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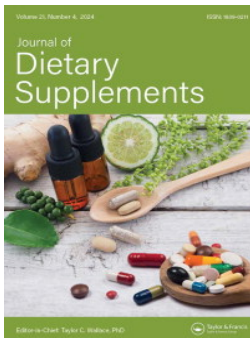
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## Response to “Comment on: A Double-Blind, Randomized, Placebo-Controlled Pilot Study Examining an Oxygen Nanobubble Beverage for 16.1-km Time Trial and Repeated Sprint Cycling Performance.”



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We thank Dr Nicholas Tiller and Prof. Asker Jeukendrup for their comment on the paper entitled ‘A Double-Blind, Randomized, Placebo-Controlled Pilot Study examining an Oxygen Nanobubble Beverage for 16.1-km Time Trial and Repeated Sprint Cycling Performance (King et al., 2023). We would like to take this opportunity to address some of the points that have been brought forward.

Tiller and Jeukendrup (2023) cite several previous research studies that have shown no effect of oxygenated beverages on O<sub>2</sub> uptake (Wilmert et al. 2002; Hampson et al. 2003; Leibetseder et al. 2006; McNaughton et al. 2007), exercise performance at sea-level (Mielke et al. 2005; Fleming et al. 2017), or exercise performance at altitude (Wing-Gaia et al. 2005). The authors also refer to a narrative review entitled ‘Ergogenic claims for oxygenated water cannot be taken seriously’ by Piantadosi (2006). We agree that the research we present should be considered in context of the above findings, hence within our introduction section, we made our best efforts to inform the readership of the Journal of Dietary Supplements of this scientific background and included all of the aforementioned studies within our citations.

Similarly, we agree with the assertion that the oxygen delivery within a beverage represents a minuscule contribution to oxygen uptake. We thank Tiller & Jeukendrup for expressing the oxygen values consumed in the beverage of only ~15 mL in energetic terms, representing only 0.073–0.075 calories, or 304–315 joules (Jeukendrup and Wallis 2005). We accept this would be inconsequential to exercise performance at both 60% VO<sub>2peak</sub> and within the 16.1 km time trial. This highlights the surprising nature of the results reported in the paper, including the improvement in 9 out of 10 participants, and an increase in mean power output of 4.1% following the O<sub>2</sub> trial, when compared with placebo. However, as stated within our introduction, the product under investigation is of a novel design, not to be directly compared with an oxygen containing beverage as utilized in previous research. Indeed, the oxygen delivery method utilizes oxygen-loaded micro and nanobubbles, which has been shown previously

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to enhance oxygen delivery when compared to oxygen saturated water, both when intravenously and orally administered (Owen et al. 2016; 2022). With this in mind, a greater quantity of oxygen may be delivered to the tissue than initially encapsulated in the consumed dose if the lecithin coated bubbles contained in the beverage act as oxygen carriers (Owen et al. 2022), much like how perfluorocarbon nanodroplets are reported to function as blood substitutes (Riess 2005). Previous research has shown promise in utilizing this novel delivery system for combating the hypoxic nature of cancer tumors (Owen et al. 2016; Nakazawa et al. 2016), indicating that the tissue infiltration is prominent and may be likely to cause similar effects in skeletal muscle tissue. This study represents the first investigation utilizing this product within sports performance, and therefore should be viewed with a fresh perspective away from the previous investigations cited above.

As commented by Tiller & Jeukendrup, our data uncover no effect on the blood lactate, heart rate, or RPE during steady-state exercise at 60%  $\text{VO}_{2\text{peak}}$ , nor was the  $\text{VO}_2$  cost of exercise reduced following the ingestion of the  $\text{O}_2$  drink. However, it is possible that alternative physiological mechanisms of oxygen transport (e.g. muscle blood flow) may have compensated for any change in arterial oxygen content to maintain oxygen delivery. Similarly, others have shown no impact on central hemodynamic, metabolic ( $\text{VO}_2$ ,  $\text{VCO}_2$ , pH) and subjective ratings during submaximal exercise in conjunction with an increase in arterial oxygen saturation and content after drug administration (Stewart et al. 2020). We observed only mild cardiopulmonary and metabolic perturbations during the 60%  $\text{VO}_{2\text{peak}}$  steady-state cycle. A more pronounced difference may have been apparent during more severe exertion when the compensability limits of oxygen transport system are reached. We estimate that the 16.1 km time trials were performed at approximately 73%  $\text{VO}_{2\text{peak}}$  which represents the boundary between the heavy and severe domains. Within our discussion of the data, we present the metabolic differences between these intensities and encourage future research to study the physiological responses through indirect calorimetry within this domain. It is a limitation of our study to have forgone the collection of inspired and expired air during the time trial, but we felt the ecological validity of the performance data may have been affected by too many measurements, including the wearing of the face mask. Similarly, the improved power output achieved in the repeated sprints was surprising, as was the lack of difference in blood gas and lactate despite this disparity in total work done, suggesting similar levels of metabolic acidosis in the face of enhanced anaerobic metabolism.

We concede that by failing to assess the efficacy of our blinding strategy we cannot rule out a placebo effect. However, to lead with this theory would undermine our research design and robust data collection methods. We conducted a randomized, double-blind, placebo-controlled trial, considered to be gold standard for the validation of treatment interventions. We meet Hurst et al. (2020) criteria for low risk of bias (random sequence generation, allocation concealment, complete outcome data, free of selective reporting). We have shown transparency in our research practice by providing a detailed description of experimental procedures, making datasets available in supplementary material, and documenting potential limitations or sources of error. We welcome the opportunity to share findings openly, so they can be replicated or indeed, refuted to foster collaboration, critical evaluation and the advancement of knowledge.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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