Carbon Monoxide

From Poison to Therapy for Cardiopulmonary Bypass–induced Lung Injury?

CARBON monoxide is popularly held as a noisome atmospheric pollutant and poison. The modern urban dweller continuously inhales low concentrations; the cigarette smoker inhales much more. Carbon monoxide binds avidly to hemoglobin, forming carboxyhemoglobin and compromising oxygen-carrying capacity, accounting for the poisonous effects that are seen at high doses. Remarkably, however, at low doses evidence points to a protective effect against tissue injury. This has been repeatedly demonstrated in a variety of experimental models. For example, several investigative groups have shown how carbon monoxide inhalation attenuates ischemia–reperfusion injury in the heart and endotoxin-induced injury in the kidney. Similarly, for the lung, there is a growing body of evidence showing protective effects against a range of injuries, including hypoxia, bleomycin, and ventilator-induced injury. Furthermore, we now know that the mammalian cell has long used carbon monoxide therapy to protect itself. Carbon monoxide is generated endogenously through the breakdown of heme in a reaction catalyzed by the enzyme heme oxygenase. Induction of this enzyme seems to downregulate heme oxygenase. Induction of this enzyme seems to protect itself. Carbon monoxide inhalation reduces pulmonary inflammatory response during cardiopulmonary bypass (CPB) model. Their data indicate potent antiinflammatory and lung-protecting effects, along with lack of significant hemodynamic effects.

The potential importance of these findings stems from the impact of acute lung injury in patients undergoing CPB. Severe acute lung injury and acute respiratory distress syndrome, while relatively uncommon (1–3%) after CPB, have a mortality of up to 50%. Lesser degrees of lung injury, such as reduced oxygenation index, increased ventilation/perfusion mismatch, and decreased lung compliance, are seen in up to 12% of CPB patients. Pulmonary injury is detectable even after otherwise uncomplicated CPB using sensitive measures of lung injury, such as protein accumulation index, bronchoalveolar lavage neutrophil, and myeloperoxidase levels. Early pulmonary dysfunction after cardiac surgery increases morbidity, including renal, neurologic, and infectious complications; duration of mechanical ventilation; intensive care unit and hospital stays; and risk of mortality. Consequently, the development of therapeutic strategies to control this response is the focus of considerable research efforts.

Goebel et al.1 here report a most interesting shift in the proinflammatory versus antiinflammatory cytokine balance. Two hundred fifty parts per million (ppm) carbon monoxide inhaled for a 1-h period after induction of anesthesia up to the initiation of a 2-h period of CPB reduced lung tissue messenger RNA and protein concentrations of the proinflammatory cytokines tumor necrosis factor α and interleukin 1β while increasing the antiinflammatory cytokine interleukin 10. These are important findings given the presumed central role of these cytokines in regulating the inflammatory response to CPB. Carbon monoxide also reduced lung tissue caspase-3 activity, an index of apoptotic cell death, and reduced histologic evidence of lung injury.

These data are consistent with a growing body of evidence that supports the contention that carbon monoxide protects against the development of lung injury in response to a variety of injuries. With regard to CPB-induced injury, there is also an indication that organs other than the lung may be protected because Lavitrano et al.4 demonstrated that carbon monoxide improved cardiac bioenergetics and attenuated myocardial apoptosis, also in a porcine model. Furthermore, circumstantial evidence points to a protective effect of carbon monoxide in patients undergoing cardiac surgery: Melley et al.5 recently reported that patients who did not generate adequate endogenous carbon monoxide had a higher mortality.

How does carbon monoxide mediate organ protection? Antiinflammatory, antioxidative, antiproliferative, and antiapoptotic effects have all been demonstrated, but the relative importance of these and the exact cellular mechanisms remain active areas of research. A fascinating aspect of the article by Goebel et al.1 is that pretreatment with carbon monoxide before CPB was effective in protecting the lung. Their findings may support the accumulating evidence that carbon monoxide can act as a trigger or mediator of preconditioning, as previously reported in heart and lung. Furthermore, in an intriguing possible mechanistic parallel with anesthetic preconditioning, carbon monoxide is reported to

inhibit electron transport chain enzymes leading to modulated supply of reducing equivalents and the generation of mitochondrial reactive oxygen species.6

Is inhalation of carbon monoxide safe? In this study, the administration of 250 ppm produced carboxyhemoglobin levels of 11% after 1 h of inhalation, which had decreased to 5.6% at 4 h after discontinuation of CPB. These levels raise the potential for tissue hypoxia, and the attendant risk of systemic organ damage. Goebel et al. provide data demonstrating that standard serum markers suggested no injury to other organs, including liver, heart, and kidney. However, these markers might not identify subtle but possibly important degrees of injury, particularly considering the brief time scale of these experiments. Although chronic exposure to carbon monoxide is reported to have no deleterious effects on the lung,7 of concern are previous observations showing potentially deleterious effects on the cardiovascular system. For example, chronic inhalation caused marked myocardial hypertrophy in rat,7 and in a clinical study involving volunteers with ischemic heart disease who briefly inhaled carbon monoxide (117 and 253 ppm), functional capacity was significantly decreased as demonstrated by ST-segment changes and onset of angina on exercise testing.8 Although studies in young, healthy human volunteers reveal no deleterious (or beneficial) effects, carbon monoxide cannot be assumed to be innocuous in older patients or in those with coexisting disease. Finally, recent laboratory work also points to potential dangers in pregnancy.9

These concerns notwithstanding, the potential to rapidly translate promising findings regarding carbon monoxide to the clinical setting is underlined by the fact that several clinical studies are currently in progress examining its effectiveness in patients with acute respiratory distress syndrome, in patients with chronic obstructive pulmonary disease, and in patients after kidney transplant.8 If the safety and efficacy of inhaled carbon monoxide is confirmed in additional preclinical CPB models, what is the likelihood of its eventual therapeutic success in the clinical arena? Over the years, multiple antiinflammatory strategies purported to attenuate CPB-related organ injury have been proposed. To name but a few, these have included corticosteroids, allopurinol, antioxidant vitamins, and serine proteinase inhibitors. Although laboratory studies have shown tissue protective effects of each of these, clinical trials have been less than compelling. Why have these antiinflammatory therapies not delivered on their promise? Perhaps because CPB-related inflammation is not as central to organ dysfunction as is commonly thought. It is notable that when off-pump cardiac surgery is compared with cardiac surgery with CPB, serum levels of inflammatory mediators are indeed attenuated, but the reported impact on clinical measures of lung injury is highly variable. Alternatively, strategies that are more selective in modulating the proinflammatory versus the antiinflammatory aspects of the response to CPB may demonstrate efficacy, where less selective approaches with their attendant side effects have failed. Is carbon monoxide such a strategy? Time will tell.

There are some limitations regarding the study of Goebel et al. that must be considered. Although carbon monoxide attenuated pulmonary inflammation and histologic injury, it did not improve physiologic indices of lung function, such as oxygenation. Furthermore, the mechanisms underlying these effects of carbon monoxide are not elucidated. Confirmation of these findings in additional CPB models, along with some mechanistic insight, is required. Nonetheless, the demonstration that carbon monoxide may reduce pulmonary inflammation and injury after CPB is an important and novel finding. Relative ease of administration, probable safety when given for short periods, and likely protective effects for multiple organs make this a fascinating agent with clear therapeutic promise. We await with interest further developments in the elucidation of the therapeutic potential of carbon monoxide.

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References