

# Characteristics of exogenous carbon monoxide deliveries

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## Abstract

Carbon monoxide (CO) has long been considered an environmental pollutant and a poison. Exogenous exposure to amounts of CO beyond the physiologic level of the body can result in a protective or adaptive response. However, as a gasotransmitter, endogenous CO is important for multiple physiologic functions. To date, at least seven distinct methods of delivering CO have been utilized in animal and clinical studies. In this mini-review, we summarize the exogenous CO delivery methods and compare their advantages and disadvantages.

**Key words:** carbon monoxide; exogenous; delivery methods; CO-releasing molecules; carboxyhemoglobin

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## INTRODUCTION

Since its toxicity was revealed by Claude Bernard in 1857, carbon monoxide (CO) has been known as a silent killer for hundreds of years. It binds very strongly to hemoglobin interrupting oxygen transport in the blood, consequently producing tissue hypoxia (Hampson et al., 2012). CO poisoning results in more than 50,000 emergency department visits annually (Hampson and Weaver, 2007) and is the second leading cause of death from non-medicinal poisoning (Sircar et al., 2015).

Two seminal findings caused a new understanding of CO. Firstly, in 1949, Sjostrand (1949) reported that CO was produced endogenously and an oxidative metabolism of heme was the source of CO in humans. Secondly, the two CO-generating metabolic enzymes, heme oxygenase-1 and heme oxygenase-2, were isolated and characterized in 1968 (Tenhunen et al., 1968). As a gasotransmitter, small amounts of endogenous CO are continuously produced and are important for multiple physiologic functions (Ryter et al., 2006; Oh and Choi, 2015). CO is now known to have a critical role in cellular functions including anti-inflammation (Li et al., 2016), anti-apoptosis (Han et al., 2015), anti-proliferative effects on smooth muscle (Duckers et al., 2001), vasodilation (Johnson and Johnson, 2008), as well

as inhibition of platelet aggregation (Katayama et al., 2000) under certain conditions and appropriate levels. In addition, CO has been implicated in the control of neuroendocrine functions, such as inhibition of the release of hormones (corticotropin-releasing hormone, arginine vasopressin and oxytocin) involved in hypothalamo-pituitary-adrenal axis activation (Mancuso et al., 1997; Navarra et al., 2000; Errico et al., 2010).

## SALUTARY EFFECTS OF EXOGENOUS CO

The amount of exogenous exposure to CO exceeding physiologic levels can result in a protective or adaptive response. The protective effects of exogenous CO may work through CO preconditioning, pretreatment or treatment. The initial evidence supporting a beneficial action of CO inhalation at low concentrations originated from a study on hyperoxic lung injury in rats, in which anti-inflammatory and anti-apoptosis effects were proposed (Otterbein et al., 1999). The salutary effects have been reproduced later in many preclinical models, for example, inflammation (Qin et al., 2015), organ transplantation and preservation (Zhou et al., 2015), acute hepatic injury (Li et al., 2013), cardiac ischemia/reperfusion injury (Stein et al., 2012), and cerebral ischemia/reperfusion injury

**Table 1: Characteristics of exogenous CO deliveries**

Exogenous CO deliveries	Advantages	Disadvantages	References
CO inhalation	No by-product else produced in the body Clinical trials are ongoing	Elevated COHb levels The effective levels in target tissue cannot be well controlled Poor delivery efficiency and no tissue specificity A special chamber or a delivery device is required	Foresti et al., 2008; Motterlini et al., 2010; Hanafy et al., 2013; Wegiel et al., 2013
CO-RMs	With minimal effects on COHb Their activities and pharmacological properties in biological systems have been studied Tissue specificity The effective levels in target tissue can be precisely controlled	More data are needed about the safety and toxicology of these molecules and their products	Motterlini et al., 2007; Foresti et al., 2008; De Backer et al., 2009; Crook et al., 2011; Romao et al., 2012; Qin et al., 2013; Wegiel et al., 2013
A hemoglobin-based CO carrier	The stability increases The safety and toxicology have been well characterized	The potential action of cell-free hemoglobin and the pharmacology of PEG are worth of considering	Vandegriff et al., 2003; Olofsson et al., 2008; Vandegriff et al., 2008; Belcher et al., 2013
CO-saturated red blood cells	No new by-product produced after off loading CO except red blood cells	Elevated COHb levels and similar to inhalation delivery The reactions and complications of blood transfusion may occur	Cabrales et al., 2013
Preservation solution with dissolved CO for grafts	Minimize the concerns associating with <i>in vivo</i> CO administration	The solubility of gaseous CO in aqueous media is poor A tightly sealed container is needed	Vreman et al., 2005; Nakao et al., 2006b, 2008; Sandouka et al., 2006; Musameh et al., 2007; Yoshida et al., 2010
CO-saturated solutions	Not very high COHb levels	An invasive method of administration	Nakao et al., 2006a; Hangai-Hoger et al., 2007
CO intraperitoneal injection	Simple	An invasive method of administration Elevated COHb levels	Gutierrez et al., 1985; Clark et al., 2003; Wang et al., 2009; De Backer et al., 2009; Liu et al., 2010

Note: CO: Carbon monoxide; COHb: carboxyhemoglobin; CO-RMs: CO-releasing molecules; PEG: polyethylene glycol.

(Queiroga et al., 2012). It is very exciting that there are four clinical trials in various phases inhaling doses of CO up to 250 ppm (Hanafy et al., 2013). The diseases involved include idiopathic pulmonary fibrosis, acute respiratory distress syndrome, kidney transplant and paralytic ileus after colon resection (Hanafy et al., 2013). To date at least seven distinct methods of delivering CO have been utilized in studies, including animal models and clinical trials. In this mini-review, we summarize the exogenous CO delivery methods.

## CHARACTERISTICS OF EXOGENOUS CO DELIVERIES

### (Table 1)

#### CO inhalation

Inhaled CO at low concentrations is the simplest delivery method. The advantages of inhalation may be listed as follows (Wegiel et al., 2013). i) CO is an inert and non-metabolized gas, accordingly no by-product else produced in the body. ii) Owing to its bad reputation as a poison, CO has been studied for more than one century. It is well understood in physiology, toxicology and

pharmacology. iii) The preclinical efficacy of inhaled CO is supported by both large and small animal models. The quantity of available literature involved is more than any other delivery methods. iv) To the most important, clinical trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) *via* inhalation are ongoing in various phases (Hanafy et al., 2013; Wegiel et al., 2013).

Although inhalation has many advantages, the questions remain for the application of the delivery method as a therapeutic. First of all, CO *via* the lungs reaches the blood, forming carboxyhemoglobin (COHb) inevitably. The intoxication may occur owing to elevated COHb levels. At the same time, it is unknown whether COHb is the optimal measure of CO poisoning. Second, although the assessment of COHb is the standard and the only reliable measure of CO exposure, its levels cannot represent CO levels in cells and tissues, that is, the effective levels in target tissue cannot be well controlled or assessed. Furthermore, this parameter has not been proved very reliable because of its poor sensitivity at low concentrations (Foresti et al., 2008). Third, owing to its



high affinity for hemoglobin, the delivery efficiency of CO from the lung to diseased tissue may be challenged. Fourth, administering CO through inhalation is delivered with no tissue specificity. Last, in animal experiments a special chamber is required for CO exposure. In clinical trials a specific delivery device or equipment is required too, and the administration is usually conducted in hospitals other than anywhere else. So far, the only device, Covox delivery system designed specifically for inhaled CO delivery has been developed by Ikaria and validated in both large animals and healthy human volunteers (Motterlini and Otterbein, 2010). It uses proprietary technology to provide quantitative delivery of CO for inhalation in proportion to the subject's body weight and independent of the subject's respiratory rate. The dose of CO delivered by the device can be set to mg per kg per hour as a pulse at the beginning of each inspiratory period. Of course, the device which has been used in clinical trials is in accord with US Food and Drug Administration manufacturing requirements (Motterlini and Otterbein, 2010).

### CO-releasing molecules (CO-RMs)

The discovery that certain transition metal carbonyls can play a role as CO-RMs has opened a promising area of CO research. CO-RMs, a group of compounds capable of carrying and liberating controlled quantities of CO in cellular systems, offer a plausible tool for studying the pharmacological effects of this gas. More than 300 articles on CO-RMs have been published so far, including CO-RM-1, CO-RM-2, CO-RM-3, CO-RM-A1 and so on. And new compounds are currently being evaluated (Romao et al., 2012).

The advantages of CO-RMs may include four aspects. i) CO-RMs can increase CO levels in the body with minimal effects on COHb (De Backer et al., 2009; Qin et al., 2013). So the intoxication of CO can be ignored. ii) Their activities and pharmacological properties in biological systems have been studied for at least more than ten years. The results indicate that these compounds are good candidates for the implementation of CO-releasing drugs (Motterlini, 2007). iii) The delivery molecules offer intriguing possibilities for tissue specificity (Wegiel et al., 2013). iv) CO liberated from CO-RMs can be precisely controlled and delivered at given concentrations through certain routes of administration.

Most of the investigations on CO-RMs in small animals indicate that the products after CO release are non-toxic or of low toxicity. However, more and diversified new data are needed about the safety and toxicology of these molecules and their products, for example, transition metals (Foresti et al., 2008). The synthesis and development of

new CO-RMs that liberate multiple CO groups per mole of compound would promote the potency of CO-mediated pharmacological effects and markedly reduce the metal overload to tissues (Crook et al., 2011).

### A hemoglobin-based CO carrier

A hemoglobin-based CO carrier is another way of administering CO. Hemospan, also known as MP4, is made by conjugation of approximately seven polymers of 5-kDa maleimide-activated polyethylene glycol (PEG) to human hemoglobin (Vandegriff et al., 2003). Although MP4 is being developed as an oxygen carrier in phase II clinical trials (Olofsson et al., 2008), the action of it as a CO carrier, that is, CO-MP4 or MP4CO is also under exploration. CO-MP4 can be made as a solution of PEG-conjugated human hemoglobin saturated with 100% CO (Vandegriff et al., 2008). Owing to the absence of hemoglobin oxidation, the stability of CO-MP4 increases.

The CO from MP4CO rapidly distributes in blood after intravenous delivery and the PEG-hemoglobin is predominantly excreted through kidney over the ensuing days. Although the safety and toxicology of CO-MP4 have been well characterized, the potential action of cell-free hemoglobin and the pharmacology of PEG are worth of considering (Belcher et al., 2013).

### CO-saturated red blood cells

In a hamster chamber window model, a new method of CO carrier was used. Resuscitation followed by hemorrhagic shock was performed infusing CO saturated red blood cells in amelioration of microvascular function and providing tissue protection (Cabrales et al., 2007). The autologous blood was collected and heparinized, then the red blood cells obtained by centrifugation were saturated with CO by simply exposing to pure CO gas for 15 minutes. COHb levels were verified before infusion. In the resuscitation group with CO saturated red blood cells, COHb levels increased to  $18 \pm 2\%$  after 15 minutes, and decreased to  $8 \pm 1\%$  after 60 minutes, and  $5 \pm 1\%$  after 90 minutes. It seems that this method is similar to inhalation delivery, because both methods carry CO through COHb. The COHb concentration should be controlled in safe range. There is no new by-product produced after offloading CO except red blood cells. Therefore no toxicity problem is present. However, contamination during the procedure to acquire CO saturated red blood cells must be avoided. And the reactions and complications of blood transfusion may occur.

### Preservation solution with dissolved CO for grafts

Organ transplantation procedure obligates cold preser-



vation and warm reperfusion of the grafts, and induces certain degrees of ischemia/reperfusion injury in all grafts. Gaseous CO may be bubbled into University of Wisconsin (UW) preservation solution, and intestine (Nakao et al., 2006b), and kidney (Nakao et al., 2008; Yoshida et al., 2010) grafts preserved in CO-UW solution were protected from ischemia/reperfusion injury associated with transplantation.

In the experiments, UW solution was vigorously bubbled at 4°C before use for 5–15 minutes with compressed CO gas mixed in air (CO concentration 0–100%, often 5%). In order to maintain soluble CO in UW solution, it was kept in the tightly sealed container with a secured lid without air layer. These grafts were flushed or perfused with CO-UW solution, then underwent static cold storage for 6 to 24 hours with tightly secured containers filled with the solutions before transplanted into recipients.

Although it is well known that solubility of gaseous CO in aqueous media is poor (Vreman et al., 2005), many studies provided evidence that effective levels of soluble CO are achieved in UW solution. Once CO was bubbled into UW solution, steady soluble CO levels were maintained during preservation period. When CO-UW was allowed to contact with the air, soluble CO was quickly released to the air, and CO levels returned to the basal level within 1 hour (Nakao et al., 2006b).

This method could minimize the concerns associating with *in vivo* CO administration and significantly promote the application of CO in a clinical setting. Further extensive studies will be required to identify what is the best range of tissue CO level providing protection and what mechanisms are involved in *ex vivo* CO delivery method.

*In vivo* administration of CO-RMs can increase CO levels, of course, in cold preservation solutions the molecules can also function. St. Thomas cardioplegic solution with CO-RMs showed less cardiac injury and improved cardiac function in isolated rat heart perfusion circuits after cold ischemic storage (Musameh et al., 2007). Celsior cold preservation solution supplemented with CO-RMs also was reported to have beneficial effects in improving renal perfusion flow rate, glomerular filtration rate and sodium and glucose reabsorption rates in isolated kidney circuit model (Sandouka et al., 2006). Meanwhile, all of the uncertainties of CO-RMs exist, including their toxicity, kinetics, and so on.

### CO-saturated solutions

Prompted by UW preservation solution and recognizing that most surgeons irrigate the peritoneal cavity with 1 or 2 L of crystalloid solution at the conclusion of an open abdominal operation, Nakao et al. (2006a) had a novel

idea. The authors found that a single intraperitoneal dose of CO-saturated Ringer's lactate solution (CO-LR) ameliorated postoperative ileus in mice. In the experiments, 100% CO gas was bubbled into Ringer's lactate solution in a 15-mL plastic tube for 5 minutes at room temperature (20°C). CO-LR was kept in a tightly capped tube without a gas layer, and the solution contained approximately 1,200  $\mu$ M CO. After induction of ileus, the peritoneal cavity was filled with 1.5 mL CO-LR followed by closure of the abdomen. COHb levels in blood rapidly increased to almost 8% at 5 minutes after administration but decreased to less than 4% within 30 minutes and continued to gradually decrease to the baseline level by 120 minutes. The levels of CO exposure are probably safe. However, this is an invasive method.

Using similar method, Hangai-Hoger et al. (2007) prepared saturated CO-saline solution to study CO on microvascular and systemic effects. But, the solution was infused intravenous into hamsters, a new route of administration.

Furthermore, early careful clinical trials documenting the safety of intraperitoneal or intravenous CO-saturated solutions administration will be necessary.

### CO intraperitoneal injection

Intraperitoneal injection with 100% CO gas has ever been used to perform a rat model of CO poisoning (Gutierrez et al., 1985; Wang et al., 2009). CO was injected intraperitoneally at a dosage of 100 mL/kg, then repeated after a certain interval. A typical poisoning symptom could be observed in several minutes with higher HbCO levels.

Liu et al. (2010) found that a single dose of CO intraperitoneal administration could protect rat intestine from injury induced by lipopolysaccharide. In the experiment, the rats were administered with 250 ppm CO intraperitoneal injection at a dosage of 2 mL/kg.

Besides the major routes of administration of CO-RMs have been mentioned above, intraperitoneal injection is another method. CO-RM-3 was freshly prepared in 0.1 mL saline and administered immediately into the peritoneum of mice at a dose of 40 mg/kg. Both the donors and the recipients received one dose before surgery. Thereafter, graft recipients received a daily dose of CORM-3 from day 1 to day 8 after transplantation. The survival rate of transplanted hearts was considerably prolonged (Clark et al., 2003). CO-RM-3 and CO-RM-A1 were also administered by intraperitoneal injection to investigate the development of postoperative ileus in mice (De Backer et al., 2009).

### CONCLUSION

So far the versatile actions mediated by exogenous CO are being studied through the methods above. Although some methods have been utilized in studies, even including



clinical trials, the questions still remain as a therapeutic. A desirable breakthrough on mechanism is needed in the near future.

#### Author contributions

XJS designed the study. HJH and QS searched the references and wrote the paper. ZHY and XJS revised the manuscript. All authors read and approved the final version of this paper for publication.

#### Conflicts of interest

The authors declare that they have no competing interests.

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