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Carbon Monoxide Poisoning, or Carbon Monoxide Protection?

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Carbon monoxide (CO) is a molecule generally presumed to be deleterious when inhaled at high concentrations, but is a marker of oxidative stress and inflammation when endogenously produced. Many reports[1–3] have focused on increased endogenous CO production in pulmonary diseases, including asthma, COPD, acute pneumonia, and ARDS. In this issue of *CHEST* (see page 904), Kobayashi and colleagues[4] add obstructive sleep apnea (OSA) to the list. In documented nonsmokers with OSA and control subjects, CO levels were measured before and after polysomnography. Although CO levels were similar in OSA patients and control subjects prior to sleep, those patients with OSA had elevations in venous CO level after sleep. Moreover, the nocturnal change in CO correlated modestly with the apnea-hypopnea index and duration of hypoxemia during sleep. Treatment with continuous positive airway pressure (CPAP) in some of these patients attenuated the rise in CO, so that treated OSA patients had no difference in CO when compared to control subjects. Linking OSA to cardiovascular morbidity, the authors conclude that "normalization of venous CO levels by CPAP therapy can potentially reduce the risk of disease associated cardiovascular events."

The authors also found concentrations of indirect bilirubin to be elevated after sleep in patients with OSA, suggesting that the sleep-related increase in CO is due to the induction of the heme oxygenase (HO) system. CO can be produced endogenously by the breakdown of heme into CO, biliverdin (subsequently degraded to bilirubin), and iron by HO.[5] There are constitutively active isoforms of HO, but HO-1 is inducible and its byproduct CO has been suggested as a marker of the activity of the enzyme. HO was initially thought to have only a "housekeeping" role (*ie*, scavenging and breaking down free heme). However, several other observations suggested that it might have greater importance. For example, HO has a conserved structure across species (even those without circulating heme), it exists in organs not thought to play a role in heme degradation, and, most importantly, its function can be induced by cellular stressors such as inflammation and infection. The HO products CO and bilirubin are now understood to be mediators and effectors that promote cytoprotection via antiinflammatory, antiapoptotic, and antiproliferative effects, and also invoke antioxidant responses. Thus, the HO system is now thought to be protective from a variety of cellular insults.

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HO-1 is induced ubiquitously in most cell types with high levels of expression in lung endothelial cells, fibroblasts, airway epithelial cells, inflammatory cells, and type II pneumoctyes. Differences between the arterial and venous CO levels suggest that the lungs produce a significant proportion of all endogenous CO.[6] HO-1 can be induced by various stimuli, including hyperoxia, inflammatory cytokines such as interleukin-6, and hypoxia. Continuous hypoxia has been extensively studied as it provides a good model for the protective effects of HO. Mice exposed to hypoxia produce inflammatory cytokines and chemokines, then develop pulmonary hypertension. However, hypoxia also up-regulates transcription of the HO-1 gene, and increases CO and bilirubin production. The HO products counteract the acute effects of hypoxia. CO is a potent vasodilator, and bilirubin acts as an antioxidant against reactive oxygen species. In fact, transgenic mice overexpressing HO-1 are protected against both pulmonary inflammation and pulmonary hypertension, while HO-1 null mice have a maladaptive response to hypoxia and subsequent pulmonary hypertension.[7,8]

In this light, the induction of the HO system and the generation of CO is likely a protective response to the stress of OSA, rather than a causative mechanism of cardiovascular morbidity. This was the conclusion reached by Chin et al[9] who found higher morning bilirubin levels in patients with OSA compared to control subjects. This difference was also ameliorated with CPAP therapy and correlated most strongly with the degree of hypoxemia. The new study by Kobayashi et al[4] is important because it suggests the functional involvement of HO in OSA, and provides a basis for CO as a marker of OSA stress. In the current study, CO levels changed within hours of the stress, could be measured easily with a venous blood draw (and possibly could be measured in exhaled breath[10]), and were affected by treatment. Other biomarkers, such as tumor necrosis factor-α and C-reactive protein, which are thought to reflect the damaging effects of apnea, have been inconsistent in their utility in OSA, as these markers have multiple influences.[11]

These data suggest several future directions. For the scientist, some questions include: what stress influences CO in OSA patients, and is it repetitive arousal, hypoxemia, or some other factors? Does CO level predict long-term cardiovascular morbidity? Is a low CO level a marker of low cardiovascular risk, or instead is it a reflection of impaired protective responses in a patient who is at increased risk of cardiovascular morbidity? While the HO gene is thought to be relatively conserved, polymorphisms in the promoter region have been associated with variable HO-1 expression and associated with higher risks of cardiopulmonary disease. In the current study, there was wide unexplained variability in CO production among patients with OSA. Are these differences due to promoter polymorphisms or other factors? How should CO be measured (by exhaled breath, serum CO level, or hemoglobin-bound CO)? And when should it be measured (during sleep or on awakening, or do elevations persist for some time)? For clinicians, assuming that the CO level has prognostic value, is it a viable biomarker that should be measured to assess disease burden? Does it reliably reflect the response to treatment? And finally, will exogenous CO one day be a therapy (as has been suggested for other pulmonary diseases) to prevent cardiovascular disease in those with OSA, perhaps in patients nonadherent to CPAP therapy?[12] We congratulate Kobayashi et al for fueling the fire on the CO discussion.

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