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EDITORIAL

Carbon monoxide inhalation for performance: dancing with the devil?

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We read with great interest the study by Urianstad et al. (1) published in this edition of the *Journal of Applied Physiology*, who investigated altitude training in conjunction with carbon monoxide (CO) administration to determine what impact such interventions have on total body hemoglobin (tHb_{mass}), maximal oxygen uptake ($\dot{V}O_{2max}$), and performance. The investigators are lauded for completing a very challenging field study that included three groups of elite athletes, 20 of whom lived and trained for 3 wk at 2,100 m elevation.

Elite male cyclists were separated into three groups: a Live High-Train High group, a Live High-Train High group that also received two daily bolus doses of CO while at high altitude (to give them an altitude "boost" after training and through the night), and a third Live Low-Train Low group. Efforts were made to ensure training and most other variables were equivalent between the groups. The investigators found that the addition of a daily CO inhalation protocol to moderate altitude exposure enhanced hematological adaptations more than moderate altitude alone, and determinants of cycling performance improved with CO inhalation compared with sea-level training. Although the results showed subject-to-subject variability, the small increases in tHb_{mass} and $\dot{V}O_{2max}$ may be big enough to generate a small but competitively significant advantage in some individuals in elite competitions where margins of victory can be small. This is important, given recent press reports and concerns speculating about the use of CO by professional cyclists in the Tour de France. It also suggests that CO dosing schemes could be optimized to enhance tHb_{mass} in a way that has minimal impact on training regimens used by elite athletes (Fig. 1).

The use of CO in professional sports has been hiding in plain sight. Due to the long circulating half-life of CO, it has been used to "tag" red blood cells for the purpose of measuring tHb_{mass} and track changes across training or altitude camps. When used in conjunction with hematocrit, it is used to measure plasma volume and total blood volume (2). However, chronic (daily) inhalation to explicitly improve hematological variables associated with performance is relatively new (3, 4). In this context, it has long been known that smokers and individuals exposed to carbon monoxide in occupational settings can become polycythemic (5). In heavy smokers, chronic increases in hematocrit are proportional to carboxyhemoglobin levels (6). CO binds avidly to the heme portion in hemoglobin, displacing a site for oxygen transport. CO also shifts the oxygen-hemoglobin dissociation curve to the left. This left shift, along with the functional inactivation of some hemoglobin for oxygen transport, reduces oxygen delivery to the kidney, engaging the "critometer" mechanism and evoking endogenous erythropoietin (EPO) release. Like NO, CO is a known endogenous gaseous signaling molecule, but the full extent of its physiological impact is unknown, particularly at relatively high levels of carboxyhemoglobin.

In healthy individuals, measures of tHb_{mass} are tightly correlated with $\dot{V}O_{2max}$ across a wide range for both variables. At an individual level, interventions that acutely increase or decrease tHb_{mass} cause directionally similar changes in $\dot{V}O_{2max}$. Because $\dot{V}O_{2max}$ is a critical determinant of competitive aerobic exercise performance, numerous strategies have emerged over the years to raise tHb_{mass} to improve athletic performance. These include *1*) altitude training and/or the use of altitude houses or tents, *2*) red blood cell transfusions (e.g., blood doping), and *3*) administration of EPO or related analogs such as xenon. In addition, in racehorses, cobalt has been used for similar purposes (7). Of these three main strategies, only the first is deemed legal based on modern ethical and doping control codes. More recently, efforts have been made to maximally expand plasma volume via heat adaptation protocols because over time they also increase tHb_{mass} (8). The mechanism for the increase in tHb_{mass} is likely that the kidney senses a reduction in hematocrit caused by plasma volume expansion stimulating EPO release and the generation of additional red blood cells, although other pathways, including specific heat shock proteins, may also contribute (9).

In the context of the aforementioned overview, there are several important questions. First, is this safe? Modest chronic levels of CO exposure likely pose no major short- or medium-term health risks. However, if used as an ergogenic aid, what is to prevent individuals and teams who seek competitive glory from trying ever higher doses? Second, although professional teams might have access to "safe" protocols and monitoring to use CO judiciously, what is to prevent those with fewer resources from "trying it" using makeshift approaches? Of note, there are ~1,200 deaths from CO poisoning in the United States annually (https://usafacts.org/articles/is-carbon-monoxide-still-a-problem-in-the-us/). Some of these deaths are suicides and some are accidental. Urianstad et al. (1) noted that 44% of the subjects incorrectly identified whether they had inhaled CO, as CO is colorless and odorless. The risk of accidental inhalation of CO is a real concern, even in ideal environments. Third, the combination of altitude exposure and CO

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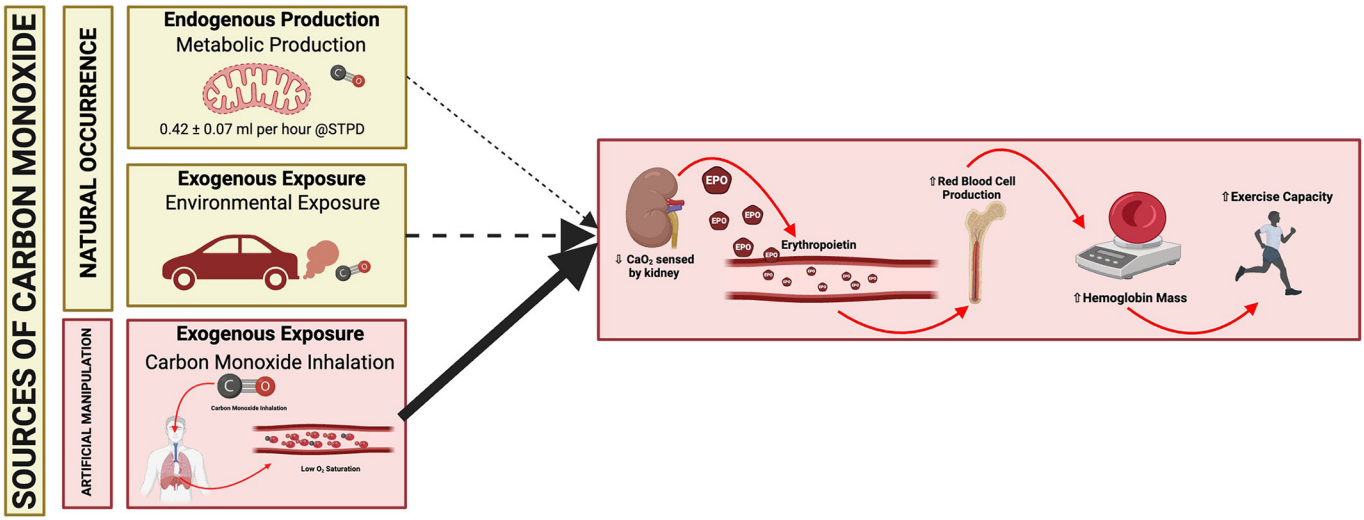

Figure 1. Endurance athletes are exposed to multiple different sources of carbon monoxide (CO), including endogenously produced sources, environmental sources through city pollution, and exhaust from combustion engines. However, these concentrations are generally much less than CO exposure through "artificial" means, such as the intentional chronic (daily) inhalation of CO. These doses of CO can increase carboxyhemoglobin levels to the extent that the lowered oxygen content is sensed by the kidney, leading to the production of EPO and an eventual increase in total hemoglobin mass. This can be sufficient to increase maximal exercise capacity and performance. Should this method of artificial blood manipulation be banned by the World Anti-Doping Agency? Figure created in BioRender.com. EPO, erythropoietin.

inhalation likely alters what are considered "safe" levels of carboxyhemoglobin. CO does not reduce oxygen saturation on a standard pulse oximeter. The authors stated their use of "safe" doses of carboxyhemoglobin. However, these standards are for sea-level elevations. Again, it is a false equivalency to suggest those same values and likely side-effects/warning signs would be at the same carboxyhemoglobin at moderate or high altitudes.

From an ethical standpoint, CO is not a banned substance by the World Anti-Doping Agency (WADA), and its occasional use to measure tHb_{mass} does not have an impact on hematological variables associated with performance (10). However, chronic inhalation of CO seems to contradict WADA rules around artificial manipulation of the blood. Equating CO inhalation to the use of hypoxic tents or chambers, as both reduce O_2 saturation, is a false equivalency on several fronts. For one, CO sufficient to raise tHb_{mass} is an artificial substance provided to athletes, as opposed to the removal of oxygen from inhaled air. An argument could be made that CO is present naturally in humans at very low levels. So are EPO and testosterone, whereas exogenous forms of EPO and testosterone are clearly banned by WADA. Would we outright ban chronic CO use if it had to be injected rather than inhaled? Forcing carboxyhemoglobin levels well beyond normal values observed even in polluted cities for the purpose of performance seems to go against fair play in sports. Finally, as pointed out earlier, there are very serious safety concerns regarding CO inhalation. That said, if the use of repeated CO administration to increase tHb_{mass} is "banned," how will the testing and detection of excess CO levels be evaluated? Due to the short half-life of CO, one can imagine that creative dosing schemes will almost certainly emerge to make detection of "pharmacological" use of CO even more challenging. Despite these difficulties, as a first step to put athletes, sports physiologists, and coaches on notice, we believe that manipulation of the blood with CO as a procedure should be explicitly banned by WADA.

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AUTHOR CONTRIBUTIONS

C.T.M. and M.J.J. conceived and designed research; M.J.J. interpreted results of experiments; C.T.M. prepared figures; C.T.M. and M.J.J. drafted manuscript; C.T.M. and M.J.J. edited and revised manuscript; C.T.M. and M.J.J. approved final version of manuscript.

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