Inhaled CO_2 to Reduce Lung Ischemia and Reperfusion Injuries
Moving toward Clinical Translation?

Partial occlusion of the pulmonary artery (PA) may contribute to the lung injury seen after complex surgical procedures such as lung transplantation, cardiopulmonary bypass, and pulmonary arterial thrombectomy or embolectomy, and even closure of patent ductus arteriosus in infants. Similar injury may also occur in the context of resuscitation after cardiac arrest or from shock states resulting in hypoperfusion and cellular dysoxia. Preclinical models have given some insight to the outcomes of PA occlusion in spontaneously breathing (1, 2) and ventilated animal models (3). Nevertheless, the precise mechanisms by which pulmonary arterial ligation causes lung injury remain poorly understood. This is further complicated by the fact that restoring pulmonary arterial perfusion, which is pivotal to restoring tissue viability, leads to a reperfusion injury, with oxidative stress and activation of inflammation further contributing to tissue injury (4, 5).

Understanding mechanisms by which PA ligation directly induces lung injury is central to developing mitigation strategies and potential therapies. In this issue of the *Journal*, Marongiu and colleagues (pp. 933–942) report the development of a model of prolonged (48 h) unilateral (left) lung PA ligation in a mechanically ventilated large animal (porcine) model (6). Left PA ligation led to progressive collapse and underventilation of the ipsilateral lung and to lung edema and overstretch of the "normal" lung, leading to maldistribution of ventilation, and resulting in a ventilation-induced lung injury of the perfused lung, with lung edema and decreased compliance, and frank histological injury. Lung infiltration with leukocytes of the innate and adaptive immune systems was demonstrated.

Marongiu and colleagues also demonstrate the potential for "therapeutic hypercapnia" (7), induced by delivering inspired 5% CO_2, in attenuating PA ligation–induced lung injury. This work extends previous studies whereby 5–6% environmental CO_2 reduced lung injury in spontaneously breathing animals after PA ligation (8). Marongiu and colleagues' data provide new insights into the mechanisms by which inspired CO_2 may exert these protective effects. Inspired CO_2 preserved the function of both the left (PA ligated) and right lungs and reduced the inflammatory response to PA ligation. Severe airway hypocapnia, which is a consequence of PA occlusion, may be directly deleterious. Hypocapnic alkalosis has been demonstrated to directly injure the lung, increasing capillary permeability and worsening ischemia–reperfusion (IR)–induced lung injury (9). Hypocapnia also alters surfactant composition and impairs function (10), which may explain the decrease in compliance in the ipsilateral lung. These effects are reversed by 5% inspired CO_2 (10). Avoidance of airway hypocapnia may therefore be an important contributor of the protective effect demonstrated.

The effects of inspired CO_2 on reducing contralateral (right) lung injury may be due to the potential for hypercapnic acidosis to attenuate the lung inflammation and injury caused by excessive mechanical stretch (11). Inspired CO_2 therapy suppresses ventilation-induced lung inflammation via a mechanism involving inhibition of nuclear factor-κB (NF-κB) activation (12, 13). Wu and colleagues found that inspired CO_2 lung IR induced injury via inhibition of the NF-κB pathway (14), while NF-κB inhibition also underlies the protective effect of hypercapnic acidosis in reducing hepatic IR injury (11), suggesting this may be key underlying mechanism of action after PA occlusion.

These findings also add to existing evidence suggesting that inhaled CO_2 may have therapeutic potential in the setting of lung IR-induced injury. Shibata and colleagues first demonstrated that inspired CO_2 attenuated IR-induced injury in the isolated rat lung (15). Subsequent reports demonstrated that inspired CO_2 reduced lung injury after *in vivo* pulmonary and systemic IR injury (16). Inspired CO_2 decreased lung injury even when initiated after the commencement of reperfusion, highlighting its clinical promise (17). Importantly, the beneficial effects of inspired CO_2 appeared to be a function of the systemic acidosis generated rather than the hypercapnia *per se*. In fact, induced metabolic acidosis also reduced IR injury, whereas buffering a metabolic or hypercapnic acidosis abolished the benefit (9).

The study has a number of limitations worth considering. First, CO_2 was applied early, at the time of PA ligation. Although this may be relevant to situations in which PA ligation is predictable, the effects of CO_2 administration at later time points would be worth exploring. Second, it is unclear whether the effects were due, at least in part, to the systemic effects of hypercapnic acidosis induced by the 5% CO_2. An interesting experiment to dissect these contributions would be to apply the inspired CO_2 only to the ligated lung, as this would determine the extent to which avoidance of alveolar hypocapnia contributes to the effects seen, while avoiding a systemic hypercapnic acidosis. Third, animals from the inspired CO_2 group were not randomized with those from other groups for technical reasons. Lastly, the rationale for the variability in group size between the control and treatment groups is unclear. Although the authors acknowledge the discrepancies and point to the variability of the development of injury, this effect should also be true for the treatment group.

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What is the relevance of the findings of Marongiu and colleagues to the critical care practitioner?

IR injury is a critical consideration is a wide range of lung injuries as well as a risk factor in many surgical procedures (18). Although the issue of reperfusion injury is not considered, it compartmentalizes the injury parameters that are incurred because of ischemia and the resultant promise of using inhaled CO_2 as a therapeutic. This study demonstrates a clear benefit of inspired CO_2 in a ligated PA model, although the intervention is at an early time point. It adds to a growing body of work accumulated to this point demonstrating the therapeutic potential of inspired CO_2 for IR injuries. This possible therapeutic option is relatively simple to implement and test and has a well-understood side-effect profile, and critical care physicians are very familiar with managing hypercapnia in critically ill patients.

In conclusion, we welcome this addition to the evolving body of evidence regarding the beneficial effects of CO_2 in acute ischemia-induced lung injuries. We look forward to following the further studies in this area in more advanced preclinical models and perhaps ultimately in clinical studies. ■

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