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A toast to health and performance! Beetroot juice lowers blood pressure and the O₂ cost of exercise

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THE PIONEERING WORK OF SCIENTISTS SUCH AS A. V. HILL (7) and August Krogh (10), investigating the dynamics of O₂ uptake during exercise, challenged our understanding of bioenergetics and energy homeostasis. Applied physiologists continue to advance our knowledge of altered energy transfer and efficiency during exercise, as exemplified by the work of Lansley and colleagues (11) in this issue of the Journal of Applied Physiology.

Lansley and colleagues (11) demonstrate that dietary NO₃⁻, administered in the form of beetroot juice (500 ml/day for 6 days), decreases resting systolic blood pressure (SBP) and O₂ consumption during walking and running. This study is part of a series of investigations, led by Prof. Jones, demonstrating the effects of beetroot juice on cardiovascular and metabolic responses to exercise (1, 2, 15). So what is novel? In this double-blind, placebo-controlled study, the authors selectively remove NO₃⁻ from beetroot juice to produce a NO₃⁻-free juice as placebo. There was no placebo effect in any of the variables measured. Thus the decrease in O₂ uptake and SBP in their investigations can be assigned to dietary NO₃⁻, rather than other compounds present in beetroot juice (e.g., polyphenols and/or quercetin). Moreover, the responses occurred in the absence of changes in phosphocreatinine (PCr) recovery kinetics (estimate of mitochondrial oxidative capacity). Lastly, the effects of dietary NO₃⁻ occurred within 2.5 h and promoted an increase in exercise tolerance (11). Whether dietary inorganic NO₃⁻ is given as beetroot juice (1, 2, 11) or pharmacologically (12), the responses are seemingly consistent across different exercise modalities, although the precise mechanisms remain unclear.

The effects of dietary NO₃⁻ are thought to be mediated via reduction to biologically active NO₂⁻ and nitric oxide (NO) molecules (13). Within the vasculature, NO elicits vasodilation through well-known pathways, including activation of soluble guanylate cyclase and subsequent elevations of cGMP levels. Augmentation of NO bioavailability through paradigms such as dietary NO₃⁻ (in addition to endogenous NO production) may enhance vasodilation and/or O₂ distribution within the contracting skeletal muscle. Specifically, NO elevates the driving pressure of O₂ in the microcirculation during contractions (5), which facilitates transcapillary O₂ flux, as dictated by Fick’s law. Interventions that increase the driving pressure of O₂ in the microcirculation blunt PCR breakdown during exercise and prolong exercise tolerance (6, 16). Thus, NO derived from dietary NO₃⁻ may improve the matching of O₂ delivery (QO₂) to O₂ uptake (VO₂) in active motor units, resulting in an elevated driving pressure of O₂ in the microcirculation during exercise that contributes to diminished PCR degradation and/or enhanced exercise tolerance. This postulate remains to be explored using techniques to measure the driving pressure of O₂ in the microcirculation and VO₂-to-QO₂ heterogeneity.

In skeletal muscle cells, the potential mechanisms whereby NO-stimulated signaling increases metabolic efficiency are puzzling. Intramyocyte proteins sensitive to NO signaling include those from mitochondria, sarcoplasmatic reticulum (SR), and myofibrils. The available evidence briefly discussed below suggests SR Ca²⁺-ATPase (SERCA) as the plausible site downstream of dietary NO₃⁻ responsible for reduced ATP cost of force production during exercise.

NO inhibits mitochondrial respiration (3). In the physiological (nanomolar) range, partial inhibition of cytochrome c oxidase enhances oxidative phosphorylation efficiency (3). The outcome of this process is a higher ATP-to-O₂ ratio, which could determine the decreased O₂ cost of exercise. However, total ATP turnover estimated by ³¹P-magnetic resonance spectroscopy was decreased with dietary NO₃⁻ (1). These results do not rule out mitochondria but suggest that we should start our search for mechanisms elsewhere.

Myofibrillar proteins are subject to modifications triggered directly (oxidation) or indirectly (kinase/phosphatase-mediated) by NO signaling. However, we expect that effects of NO on the contractile apparatus would elicit responses opposite to those described by Lansley et al. (11). Specifically, NO decreases actomyosin ATPase activity of permeabilized single fibers, which is accompanied by decreases in force and shortening velocity (14). NO₂⁻ or NO donors increase SR Ca²⁺ release without effects on muscle force or power output (14). Sequestration of the additional Ca²⁺ into the SR by SERCA would raise the ATP demand of force/power generation. On the basis of these findings and the cross-bridge theory of muscular contraction (8), it is difficult to envision a mechanism for reduced ATP cost of force generation involving actin-myosin interactions.

SERCA is a potential candidate responsible for the reduced ATP cost of force production elicited by dietary NO₃⁻. The stoichiometry of Ca²⁺ transport to ATP hydrolysis by SERCA is 2:1 in isolated preparations (4). However, when conditions mimic the intracellular environment, the stoichiometry ranges from 0.3 to 0.6 (4). This reflects ATP hydrolysis that is uncoupled from translocation of Ca²⁺ into the SR. One possibility is that dietary NO₃⁻ increases the stoichiometric efficiency of SERCA. NO decreases SERCA activity and Ca²⁺ uptake in isolated SR membrane preparations (9), but it seems that ATPase activity decreases by a greater extent than Ca²⁺ uptake. Hence, NO may increase the energetic efficiency of Ca²⁺ transport by SERCA, a hypothesis that needs to be examined in detail.

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The novel findings of Lansley et al. (11) have several clinical implications (13). A dietary therapy that lowers blood pressure and increases exercise tolerance may obviate the use of expensive drugs with potentially deleterious side effects. However, before beetroot juice can be safely used in the clinical setting, further research is necessary to address questions pertaining to the applied aspects of dietary NO₃, including 1) defining the dose dependence, 2) determining the impact on human health of prolonged supplementation, and 3) evaluating the effects of chronic dietary supplementation on adaptations elicited by exercise training. Answers to the following research questions for basic scientists are needed to clarify the mechanisms of action of inorganic NO₃: 1) Are the effects of dietary NO₃ consistent among striated muscles or exclusive to skeletal muscles? If the myocardium responds in a similar fashion to skeletal muscle, beetroot juice will emerge as a powerful therapy for patients with angina. 2) Does the cGMP pathway mediate the effects of inorganic NO₃ on O₂ cost of force production? 3) What site(s) of action and posttranslational modification(s) of proteins confer the effects of dietary NO₃ on muscle metabolism?

Investigations such as that performed by Lansley et al. (11) certainly challenge our understanding of integrative physiology. We can be cautiously optimistic that a relatively simple approach for treating cardiovascular perturbations and exercise intolerance is within our sight.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**REFERENCES**


