes and subsequently interacts with hydroxide or residual water (H_2O) within the absorbent, generating CO. Adapted from reference 20.

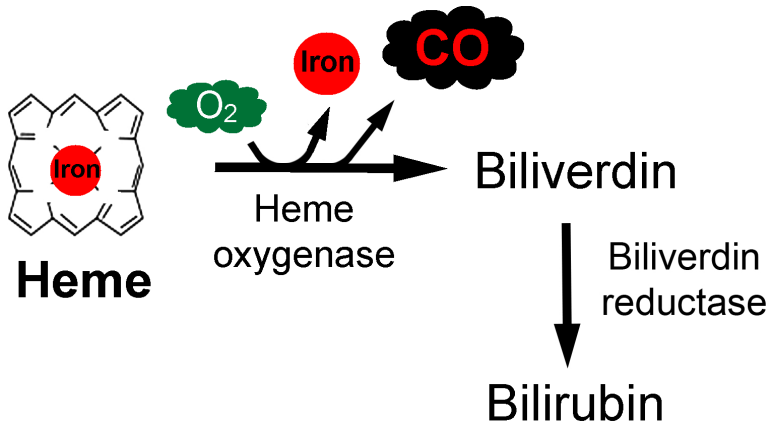

Figure 2. Heme catabolism pathway

In the presence of oxygen (O_2), heme oxygenase catalyzes the breakdown of heme, generating equimolar amounts of free iron, biliverdin, and carbon monoxide (CO).

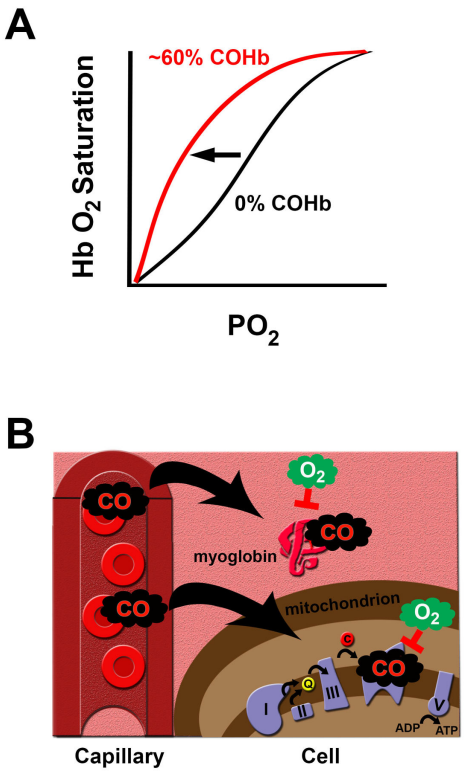

Figure 3. Overt carbon monoxide (CO) toxicity

A. CO shifts the oxygen (O_2)-hemoglobin (Hb) dissociation curve to the left (as indicated by the arrow) when critical levels of carboxyhemoglobin (COHb) are formed. Representative curves for 60% COHb (red curve) and 0% COHb (black curve) are depicted. PO_2 is partial pressure of oxygen. The consequence of a left-shifted curve is impaired tissue delivery of oxygen. **B.** Following exogenous exposure, CO diffuses from the blood into tissues and cells and can bind to myoglobin within the cytosol and cytochrome oxidase (complex IV of the electron transport chain) within mitochondria. High concentrations of CO impair O_2 availability and inhibit aerobic cellular energy (adenosine triphosphate [ATP]) production.

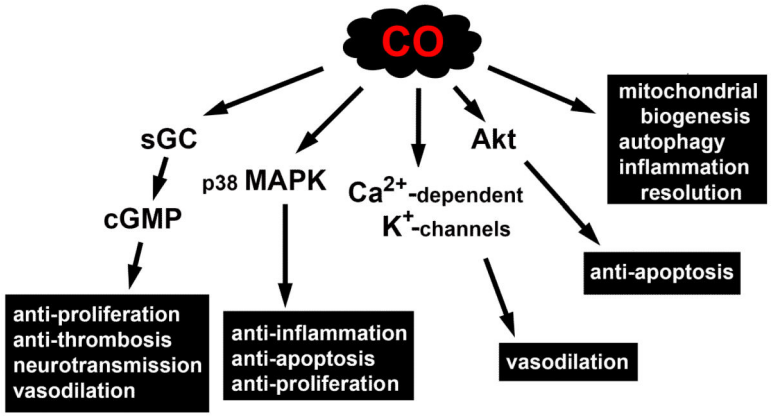

Figure 4. Biological activity of low concentration carbon monoxide (CO)

Various cellular pathways known to be affected by low dose CO are depicted. CO-mediated signaling includes stimulation of soluble guanylate cyclase (sGC) to produce cyclic guanosine 3′,5′-monophosphate (cGMP), modulation of p38 mitogen-activated protein kinase (MAPK), activation of calcium (Ca^{2+})-dependent potassium (K^{+}) channels, induction of protein kinase B (Akt) phosphorylation via the phosphatidylinositol 3-kinase/Akt pathway, stimulation of mitochondrial biogenesis, induction of autophagy, and acceleration of inflammation resolution.

Table

Carbon dioxide absorbent composition and peak carbon monoxide generation.

	Chemical composition (%)						Peak CO (ppm) when fully desiccated	
Absorbent	**$Ca(OH)_2$**	**KOH**	**NaOH**	**LiOH**	**$Ba(OH)_2$**	**H_2O**		**Refs**
Baralyme®	74	4.6	0		11	14	~20,000	13,20
Classic Soda lime		2.6	1.3			15	~2,500	13,20
Medisorb®	81	0.003	1.0			18	~13,000	31
Spherasorb®	84.5	0.003	1.5			14	~9,000	31
LoFloSorb®	84					16	525	31
Superia®	79.5					17.5	~30	31
Amsorb®	83.2					14.4	0	31
Lithium Hydroxide				99		1	0	31

$Ba(OH)_2$, barium hydroxide; $Ca(OH)_2$, calcium hydroxide; CO, carbon monoxide; H_20, water; KOH, potassium hydroxide; LiOH, lithium hydroxide; NaOH, sodium hydroxide; ppm, parts per million; refs, references. Peak CO generation determined with various volatile anesthetics as detailed in indicated reference(s). Amsorb® is a product of Armstrong Ltd., Coleraine, Northern Ireland; Baralyme® was a product of Chemetron Medical Division, Allied Healthcare Products, St. Louis, MO; Medisorb® is a product of Datex Ohmeda, Helsinki, Finland; Spherasorb® and LoFloSorb® are products of Intersurgical, Wokingham, Berkshire, United Kingdom; Superia® is a product of Datex Ohmeda, Hoevelaken, The Netherlands.