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Carbon Monoxide Urban Air Pollution: Cardiac Effects

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1. Introduction

Heart disease is a leading cause of death world-wide. The development of heart pathological phenotype results from a complex interplay between genetic and environmental factors. Among environmental factors, recently the deleterious health effects of urban air pollution were pointed out in epidemiological studies (Bhatnagar, 2006, Brook et al., 2004) and a particular attention is then paid to micro and nano-particles air pollution. However, some gazes, such as SO_2, NO_x, O_3, CO_x, could also be reported to have potential deleterious cardiovascular health effects. Particularly, carbon monoxide (CO) resulting from the partial oxidation of carbon-containing compound is reported in epidemiological studies as one of the main pollutants responsible for the development of cardiovascular diseases (Bell et al., 2009, Stieb et al., 2009). Indeed, at low concentration, as may be found in urban environment, CO has been correlated with hospital admissions, mortality and morbidity related to cardiovascular dysfunctions (Bell et al., 2009, Burnett et al., 1997).

Today, the cardiac effects of CO poisoning, corresponding to acute exposure to very high concentrations of CO (1000 – 10000 ppm), were largely studied and are known as the consequence of tissue hypoxemia resulting from the high affinity of CO for blood haemoglobin. However, at low concentrations, as classically found in urban environment, such a hypoxemia could not be considered as a trigger of CO-induced cardiac incoherencies. Then, although some epidemiological evidences that CO air pollution could play a key role in the deleterious effects of prolonged exposure to urban air pollution, today, whether this gaze could be considered as a main risk factor in the development of cardiac diseases, is less understood. Therefore, the aim of this review was to explore, based on experimental literature, the potential link between exposure to such an environmental pollutant and occurrence of cardiac disturbances.

2. CO in urban environment

The purpose of this review is not to discuss on the level of CO measured in urban area. However, in order to focus our review on concentrations corresponding to those measured in urban environment, we first have to consider the range of urban CO concentration observed in environmental studies.

In urban area the most common sources of CO are cigarette smoke and vehicle exhaust (Cunnington and Hormbrey, 2002). In the US, daily mean ambient levels of CO range from 0.5 to 2 ppm (Samet et al., 2000). Exhaled CO levels range from 0 to 21 ppm in non smokers, and from 2 to 50 ppm in smokers (Jones and Lam, 2006). The highest levels of CO exposure were found in car park/garages (12 ppm), private car/taxi (11 ppm) and bar/pub/nights club (8 ppm) (Chau et al., 2002). Then, in urban environments CO concentration usually varies from 2 to 40 ppm, but during heavy traffic or when peoples are exposed to second-hand cigarette smoke it may be as high as 170 ppm (Bevan, 1991, Stern et al., 1988, Wright et al., 1975). Although CO levels are relatively low in urban environment, data from the APHEA-2 project (Air Pollution and Health: A European Approach) studying the relation between air pollution and total cardiovascular mortality in 19 European cities, reported a significant association of CO with cardiovascular mortality (Samoli et al., 2007).

3. Regular exposure to low CO level and phenotypical remodelling of the heart

3.1 Acute low level CO exposure

The acute effects of such low levels of CO on the myocardium are today few studied and results are contradictory and conflicting. Thom et al., (Thom et al., 1999, Thom et al., 2000) discussed that carboxyhemoglobin (HbCO) values associated with levels of CO found in urban area are so low that tissue hypoxemic stress is doubtful and compensatory physiological mechanisms certainly are sufficient to maintain tissue oxygenation. These authors reported yet, on cultured endothelial cells, that acute exposure to low concentrations of CO cause a nitric oxide (NO)-dependent oxidative stress, since CO deleterious effects were inhibited by the addition of N^{ω}nitro-L-arginine methyl ester to inhibit NO synthesis (Thom et al., 2000). In this study, the reaction of NO with superoxide anion to form the highly cytotoxic peroxynitrite is mentioned as a main trigger of lethal CO effects. Indeed, it is today well established that acute CO exposure was associated with higher reactive oxygen species production (Piantadosi, 2002). Indeed, CO molecules form relatively tight complexes with heme proteins (instead of O_2) responsible for mitochondrial and non-mitochondrial reactive oxygen species production (Piantadosi, 2008). Regarding its mitochondrial effects, it was shown that CO binds to cytochrome-c-oxidase altering mitochondrial electron transport chain and then, especially in metabolically active tissues like heart, induced reactive oxygen species production (D'Amico et al., 2006, Zuckerbraun et al., 2007). CO-dependent reactive oxygen species production could also occur via non-mitochondrial sources, notably NADPH oxidase and nitric oxide synthase (NOS) (Piantadosi, 2008); however this is not yet clearly established in the scientific literature.

During CO exposure, the interaction between reactive oxygen species and NO, mentioned above, could also contribute to alter the regulation of coronary blood flow and then the regulation of myocardial perfusion. Indeed, it is today well known that NO play a major role in the coronary vasomotor response of the myocardium. Therefore, we can note that a myocardial dysfunction and a potential cardiac hypoxia in heart of rats inhaling CO for 90 min at 250 ppm was previously reported (Favory et al., 2006). In this model, myocardial hypoxia was explained by coronary endothelium dependent abnormalities. Such a coronary-dependent impairment of myocardial perfusion could then contribute to exacerbate tissue hypoxia.

3.2 Prolonged low level CO exposure

CO molecule, promoting reactive oxygen species dependent signalling molecules, could have biological significance in the adaptation of cells to hypoxia. However, whether

recurrent exposure to low levels of CO could participate to the deleterious effects of urban CO exposure is not today well understood. Recently, Bye et al. (Bye et al., 2008) reported, in a model of rats exposed to CO levels experienced by heavy smokers (18 months, 5 days a week at 200 ppm), a pathological remodelling of the heart, characterized by impaired Ca^{2+} handling and increased growth factor signalling. This pathological hypertrophy of the heart was associated in-vivo with reduced aerobic capacity. In model simulating CO exposure at level found in cigarette smoke (200 ppm for 14 consecutive days), the use of LU135252, a selective inhibitor of type A endothelin (ET-1) receptors (ET_A), in drinking water, markedly prevents right ventricular hypertrophy but not left ventricular, suggesting then a role of ET-1 in the right ventricle and/or in the pulmonary circulation during CO exposure (Loennechen et al., 2002). In another model, closer to urban area pollution, Andre et al. (Andre et al., 2010) reported that 4 weeks of CO exposure at low levels (30-100 ppm 12 hours/day) in healthy rats, promotes heart arrhythmias, even in absence of CO in the environment. This propensity was exacerbated during a β-adrenergic stress. This phenomenon is explained in this work by a pathological cardiomyocytes remodelling. Indeed, in this model of rats, following 4 weeks of CO exposure at low level, both contraction and relaxation of single cardiomyocytes were altered. Several changes explained this alteration of cells function, including decreased Ca^{2+} transient amplitude, decreased Ca^{2+} sensitivity of myofilaments and increased diastolic intracellular Ca^{2+} subsequent to reduced SERCA-2a expression and increased Ryanodine receptor (RyR) phosphorylation (on the PKA-dependent site Ser^{2809}). Authors evoked β-adrenergic stress as a potential trigger of this phenotypical cardiac myocytes remodelling. Indeed, at the cardiomyocytes level, β-adrenergic stimulation activates PKA, which phosphorylates both Ca^{2+} handling proteins involved in excitation-contraction-coupling and myofilaments regulatory proteins. This hypothesis is endorsed by the lower β-adrenergic response in animals exposed to CO pollution. Because reactive oxygen species could also activate PKA in the heart (Marx et al., 2000) and CO is well known to activate reactive oxygen species production, the authors also hypothesized that oxidative stress could be a main trigger of this specific remodelling. This is supported by the impairment of heart enzymatic antioxidant status in CO exposed rat hearts and increased activity of thioredoxin reductase confirming then, in this model, that CO, even at very low levels, was responsible for heart oxidative stress. Finally, prolonged CO exposure (50 ppm during 3 weeks) in rats with pathological right ventricular hypertrophia was reported to induce RV tissue necrosis (Gautier et al., 2007). The authors reported then, that CO-induced alteration of the right ventricular perfusion could play a key role in this phenomenon.

4. Prolonged low level CO exposure and ischemic pathology of the heart

Myocardial infarction due to ischemia reperfusion remains today a major cause of morbidity and mortality in western nations. Those myocardial ischemia-reperfusion injuries result in cardiac dysfunction, arrhythmias, as well as irreversible myocytes damages (Murphy and Steenbergen, 2008). Sensitivity of the myocardium to ischemia-reperfusion-induced cellular injuries is recognized today to be the result of a complex interplay between genetic, pathological and environmental factors.

4.1 Acute CO exposure and Ischemic pathology of the heart

Regarding ischemic pathologies of the heart the effect of CO is today still controversial. Indeed, CO is classically used to pre-condition the heart and then reduce its vulnerability against ischemia-reperfusion (Clark et al., 2003, Fujimoto et al., 2004, Stein et al., 2005). Indeed, since the study of Clark et al. (Clark et al., 2003) has reported the cardioprotective

effects of a water soluble CO releasing molecule, named CORM-3, many studies tested whether CORM-3 or acute CO exposure could reduce the severity of myocardial ischemia-reperfusion injuries. Today, CORM-3 is known as reducing the severity of ventricular fibrillation (Bak et al., 2003) and the size of infracted area (Clark et al., 2003) without altered HbCO concentration (Guo et al., 2004). In the same way, exogenous CO in perfusion buffer of isolated heart (0.01 or 0.001%) was reported to improve myocardial post-ischemic recovery (Bak et al., 2005). Finally, acute inhaled CO exposures (from few hours to 24 hours) at high levels (from 500 to 1000 ppm) were reported to be able to precondition the heart against such a coronary artery occlusion (Fujimoto et al., 2004). P38 mitogen activated protein kinase (p38MAPK) and akt-eNOS-GMPc pathway were reported to be mainly implicated in this cardioprotective effects of inhaled CO.

4.2 Prolonged CO exposure and ischemic pathology of the heart

All in all, those results mainly suggest that CO possesses some cardioprotective properties. However, this is not in accordance with numerous epidemiological studies reporting the potential toxicological properties of this gas in air pollution (see above). In addition, it was reported in some experimental models, that regular exposure to environmental tobacco smoke, in which CO is one of the main toxic components (CO concentration about 90 ppm), increases infarct size (Zhu et al., 1996, Zhu et al., 1994). Finally, the pathologic phenotypical remodeling of heart contractile cells, as mentioned above, could be taken to suggest that prolonged CO exposure could deleteriously influence heart vulnerability to ischemia-reperfusion. Then, in regard to this phenotypical remodelling of cardiomyocytes, some authors were recently interested in evaluating the influence of prolonged CO exposure on heart sensitivity to ischemia-reperfusion, and the potential link between regular exposure to CO and mortality from cardiac incoherencies during such an ischemic stress. In such experimental work, prolonged CO exposure, simulating urban environmental pollution (30-100 ppm 12 hours/day), was reported to exacerbate rat heart ischemia-reperfusion injuries (Figure 1) (Meyer et al., 2010). This higher vulnerability was characterized in CO rats' myocardium by i) lower recovery of myocardial function and coronary blood flow during post-ischemic reperfusion, ii) higher severity of reperfusion arrhythmias, characterized notably by higher propensity of ventricular fibrillation, and iii) higher infarct size and cells death. This phenomenon is mainly explained in this study by exacerbated oxidative stress. Indeed, increased lipid peroxidation was measured in heart of CO exposed rats after 30 min of reperfusion. This could be logically explained by reduced enzymatic antioxidant defence capacities reported in CO rats' myocardium. Then, it is of interest to note that in this work, at cardiomyocyte level, an antioxidant strategy (N-Acetyl-Cysteine infusion) during anoxia-reoxygenation, was able to normalize post-ischemic functional recovery in CO rat heart cells (evaluated by sarcomere length shortening). These effects seem to be mediated by a normalization of cytosolic Ca^{2+} concentrations. In the same way, in another study, the authors evaluated whether, a cardioprotective strategy, such as exercise, was able to prevent the deleterious effects of CO exposure on cardiomyocytes phenotypical remodelling and then influences heart sensitivity to ischemia-reperfusion (Farah et al., 2010). In this work, it is reported that moderate exercise, specifically designed to follow the recommendation of the World Health Organisation, conducted 4 weeks before CO exposure and all along CO exposure period, prevented the pathological remodelling of the heart, including normalization of myocardial antioxidant status and Ca^{2+} handling. The last result could be notably explained by beneficial effects of exercise training on SERCA-2a expression which restored intra-cellular Ca^{2+} homeostasis. Finally, a main result of this work was that this strategy markedly reduced the vulnerability of CO rat hearts to ischemia-reperfusion.

Figure 1.

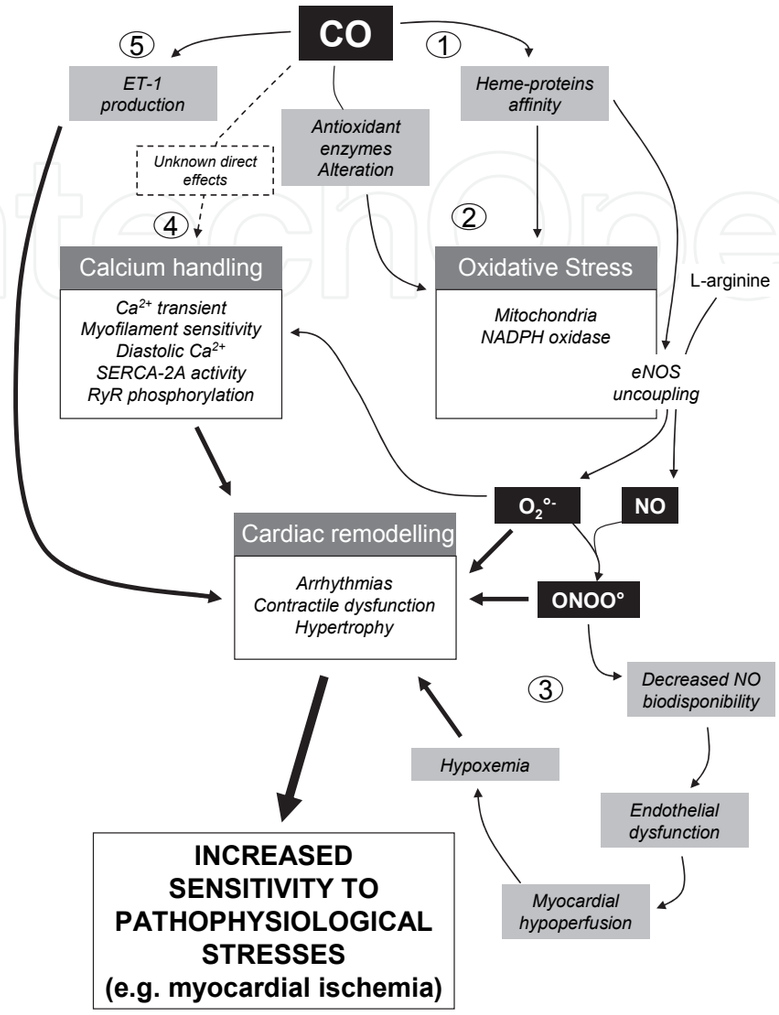

Fig. 1. Potential mechanisms involved in chronic low level CO exposure-induced increased cardiac sensitivity to ischemic stress.

Potential mechanisms involved in chronic low level CO exposure-induced increased cardiac sensitivity to ischemic stress. This figure summarize how as a result of CO effects, the cardiovascular system developed a pathological phenotype which renders the heart more sensitive to myocardial infarction. **1:** CO ability to bound to heme proteins lead to an increased ROS production; **2:** The activation of ROS production associated with reduced antioxidant enzyme defences result in significant CO-induced oxidative stress, leading then to contractile dysfunction and higher occurrence of ventricular arrhythmias; **3:** CO induced potential production of superoxide anion instead of NO (eNOS uncoupling) reduced NO bioavailability. This could lead to coronary artery endothelium dysfunction and then to myocardial hypoxemia; **4:** Ca^{2+} handling play a major role in excitation-contraction coupling. Although today there is no evidence for direct CO effects on Ca^{2+} handling proteins, it is recently demonstrated that prolonged CO exposure markedly altered Ca^{2+}. This could be mediated by CO-induced ROS production; **5:** Probably as a stress signalling pathway, CO induced an increased endothelin (ET-1) production leading then to heart remodelling.

5. Conclusion

Today, among environmental pollutants, CO is less considered, notably because of its very low concentration in urban environment. However, today, such a review of the experimental literature points out that, even at very low concentrations that can be found in urban environment, CO has potential high toxicological properties, and the heart appears to be particularly sensitive to this gas. Indeed, despite during *in-vivo* experiments, at the integrated level, prolonged CO exposure has no major consequence on healthy heart, and induced only modest adaptations with no apparent fatal issue, at the cellular level, those modest events and adaptations hide a compensated pathological remodelling of cardiomyocytes phenotype. Then, one of the main assessments of the present review is that prolonged exposure to low CO level results in a compensated phenotypical remodelling which could render the heart more vulnerable to stress and more particularly to pathological stresses. Therefore, among the numerous environmental air pollutants, exposure to CO pollution seems to be an important risk factor for the development of cardiovascular pathologies.

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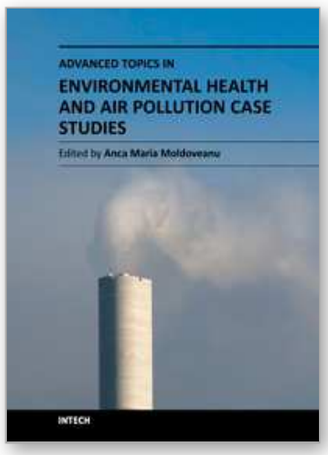

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The book describes the effects of air pollutants, from the indoor and outdoor spaces, on the human physiology. Air pollutants can influence inflammation biomarkers, can influence the pathogenesis of chronic cough, can influence reactive oxygen species (ROS) and can induce autonomic nervous system interactions that modulate cardiac oxidative stress and cardiac electrophysiological changes, can participate in the onset and exacerbation of upper respiratory and cardio-vascular diseases, can lead to the exacerbation of asthma and allergic diseases. The book also presents how the urban environment can influence and modify the impact of various pollutants on human health.

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