*Scandinavian Journal of Medicine & Science in Sports*

WILEY

EDITORIAL

# Repeated Carbon Monoxide Inhalation in Sports: A New Frontier or a Dangerous Gamble?

Billy Sperlich[1] | Hans-Christer Holmberg[2,3,4] | Marcos Martin-Rincon[5] | Øyvind Skattebo[6] | Jamie F. Burr[7] | Jostein Hallen[6] | Robert C. Boushel[4] | Jose A. L. Calbet[4,5,6]

[1]Integrative and Experimental Exercise Science and Training Science, Institute of Sport Sciences, University of Würzburg, Würzburg, Germany | [2]Department of Health, Education and Technology, Luleå University of Technology, Luleå, Sweden | [3]Department of Physiology and Pharmacology, Biomedicum C5, Karolinska Institutet, Stockholm, Sweden | [4]School of Kinesiology, Faculty of Education, University of British Columbia, Vancouver, British Columbia, Canada | [5]Department of Physical Education, and Research Institute of Biomedical and Health Sciences (IUIBS), University of las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain | [6]Department of Physical Performance, Norwegian School of Sport Sciences, Oslo, Norway | [7]Department of Human Health & Nutritional Science, University of Guelph, Guelph, Ontario, Canada

**Correspondence:** Jose A. L. Calbet (jose.calbet@ulpgc.es)

**Received:** 9 December 2024 | **Accepted:** 10 December 2024

**Funding:** The authors received no specific funding for this work.

Over the past decade, carbon monoxide (CO) inhalation has garnered significant interest in exercise science due to its potential to enhance oxygen transport capacity and performance through hypoxia induced erythropoiesis. Carbon monoxide binds to hemoglobin (Hb) with an affinity 220–240 times greater than that of oxygen ($O_2$), reducing the blood's oxygen-carrying capacity and shifting the oxygen dissociation curve leftward. This mechanism may trigger compensatory erythropoiesis, leading to an increase in hemoglobin mass (Hbmass), thereby theoretically improving oxygen delivery and enhancing endurance performance with chronic inhalation.

The potential risks of CO exposure have been recognized since 1857, when Claude Bernard demonstrated that CO impairs the oxygen-carrying ability of hemoglobin, resulting in asphyxia. Due to the slow dissociation of CO from hemoglobin, accidental over-administration can result in severe outcomes, including permanent multiorgan damage or death. Carbon monoxide is classified as a medical gas that requires stringent industrial production, certification, and storage to avoid contamination or the formation of toxic substances in gas cylinders. Although low-dose CO administration is considered safe under medical supervision, the long-term side effects of chronic CO inhalation remain largely unexplored.

## 1 | Carbon Monoxide Effects Extend Beyond Merely Binding to Hemoglobin

Carbon monoxide's effects extend beyond hemoglobin binding. Carbon monoxide can upregulate nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor regulating over 250 genes involved in redox balance, mitochondrial biogenesis, metabolism, detoxification, cytoprotection, inflammation, immunity, autophagy, cell differentiation, and xenobiotic metabolism [1]. Inhalation of CO (200 ppm, 1 h/day for 5 days) has been shown to induce significant changes in the human vastus lateralis muscle [2], including increased protein expression of heme oxygenase-1 (HO-1) and elevated mRNA levels of mitochondrial transcription factor A (Tfam), cytochrome c, cytochrome oxidase subunit IV (COX IV), COX I, and NADH dehydrogenase subunit 1 (NDI) [2]. Furthermore, CO inhalation increased capillarization, mitochondrial density, citrate synthase activity, myoglobin content, and GLUT4 protein levels along with its sarcolemmal localization in human skeletal muscle [2]. In a related study employing a similar protocol (100 ppm, 1 h/day for 5 days), the same research group observed elevated expression of HO-1, superoxide dismutase 2, and mRNA levels associated with proteins involved in mitochondrial fusion [3].

## 2 | Studies on CO Inhalation—Impact on Hbmass, $VO_2$Max, and Beyond

In 2019, a study of six well-trained male soccer players reported that CO inhalation at a dose of 1 mL/kg body mass for 2 min in $O_2$ (4 L) before treadmill training, performed five times per week for 4 weeks, increased Hbmass by 3.7% and $VO_2$max by 2.7% [4]. However, the control group, which undertook similar training without CO inhalation, experienced a comparable 2.8% increase in Hbmass, complicating any definitive conclusions [4].

In a subsequent study, Schmidt et al. [5] administered CO to 11 moderately trained males at a daily dose of 1 mL/kg body mass in the morning, followed by additional doses every 4 h to maintain carboxyhemoglobinaemia (COHb) levels between 4% and 8%. After 2 and 3 weeks, Hbmass increased by 3.3% and 4.8%, respectively, though the observed 2.8% improvement in $VO_2$max did not reach statistical significance. Notably, neither of these studies assessed endurance performance directly.

More recently, Urianstad et al. [6] investigated 31 elite male cyclists ($VO_2$max: 73–75 mL/(kg.min)) in a study comparing three groups: Live-High Train-High with CO inhalation, Live-High Train-High at 2100 m above sea level, and Live-Low Train-Low. The CO group inhaled the gas twice daily to achieve a COHb concentration of ~10%. This group demonstrated a 5.8% increase in Hbmass, while minimal or no changes were observed in the other groups.

Collectively, these studies suggest that daily CO inhalation over 2–3 weeks may increase Hbmass and, potentially, $VO_2$max. The findings by Urianstad et al. [6] further indicate that CO inhalation may amplify the erythropoietic response to altitude exposure in athletes. Interestingly, athletes living and training at altitude with CO supplementation showed greater increases in Hbmass than those training at altitude alone. However, improvements in $VO_2$max and performance were similar in both altitude-trained groups, suggesting no additional performance benefit from CO inhalation beyond that observed with altitude training. This raises an important question: why did the additional Hbmass from CO inhalation not translate into enhanced performance in elite cyclists, who are typically highly responsive to even minor increases in oxygen delivery?

Athletes seeking to enhance Hbmass might consider combining CO inhalation with hypoxic or heat training [7–10] to further boost the erythropoietic response [6]. Additionally, skeletal muscle adaptations to CO inhalation mimic some of the responses to endurance training [2, 3]. However, whether these effects occur in highly trained athletes remains unknown. Although CO has vasodilatory effects [11] and may protect against neurodegeneration [12] while conferring potentially cardio- and neuroprotection against acute ischemia [13–15] and suppressing pro-inflammatory cytokines while promoting anti-inflammatory mediators [16], there are currently no FDA-approved clinical applications for CO as a therapeutic agent. Thus, whether CO's anti-inflammatory and antioxidant properties can be harnessed to aid athletic recovery remains unclear.

## 3 | Health Risks of Carbon Monoxide Supplementation

As mentioned, CO supplementation poses significant health risks due to its high affinity for hemoglobin, which can potentially lead to dangerous levels of COHb, hypoxic damage, and even death. These risks are particularly concerning for athletes who may attempt unsupervised use, which significantly increases the likelihood of severe adverse effects. Additional risks may arise if gas cylinders are contaminated or not certified for medical use. Moreover, the chronic effects of CO exposure are largely unknown. CO binds to myoglobin, neuroglobin, cytoglobin, cytochrome c oxidase, monooxygenases (e.g., cytochrome P-450, nitric oxide synthase, dopamine β-hydroxylase), cystathione β-synthase, and nicotinamide adenine dinucleotide phosphate oxidase (NOX), among other enzymes, potentially reducing or blocking their enzymatic activity or altering their function. The impact of these effects on training adaptation and overall health remains uncertain.

## 4 | Ethical Considerations and Competitive Fairness

Beyond the health risks, CO supplementation raises ethical concerns regarding fairness in competition. It can be argued that repeated inhalation of carbon monoxide is a doping method that may, in addition to enhancing limiting factors to endurance performance, mask other doping procedures, such as autologous blood transfusions and the misuse of erythropoiesis-stimulating agents like erythropoietin (EPO) by altering biological passport markers. This parallels the challenges of monitoring athletes using altitude training, where fluctuating Hbmass complicates the detection of EPO misuse or blood doping. The potential for CO to obscure key blood parameters warrants further scrutiny, as it could allow athletes to evade detection of other performance-enhancing drugs.

To qualify for the WADA prohibited list, a substance or method must typically satisfy any two out of three criteria (https://www.wada-ama.org/en/prohibited-list):

1. It has the potential to enhance or enhances sport performance.
2. It represents an actual or potential health risk to the athlete.
3. It violates the spirit of sports.

Repeated inhalation of CO satisfies all three and should be banned. However, testing of hemoglobin mass by CO rebreathing is essential for physiological assessment and should remain allowable under controlled conditions. WADA's challenge is to monitor, detect, and discourage its use.

## 5 | Conclusion

While CO may have some beneficial effects as a therapeutic agent in specific medical contexts, the risks associated with its use as a performance-enhancing supplement far outweigh any potential benefits. The limited performance improvements

observed, coupled with significant toxicity risks and ethical concerns, render CO supplementation unsuitable for athletes. The World Anti-Doping Agency (WADA) should express concern and discourage the use of CO outside strictly controlled therapeutic applications.

---

**Conflicts of Interest**

There is no conflict of interest to declare apart from using Carbon Monoxide to measure blood volume in human research by most co-authors.

**Data Availability Statement**

The authors have nothing to report.

**References**


1. M. Martinez-Canton, V. Galvan-Alvarez, M. Martin-Rincon, J. A. L. Calbet, and A. Gallego-Selles, "Unlocking Peak Performance: The Role of Nrf2 in Enhancing Exercise Outcomes and Training Adaptation in Humans," *Free Radical Biology & Medicine* 224 (2024): 168–181.

2. S. R. Pecorella, J. V. Potter, A. D. Cherry, et al., "The HO-1/CO System Regulates Mitochondrial-Capillary Density Relationships in Human Skeletal Muscle," *American Journal of Physiology. Lung Cellular and Molecular Physiology* 309, no. 8 (2015): L857–L871.

3. M. A. Rhodes, M. S. Carraway, C. A. Piantadosi, et al., "Carbon Monoxide, Skeletal Muscle Oxidative Stress, and Mitochondrial Biogenesis in Humans," *American Journal of Physiology. Heart and Circulatory Physiology* 297, no. 1 (2009): H392–H399.

4. J. Wang, Y. Ji, L. Zhou, Y. Xiang, I. Heinonen, and P. Zhang, "A New Method to Improve Running Economy and Maximal Aerobic Power in Athletes: Endurance Training With Periodic Carbon Monoxide Inhalation," *Frontiers in Physiology* 10 (2019): 701.

5. W. F. J. Schmidt, T. Hoffmeister, S. Haupt, D. Schwenke, N. B. Wachsmuth, and W. C. Byrnes, "Chronic Exposure to Low-Dose Carbon Monoxide Alters Hemoglobin Mass and $VO_2$max," *Medicine and Science in Sports and Exercise* 52, no. 9 (2020): 1879–1887.

6. T. Urianstad, S. Villanova, I. Odden, et al., "Carbon Monoxide Supplementation: Evaluating Its Potential to Enhance Altitude Training Effects and Cycling Performance in Elite Athletes," *Journal of Applied Physiology* 137 (2024): 1092–1105.

7. L. Nybo, B. Ronnestad, and C. Lundby, "High or Hot-Perspectives on Altitude Camps and Heat-Acclimation Training as Preparation for Prolonged Stage Races," *Scandinavian Journal of Medicine & Science in Sports* 34, no. 1 (2024): e14268.

8. B. R. Ronnestad, O. M. Lid, J. Hansen, et al., "Heat Suit Training Increases Hemoglobin Mass in Elite Cross-Country Skiers," *Scandinavian Journal of Medicine & Science in Sports* 32, no. 7 (2022): 1089–1098.

9. L. Oberholzer, C. Siebenmann, C. J. Mikkelsen, et al., "Hematological Adaptations to Prolonged Heat Acclimation in Endurance-Trained Males," *Frontiers in Physiology* 10 (2019): 1379.

10. D. J. Astridge, M. McKenna, A. Campbell, and A. P. Turner, "Haemoglobin Mass Responses and Performance Outcomes Among High-Performance Swimmers Following a 3-Week Live-High, Train-High Camp at 2320 m," *European Journal of Applied Physiology* 124, no. 8 (2024): 2389–2399.

11. W. Lu, X. Yang, and B. Wang, "Carbon Monoxide Signaling and Soluble Guanylyl Cyclase: Facts, Myths, and Intriguing Possibilities," *Biochemical Pharmacology* 200 (2022): 115041.

12. K. N. Rose, M. Zorlu, A. Fassini, et al., "Neuroprotection of Low Dose Carbon Monoxide in Parkinson's Disease Models Commensurate With the Reduced Risk of Parkinson's Among Smokers," *npj Parkinson's Disease* 10, no. 1 (2024): 152.

13. L. E. Otterbein, R. Foresti, and R. Motterlini, "Heme Oxygenase-1 and Carbon Monoxide in the Heart: The Balancing Act Between Danger Signaling and pro-Survival," *Circulation Research* 118, no. 12 (2016): 1940–1959.

14. K. A. Hanafy, J. Oh, and L. E. Otterbein, "Carbon Monoxide and the Brain: Time to Rethink the Dogma," *Current Pharmaceutical Design* 19, no. 15 (2013): 2771–2775.

15. H. Soni, P. Patel, A. C. Rath, M. Jain, and A. A. Mehta, "Cardioprotective Effect With Carbon Monoxide Releasing Molecule-2 (CORM-2) in Isolated Perfused Rat Heart: Role of Coronary Endothelium and Underlying Mechanism," *Vascular Pharmacology* 53, no. 1–2 (2010): 68–76.

16. M. T. Amano and N. O. Camara, "The Immunomodulatory Role of Carbon Monoxide During Transplantation," *Medical Gas Research* 3, no. 1 (2013): 1.