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# Carbon dioxide as a drug in neonatology

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Carbon dioxide ($CO_2$) is a naturally occurring colorless gas, which is a by-product of aerobic respiration. In clinical medicine, elevated $CO_2$ levels can be a marker of respiratory failure, and if levels are too low, $CO_2$ is associated with complications such as periventricular leukomalacia. Several groups have reported that derangements in circulating $CO_2$ levels from the normal range of 35–45 mmHg are associated with poor outcomes in neonatal encephalopathy (NE), with hypocarbia ($pCO_2 < 35$ mmHg; 4.6 kPa) being particularly harmful.[1] In neonates, both minimum $pCO_2$ and cumulative $pCO_2 < 35$ mmHg were associated with poor outcome. Moreover, death and/or disability increased with greater cumulative exposure to $pCO_2 < 35$ mmHg in babies with NE ($n = 204$).[2]

Recently, this journal published the Hypoxic–Ischemic Encephalopathy Therapy Optimization in Neonates for Better Neuroprotection with Inhalative $CO_2$ (HENRIC) study on 5% $CO_2$ insufflation to prevent hypocarbia in newborns with NE. This feasibility and safety trial focused on outcomes associated with NE, a condition associated with hypoxia, ischemia, and inflammation.[3] Szakmar et al. demonstrated that 5% $CO_2$ administration was both safe and feasible in infants with NE.[3] Thus, this pilot study could pave the way for larger randomized trials investigating the efficacy of controlled normocapnia through 5% $CO_2$ inhalation on long- term neurodevelopmental outcomes. Modulation of $CO_2$ levels in infants with NE in this way is a potentially exciting novel intervention, which should be considered in the context of $CO_2$ as an important signaling molecule.

Historically, $CO_2$ has been considered as a waste product of metabolism that needs to be effectively removed from the body via the lungs. An increase in inhaled $CO_2$ levels will elicit a rapid brain-stem-mediated increase in rate and depth of breathing in order to try and "blow-off" the excess $CO_2$. More recently, $CO_2$ is understood to have more lasting effects through the modulation of distinct subsets of genes, including those associated with the immune system.[4] Indeed, there are several animal and cell-based studies demonstrating a modulatory effect of $CO_2$ on immune signaling. Hypercapnia can potentially dampen systemic pro-inflammatory responses. This can be mediated at least in part via suppression of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation, which is a protein complex that controls DNA transcription and cytokine production. NF-κB-dependent signaling can also be cytoprotectant with roles in mediating apoptosis, cell survival, and wound repair.

Elevated $CO_2$ levels alters the localization, processing, and protein–protein interactions of key members of the NF-κB family.[5–7] Hypercapnia suppresses NF-κB-dependent signaling and in turn inhibits the expression of important NF-κB-regulated pro-inflammatory markers, for example, interleukin-8 (IL-8), IL-6, and tumor necrosis factor-α.[6,8] Other proposed anti-inflammatory mechanisms include decreased neutrophil intracellular oxidant production and decreased release of IL-8 from endotoxin-stimulated cells, as well as the inhibition of a phagocyte influx. Furthermore, therapeutic hypercapnia has even been found to reduce markers of inflammation in response to one-lung ventilation in lobectomy patients.[9] $CO_2$ causes diffuse vascular damage as neutrophils are stimulated to produce microparticles that contain high concentrations of IL-1β.[10] Increased $CO_2$ caused inflammasome components ASC, NLRP3, caspase-1, thioredoxin-interacting protein, and calreticulin oligomerization causing IL-1β synthesis. An increased production rate of microparticles containing elevated amounts of IL-1β persists for hours after short-term exposures to elevated $CO_2$.[11] Thus, there is a substantial amount of evidence linking elevated $CO_2$ with altered cytokine expression.

While hypercapnia may have important anti-inflammatory effects on the immune system, the evidence is clear that hypercapnia is detrimental in the context of infection. Several studies have linked elevated levels of $CO_2$ with worse outcomes in response to infection.[12,13] Furthermore, severe hypercapnia $PaCO_2 > 6.6$ kPa (50 mmHg) was independently associated with higher intensive care unit mortality in acute respiratory distress syndrome in adults.[14] Thus, the current view is that hypercapnia is detrimental in the context of infection due to immunosuppression, but may be beneficial in the context of destructive inflammation due to suppression of inflammatory pathways. Thus, in the clinical setting where $CO_2$ levels are being manipulated, it will be crucial to titrate the therapeutic dose of $CO_2$ to promote beneficial outcomes and avoid adverse consequences. In preterm infants, permissive hypercapnia has been commonly used in regular clinical practice, despite a lack of rigorous evidence from clinical trials.[15]

In addition to its effects on gene expression and immune signaling, $CO_2$ is also a potent regulator of cerebral blood flow. Hypocapnia leads to vascular constriction and reduced blood flow, which is then linked to reduced brain oxygenation and risk of NE. In the HENRIC trial, the authors did not observe a change in cerebral blood flow in response to $CO_2$ inhalation in the small number of patients studied. Cerebral blood flow measurements should however be treated with caution in infants with NE and/or the very young as NE-associated brain injury can blunt the $CO_2$ response and vascular reactivity can be transiently absent in the newborn.[16]

In summary, the pro-inflammatory response in NE may be exacerbated by hypocarbia and manipulating $CO_2$ may be immunomodulatory. Although oxygen parameters and therapies have been closely studied, they are not completely defined, especially in resuscitation.[17–19] Similar detailed studies are needed to define $CO_2$ parameters. Manipulation of $CO_2$ may hold promise as an immunomodulator, but more research is required to define safe parameters and dose responses.[20] Regular, detailed, and reliable $CO_2$ monitoring is vital and underlying signaling mechanisms need further evaluation.

## AUTHOR CONTRIBUTIONS

E.J.M. and E.P.C. conceived and wrote the manuscript.

## ADDITIONAL INFORMATION

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