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EDITORIAL COMMENT

# More Than Clean, Sustainable, and Renewable Energy Source

## New Therapeutic Role for Hydrogen?*

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In this issue of *JACC: Basic to Translational Science*, Shirakawa et al[1] reported that inhalation of $H_2$ inhibited the formation and release of neutrophil extracellular traps (NETs) or NET components in the lipopolysaccharide-induced sepsis using mice and aged minipigs, suggesting that $H_2$ may serve as a novel therapeutic strategy for inflammatory diseases involving neutrophil activation such as infectious diseases, including COVID-19. The authors demonstrated that phorbol-12-myristate-13-acetate–stimulated human neutrophils exposed to H2 exhibited reduced citrullination of histones and release of NET components compared with control subjects; mechanistically, H2-mediated neutralization of hypochlorous acid produced during oxidative bursts suppresses DNA damage.

Hydrogen has been shown to scavenge the hydroxyl radical (•OH) and acts as an antioxidant agent to exert various pathological conditions, including brain ischemia/reperfusion injury, experimental liver injury, and diabetes. Moreover, hydrogen was shown to have beneficial effects on cancer. Although hydroxyl radical scavenging activity has been regarded as the primal action of hydrogen, there are several other potential mechanisms in which hydrogen may play roles, eg, certain enzymes may become activated when they interact with hydrogen, or hydrogen gas may suppress auto-oxidation of lipid mediators and modify downstream signaling.[2]

The authors have shown for the first time that hydrogen may suppress NET formation via reduced $Ca^{2+}$-dependent $PADI_4$ activation through reduction of hypochlorous acid production.

NET formation has been considered one of the key mechanisms of neutrophil activation. Recently, accumulating studies indicated the critical role of NET during early phase of inflammation, which sustained to enhance further inflammatory response instead of its resolution. The critical mechanism of NET formation is the citrullination of histones, which disrupts chromatin formation, leading to break down of the neutrophil cell membrane and subsequently the process of NET formation. NET has been shown to be involved in not only acute inflammation, such as infectious diseases, but also allergic reactions, autoimmune diseases, or atherosclerosis.[3] Moreover, several papers indicated that NET formation plays a role during systemic thrombo-inflammatory catastrophes during COVID-19 severe respiratory failure. Based on these notions, $H_2$ gas inhalation has been tried in a clinical study for COVID-19 pneumonia among various anti-inflammatory therapeutic approaches and has shown some beneficial effects.

The authors' experimental data using mice and aged minipigs may link these clinical benefits and molecular mechanisms. Considering the potential next global surge of COVID-19 pandemic, the beneficial effect of $H_2$ gas inhalation should be critically evaluated to provide more detailed indications for a broad therapeutic method.

As mentioned, Shirakawa et al[1] proposed a novel therapeutic method for thrombo-inflammatory conditions; however, several fundamental questions need to be addressed in the future to better

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understand this issue. First, what is the primal target of hydrogen in the context of NET formation? A recent report suggested that the direct scavenging activity of hydrogen may not be strong enough to expect any biological consequence; thus, a definitive explanation of how hydrogen reduces excess oxidative stress may be crucial. Second, the authors considered that hydrogen reduces CXCR4-dependent NET formation in neutrophils. Because CXCR4 has been shown to play a role in NET initiation in the lung residual neutrophils, a more general role for CXCR4 in systemic NET formation still remains to be understood.[4] Third, the pathophysiological relevance of phorbol-12-myristate-13-acetate as an inducer for NET formation should be further refined dependent upon the context of given pathophysiological conditions. Nonetheless, the authors indicated a novel important pathway to modulate NET formation through hydrogen inhalation, which will become another new therapeutic approach for severe respiratory infection including COVID-19.

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