Inhaled CO in the treatment of acute lung injury

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ACUTE LUNG INJURY is characterized by the loss of barrier function of the alveolar epithelial and pulmonary capillary endothelial cells along with acute inflammation (19). Epidemiological studies suggest that aspiration of gastric contents is a major clinical risk factor for the development of severe lung injury, with the consequence of mortality in the range from 40–50% (1, 6, 14). Although acid itself may directly injure the lung, several lines of evidence indicate that a network of inflammatory cytokines and chemokines perpetuate lung injury following acid aspiration and that interruption of the inflammatory cascade can lead to improved outcomes (3, 4, 8). As neutrophils represent the major inflammatory cell type recruited to the lung following acid aspiration, a focus of work to date has been on modulation of neutrophil chemotaxis, adhesion, and function (3, 8). Despite great progress in the past three decades in elucidating the mechanisms of acute lung injury, there are currently no therapies available to clinicians that have proven efficacy in halting the inflammatory sequelae of acid aspiration. As the populations of industrialized nations continue to age and the number of individuals with chronic illness or disabilities continues to rise, the prevalence of aspiration-related lung injury will also increase. The identification of therapies that can ameliorate the outcome of gastric aspiration is therefore an issue of increasing urgency, and one with the potential to significantly impact clinical outcomes and health care costs.

In this issue of J Appl Physiol, Nemzek et al. (11) propose low-dose inhaled carbon monoxide (CO) as a potential therapy for acid-induced acute lung injury. CO is a biologically active gaseous molecule with a wide range of physiological properties, including well-described anti-inflammatory effects (2, 12, 13). Increased levels of CO are produced in response to cellular stress (2, 12, 13, 15), and the administration of inhaled CO has been shown to confer protection in both inflammatory and non-inflammatory disease models (15). In particular, recent studies have demonstrated that inhaled CO confers protection in various animal models of acute lung injury such as hyperoxia, ventilator-induced lung injury, and sepsis (15). Endogenous CO is produced during the catabolism of heme by heme oxygenase; the inducible form of the enzyme, heme oxygenase-1, is highly induced in the setting of lung injury (15). As CO has been shown to both dampen inflammation and protect against cell death, there is good reason to ask whether CO might play a beneficial role in the setting of acute lung injury caused by acid aspiration.

The authors hypothesized that inhaled CO might limit the degree of lung injury following acid aspiration by attenuating proinflammatory cytokine production and neutrophil recruitment. Using a murine model, they tested whether continuous exposure to 500 ppm CO would alter airway and peripheral neutrophil counts, histological lung injury score, and vascular permeability. While CO exposure led to decreased airway neutrophil counts and less lung injury at early time points, this effect was not sustained beyond the first 6 h. Twenty four hours following intratracheal acid instillation, lung injury was equally severe in the CO-treated and control animals. The authors found no difference in loss of fluid barrier function between treatment groups, nor did they see any difference in peripheral or airway levels of CXC chemokines or CXCR2 expression. Interestingly, the mice receiving CO did exhibit lower levels of CD11b-positive neutrophils in the peripheral blood, suggesting that inhaled CO was capable of altering activation of circulating neutrophils.

On the basis of previously reported results, CO would be expected to quell inflammation and downregulate leukocyte recruitment to the lung following injury. Had the studies by Nemzek et al. (11) concluded at the 6-h time point following acid instillation, these expectations would have been borne out. The inclusion of the later time point distinguishes the current study from previously published work, however, and may provide an important clue about the mechanism of action of CO. The finding that CO delays but does not prevent migration of neutrophils to the site of inflammation raises several broad possibilities. The degree and nature of injury caused by acid may overwhelm the limited protection afforded by CO. The authors allude to this possibility by suggesting that CO might prevent CD11b-dependent neutrophil migration to uninjured lung while having no impact on neutrophil migration to directly injured areas, where CD11b does not play a role (10). Another possibility is that tachyphylaxis may develop in response to CO. Signaling events triggered by CO may not be sustained; for instance, the effects of CO on MAPK signaling pathway activation in vitro are robust but frequently transient (9). It may be that in this model of lung injury, early signaling events are counterbalanced by proinflammatory forces, and the impact of CO is therefore short lived. A third possibility is that CO is affecting mechanisms of inflammation that are at work early in the course of disease but are not important in later stages. For instance, the expression of inflammatory cytokines and chemokines follow distinct time courses, and CO might affect only those expressed in the first several hours following injury.

The literature addressing the impact of CO on leukocyte function is not yet well developed and sometimes contradictory. For instance, whereas CO has been shown to reduce leukocyte rolling, adhesion, and transmigration induced by carrageenan to the peritoneal cavity (5), CO was shown in a separate study to have no effect on H2O2-induced rolling and adhesion of leukocytes in a rat model (7). Similar to the current study, the CO-releasing molecule CORM-3 has been shown to inhibit upregulation of CD11b in vitro (18). On the other hand, exogenous CO had no effect on TNF-driven E-selectin, ICAM-1, or VCAM-1
expression in endothelial cells (17). Therefore, while the bulk of published studies indicate that CO can reduce neutrophil migration to injured tissues, the mechanism of this effect is not yet well understood.

One important question raised by Nemzek and colleagues (11) is how the dosing of CO might have affected the outcome of their studies. The concentration of 500 ppm is near the upper end of the range used in published studies of lung injury (15). That this dose of inhaled CO had a measurable effect on both circulating and airway neutrophils suggests that the negative findings reported were not due to underdosing. One might ask, however, how this level of CO inhaled by the mice compares with physiological yields of CO derived from heme oxygenase? Although the basal production of CO derived from the degradation of heme can be estimated, the amount of CO produced by HO-1 under conditions of stress is unknown. Moreover, it is not known how much is produced by individual cell types, over what distance the CO might diffuse, and what molecules constitute the critical targets for CO. Despite these questions, studies using empiric pharmacological doses of CO such as this one indicate that inhaled CO can meaningfully alter physiological responses to stress and injury. It is critical to obtain key pharmacokinetics and dosing data in preclinical and clinical studies in specific disease models or human diseases themselves in moving forward to potential application in humans in the future.

This study raises important questions about how CO might regulate lung injury and inflammation. Do neutrophils represent a direct target of CO in vivo? Is inhaled CO acting primarily locally in the lung or systemically? Might variable production of CO in humans protect or predispose to the development of acute respiratory distress syndrome following aspiration lung injury? As the answers to these questions become clearer, we will gain a better understanding of the pathophysiology of acute lung injury, and we will be closer to viable therapeutic options for treating the patients who suffer from its consequences.

REFERENCES