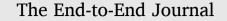
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## The role of carbon monoxide and heme oxygenase-1 in COVID-19

Farsalinos et al. [1] reported low smoking prevalence of hospitalized COVID-19 patients in China and proposed that nicotine could have protective effects against COVID-19 by enhancing the cholinergic anti-inflammatory pathway [2]. Many published reports emphasized that smoking increased the severity of COVID-19 [3] but these studies were of patients who had already developed COVID-19 and did not evaluate the risk of smokers on contracting COVID-19. Accurate accounting of smokers in COVID-19 is therefore important for the research of any protective effect of nicotine in COVID-19.

While nicotine may be studied for its anti-inflammatory properties, it has also undesirable effects like constricting blood vessels, raising blood pressure and posing hazards to cardiac and respiratory health [4]. Beyond nicotine, we hypothesize that two other protective agents, low level carbon monoxide (CO) and heme oxygenase-1 (HO-1), may play a role in COVID-19 and can be studied with or without an association with smoking.

Low level CO had been shown to be vasodilatory and have anti-inflammatory properties in the experimental treatment of tissue injuries including lung disorders [5,6]. CO level being used in clinical trial with acute respiratory distress syndrome (ARDS) ranges from 100 to 200 ppm [7]. The mean exhaled CO level of smokers had been reported to be  $17 \pm 8.5$  ppm [8]. So it is reasonable to consider whether low level CO applied short term (e.g. 90 min each day for several days) [7] can be used to mitigate tissue injury caused by COV-19 while the harm or benefit of low level CO from long-term smoking remains a topic of on-going research [9].

Beyond being an external source of CO, smoking is also associated with the induction of HO-1 [10], a known anti-oxidative, cytoprotective and antiapoptotic enzyme [5,6,10,11] which is presumably elevated as a response to the ravages of smoking. The cytoprotective role of HO-1 stems from its degradation of heme to endogenous CO and biliverdin/bilirubin which are anti-inflammatory agents as well as iron which is recycled to maintain iron homeostasis [5,6,11]. Extensive HO-1 literature reported that the cytoprotective role of HO-1 was most effective when HO-1 could be independently induced before an oxidative insult took place [12–16]. The question here is the role of HO-1 as a prophylaxis and whether previously induced HO-1 could render tissue protection against new inflammatory insults from COVID-19.

Despite the possible contribution of induced HO-1, smoking is extremely harmful. Fortunately, A wide variety of stress stimuli other than smoking can induce HO-1 [5,17]. Experimental HO-1 inducers often include hemin [12], heme arginate16 and Cobalt protoporphyrin (CoPP) [15]. A few other examples of HO-1 inducers are cited here just to illustrate the huge variety. Physical exercise [18] and curcumin [19,20] can induce HO-1. Even stressing the skin surface locally by rigorous massage had been reported to activate systematic elevation of HO-1 in multiple organs [21]. Which among the myriad stimuli will be safe or sufficient to induce enough HO-1 to moderate the development of COVID-19 are topics of future research.

The highly reasonable idea that COVID-19 should by itself induce strong HO-1 responses merits investigation to obtain verification. Many clinical features of COVID-19 match the known stress stimuli which can induce HO-1. Such stress stimuli include but are not limited to hypoxia [22], activated macrophages [23,24], neutrophils [25] and extracellular traps (NETS) [26] developed in immune responses, thrombosis [27,28], blood vessel and endothelial tissue [11,29] inflammation, respiratory epithelial cell [11,29] damage and lung injuries [5,6,29]. If HO-1 and endogenous CO can be established to be elevated in COVID-19, they can be explored either for their hypothesized protective pathways or as potential biological markers for the development of excessive inflammation and respiratory or vascular tissue damages of symptomatic patients with COVID-19.

More intriguingly, since there is currently no clear explanation on why many confirmed COVID-19 patients remain asymptomatic throughout the course of the infection, we can examine if the symptom-free status of these patients is associated with a baseline HO-1 or CO level much higher than that of healthy controls. The hypothesis is that at least some of asymptomatic patients could have elevated baseline HO-1 and CO to provide protection before they are infected by COVID-19. In our search for candidates to study the reason for their asymptomatic status in COVID-19, the investigation of smokers merits attention. Individuals with hemolytic anemia traits like sickle cell trait or thalassemia trait could also be evaluated on whether they have elevated HO-1 levels [30] which would offer them some advantages in COVID-19.

To establish the role of HO-1 in COVID-19, one normally needs minimally invasive blood or tissue sampling of HO-1. An alternative and noninvasive way to measure HO-1 is to consider CO as an index of HO-1 and measure carboxyhemoglobin (SpCO) by a portable pulse CO-oximeter. Elevated SpCO from baseline had been reported in active asthma and allergic rhinitis [31], cystic fibrosis [32] and sickle cell disease [33]. Aside from the measurement of SpCO using a pulse CO-oximeter, elevated carboxyhemoglobin level measured by a blood gas analyzer had been reported in many disorders including pneumonia [34], idiopathic pulmonary fibrosis (IPF) [34], hemolytic anemia [30] and colorectal cancer [35]. If the sensitivity of SpCO measurement can be established in COVID-19, SpCO measurement is simple and convenient enough to be used for a point-of-care measurement like body-temperature measurement for screening of any initial inflammatory responses of COVID-19; SpCO may also be considered for continuous monitoring of developing cytokine storm of hospitalized COVID-19 patients.

The hypothesis of induced HO-1 and its product CO being useful for diagnostic or therapeutic management of the overreaction of inflammatory responses of COVID-19 would require future studies for verification.

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## **Declaration of Competing Interest**

The authors report no declarations of interest.

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