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Review

Carbon monoxide exposure in the urban environment: An insidious foe for the heart?☆

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ABSTRACT

Since Claude Bernard first demonstrated in the 19th century that carbon monoxide (CO) poisoning occurs through hemoglobin binding, CO has proven to be more than simply a toxic gas, and to possess complex biological properties. In this review, we highlight the dual nature of CO in cardiovascular function, from endogenous and therapeutic properties to harmful aspects. Focussing on exposure to low environmental CO levels, the most common but least studied form of exposure, we summarize the pathophysiological effects of CO *in vivo* and *in vitro*, from cardiac disorders to phenotypic remodelling of cardiomyocytes, based on clinical observations and experimental studies. While acute exposure to low CO levels is considered beneficial and cardioprotective, prolonged exposure appears deleterious, mainly due to alterations in redox status, ion homeostasis, intracellular Ca^{2+} handling, and sympathovagal balance. We emphasize that, despite its fascinating therapeutic potential at low levels, regular exposure to CO may have significant consequences on cardiovascular health and must be considered a cardiovascular risk factor.

1. Introduction

During the past few decades, carbon monoxide (CO) has received a great deal of scientific attention because of its biological properties as a signalling molecule. The endogenous production of CO, resulting from the breakdown of heme proteins by the enzyme heme oxygenase (HO), has been described, notably in the respiratory and cardiovascular systems (Durante et al., 2006; Olson et al., 2012; Peers and Steele, 2012). Organisms are also exposed to exogenous CO from various sources including second-hand smoke, vehicular exhaust, industrial emissions, *etc.* which can be deadly at high concentrations (Soslow and Woolf, 1992). Toxicity occurs mainly through the inhalation of this colourless and odourless gas. Since CO has a high affinity for hemoglobin, forming carboxyhemoglobin (Hb_{CO}) in the blood, it can promote tissue hypoxia resulting from the inhibition of oxygen intake (Hlastala et al., 1976).

The respiratory and cardiovascular effects of CO poisoning, induced by acute exposure to high CO levels (1000–10,000 ppm; 4.16×10^{-5}–4.16×10^{-4} mol L^{-1}), have been widely studied and recognized to result primarily from tissue hypoxia (Anderson et al., 1967; Kolarzyk, 1994). Recent studies have also highlighted the biological effects of low CO concentrations in these systems, although the consequences of prolonged exposure to low CO levels have been less studied and are more controversial. However, the APHEA-2 study (Air Pollution and Health: A European Approach) examining the relationship between air pollution and total cardiovascular mortality in 19 European cities shows a significant association between ambient CO and cardiovascular mortality (Samoli et al., 2007). Environmental CO pollution also has an impact on hospital admissions for respiratory and cardiovascular disorders (Bener et al., 2009; Morris and Naumova, 1998). In urban environments, average CO levels typically vary from 2 to 40 ppm (8×10^{-8} to 1.8×10^{-6} mol L^{-1}), but may be as high as 500 ppm (2×10^{-5} mol L^{-1}) during heavy traffic or when individuals are exposed to second-hand cigarette smoke (Bevan et al., 1991; Stern et al., 1988; Waller et al., 1961; Wright et al., 1975). Interestingly, at low environmental CO levels, the Hb_{CO} concentrations seen in humans are so low (4–6%) that direct hypoxic stress seems unlikely. In this review, we focus on the toxic effects and the cardiac risks associated with CO exposure with special emphasis on its effect following prolonged inhalation of environmental CO.

2. CO, a double-edged sword: from harmful effects to therapy

Claude Bernard first proposed in 1865 that CO toxicity results from the formation of Hb_{CO}. Indeed, the affinity of hemoglobin for CO is 200–250 times greater than its affinity for oxygen

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(Rodkey et al., 1969). The formation of Hb_{CO} instead of Hb_{O2} results in reduced oxygen delivery and tissue hypoxia. Besides tissue hypoxia, controversy persists as to whether CO also has direct toxic effects that could be mediated by its binding to reduced transition metal complexes, especially heme proteins such as cytochromes (Piantadosi, 2008), myoglobin (Sokal et al., 1984) and NOS (Wu and Wang, 2005). There are more and more experimental evidences to suggest that CO also plays a pivotal role in cell signalling, in cardioprotection and in the prevention of systemic and pulmonary hypertensions. The transition between the physiological, adaptive and toxic effects of CO has been determined by a concentration-time relationship (Piantadosi, 2008). Considering this, in the USA, the National Ambient Air Quality Standard for CO has been set at 35 ppm (1.3×10^{-6} mol L^{-1}) for an average exposure of 1 h and 9 ppm (3.7×10^{-7} mol L^{-1}) for an average exposure of 8 h. Hb_{CO} levels resulting from such CO exposure remain lower than 10%. In this context, compensatory responses are sufficient to maintain tissue oxygenation, and the potential hypoxic effects of CO are negligible (Koehler et al., 1982; Mayevsky et al., 1995).

Under normal conditions, low levels of endogenous CO produced by HO actively regulate key intracellular pathways and critical physiological functions (Schmidt et al., 2012), making CO an intracellular messenger similar to NO (Pannen et al., 1998). These endogenous effects are of particular value in pathophysiological situations. The substantial contribution of CO to the protective effects of induced HO activity has recently been recognized, in particular in the cardiovascular and respiratory systems, and includes vasoactive, anti-oxidative, anti-inflammatory, anti-apoptotic, and anti-proliferative properties (Bauer and Pannen, 2009; Ryter et al., 2007). In the context of ischaemic pathology, CO can be used to precondition the heart, and thus to reduce its vulnerability to ischaemia-reperfusion (I/R) in cardiac tissue (Fujimoto et al., 2004; Stein et al., 2005) and in lungs (Zhang et al., 2003). The perfusion of an isolated heart with a solution containing 0.001 to 0.01% (3.5×10^{-4} to 3.5×10^{-3} mol L^{-1}) of CO also improves post-ischaemic myocardial recovery (Bak et al., 2005). Similarly, the acute inhalation of high levels of CO (between 500 and 1000 ppm; *i.e.* between 2×10^{-5} and 4.16×10^{-5} mol L^{-1}) protects the heart against the deleterious effects of coronary artery occlusion (Fujimoto et al., 2004). This has led to the development of water-soluble CO-releasing molecules (CORMs) that liberate controlled amounts of CO in biological systems, and that are currently being investigated to tailor therapeutic approaches for the prevention of vascular, pulmonary and cardiac dysfunctions, inflammation, tissue ischaemia and organ rejection (Motterlini et al., 2005; Musameh et al., 2006; Nakao and Toyoda, 2012; Schmidt et al., 2012; Zhou et al., 2009). For example, CORM-3 reduces the severity of ventricular fibrillation (Bak et al., 2003) and the size of the infarcted area during I/R, without altering Hb_{CO} concentration (Guo et al., 2004). Comparable effects have been observed *in vitro* with acute CO, which limits the necrosis of cardiomyocyte-derived H9c2 cells subjected to ischaemia (Uemura et al., 2005). CORMs are also beneficial after hypoxia-reoxygenation in H9c2 cells or during I/R in mice and pigs *in vivo* (Lavitrano et al., 2004). Finally, in blood vessels, CO produced by HO elicits smooth muscle relaxation (Kaide et al., 2001; Wang et al., 1997) through a cGMP-dependent pathway and an impaired HO/CO system might constitute one of the pathogenic mechanism of hypertension (Durante et al., 1997; Ndisang et al., 2004). Whereas prolonged exposure to alveolar hypoxia induces pulmonary vascular remodelling, which results in the development of pulmonary artery hypertension (Reeves et al., 1979), it has thus been tested as an anti-hypertensive strategy for pulmonary arterial hypertension, in which daily exposure to low doses of CO (250 ppm; 1×10^{-5} mol L^{-1}) for short periods of time (1 h) reverses hypertension and thereby reduces right ventricular hypertrophy

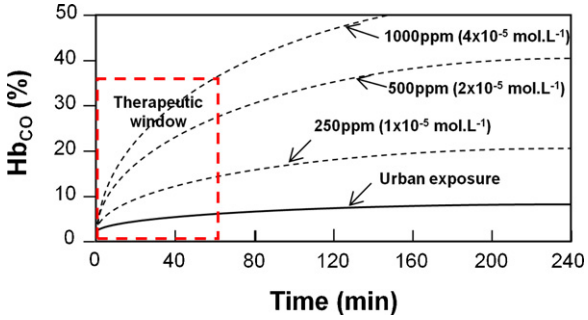

Fig. 1. Therapeutic *versus* harmful windows of CO effects. Representative time course of carboxyhemoglobin levels (Hb_{CO}, in %) during exposure to different carbon monoxide air concentrations (from mean urban air concentration to 1000 ppm, *i.e.* $\approx 4 \times 10^{-5}$ mol L^{-1}). A potent therapeutic window exists when the heart is acutely exposed (for less than 1 h) to moderate CO levels (lower than 1000 ppm; $\approx 4 \times 10^{-5}$ mol L^{-1}).

(Zuckerbraun et al., 2006). These protective effects occur *via* both reduced growth and increased apoptosis of vascular smooth muscle cells, and require a functional eNOS/NOS3 pathway and seems independent of the effect of CO on breathing (Hausberg and Somers, 1997; Vogel and Gleser, 1972). Nevertheless, once again, the CO effect appears to be complex since continuous inhalation of CO (50 ppm; 2×10^{-6} mol L^{-1}, 3 weeks) induces a right ventricle ischemia and severe dysfunction in rat with hypoxic pulmonary hypertension (Gautier et al., 2007), suggesting that CO effects depend on the dose, the duration of exposition and the underlying pathology. The antihypertensive effect of the HO/CO system also depends on the stage of the pathology and the interaction with other gasotransmitters (Ndisang et al., 2004; Ndisang and Wang, 2003). The interaction of CO and NO is of special interest in this regard (Johnson et al., 2003). It was also proposed that in Dahl salt-sensitive rats the increased CO production participates to the establishment of hypertension by impairing the vasorelaxant effect of acetylcholine or of NO donors in muscles arterioles (Johnson et al., 2003, 2004; Johnson and Johnson, 2003; Manson et al., 2003). In addition, the effect of CO on NO depends on the CO concentration: low levels of CO (0.001–0.01 μmol L^{-1}) stimulate NO release, while high doses (>1 μmol L^{-1}) inhibit NO-synthase (Thorup et al., 1999). CO may also regulate arterial pressure *via* the modulation of baroreflex. In particular, CO modulates the release of neurotransmitters as corticotropin (Pozzoli et al., 1994), which has potent effect on respiratory parameters (Mann et al., 1995). CO could also regulate the neuronal firing rate in several nuclei of the locus coerulus and nucleus of the solitary tract (Johnson et al., 1997; Pineda et al., 1996). Endogenous CO production in the nucleus of the solitary tract has been shown to maintain normal blood pressure by suppressing the activity of the sympathetic nervous system (Durante et al., 2006).

To summarize, acute exposure (less than 1 h) to moderate CO levels (below 1000 ppm; 4×10^{-2} mol L^{-1}) has genuine therapeutic potential (Fig. 1). However, prolonged exposure to similar or higher concentrations (1000–10,000 ppm; 4.16×10^{-5} to 4.16×10^{-4} mol L^{-1}) can be deleterious to the cardiovascular system.

3. Morphologic and functional consequences of prolonged CO exposure in the heart

The effects of prolonged low-level CO exposure in humans, as seen in urban areas, are inferred mostly from epidemiological studies and correlations between air quality and cardiovascular outcome. It is also particularly difficult to distinguish the effects of CO from those of other atmospheric pollutants. In this regard,