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Nitric Oxide

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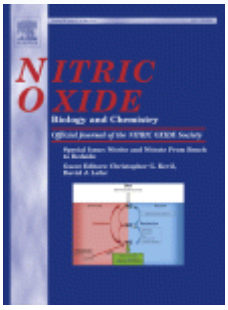
Nitrite and Nitrate From Bench to Bedside



Nitrite and nitric oxide metabolism in peripheral artery disease

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Abstract

Peripheral artery disease (PAD) represents a burgeoning form of cardiovascular disease associated with significant clinical morbidity and increased 5 year cardiovascular disease mortality. It is characterized by impaired blood flow to the lower extremities, claudication pain and severe exercise intolerance. Pathophysiological factors contributing to PAD include atherosclerosis, endothelial cell dysfunction, and defective nitric oxide metabolite physiology and biochemistry that collectively lead to

intermittent or chronic tissue ischemia. Recent work from our laboratories is revealing that nitrite/nitrate anion and nitric oxide metabolism plays an important role in modulating functional and pathophysiological responses during this disease. In this review, we discuss experimental and clinical findings demonstrating that nitrite anion acts to ameliorate numerous pathophysiological events associated with PAD and chronic tissue ischemia. We also highlight future directions for this promising line of therapy.

Highlights

► Nitrite anion is important in the functional and pathophysiological responses in PAD. ► We discuss NO bioavailability in PAD and plasma nitrite as a source of NO in hypoxia. ► We discuss endogenous and exogenous sources of plasma nitrite. ► We review the effects on vascular structure, function and physical performance. ► We highlight basic findings translated to animal and human models.

Keywords

- Ischemia;
- Angiogenesis;
- Arteriogenesis;
- Vasodilation;
- Exercise;
- Blood flow

Figures and tables from this article:

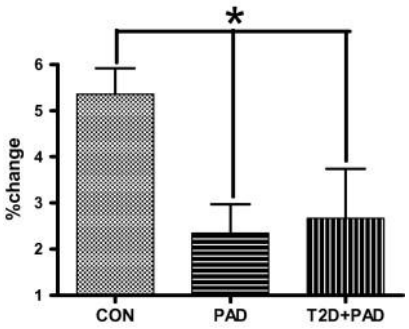

Fig. 1. Brachial artery flow mediated dilation peak percent changes in diameter from baseline. All values are statically adjusted for differences in age between groups. · = Significantly different at the $p < 0.05$ level. CON = subjects with two or more risk factors for CVD but no clinical disease, PAD = subjects with diagnosed PAD, T2D + PAD = subjects with diagnosed PAD in the presence of Type II Diabetes Mellitus. Adapted from Allen et al. [37].

Figure options

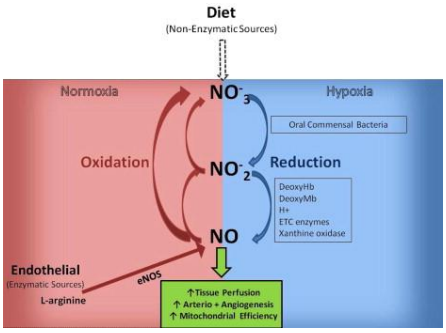

Fig. 2. Nitrate–nitrite–nitric oxide formation/recycle pathways. In the presence of oxygen endothelial nitric oxide synthase (eNOS) catalyzes the oxidation L-arginine to NO. NO can exhibit biological effects and has been shown to increase tissue perfusion along with angio- and arteriogenesis in PAD models. NO may also be rapidly oxidized to nitrite (NO_2^-) and nitrate (NO_3^-). A secondary source of vascular NO is via diet. Consumption of food stuffs high in inorganic nitrate (green leafy vegetables, beetroot) have been shown to increase plasma nitrate which can be secreted in saliva and reduced to nitrite by commensal bacteria in the mouth. Nitrite can then be further reduced to NO (and other biologically active nitrogen oxides) via several mechanisms which are expedited under hypoxic conditions. Hence, although some of the circulating nitrate and nitrite are excreted in the kidneys they are also able to be recycled back to NO.

Figure options

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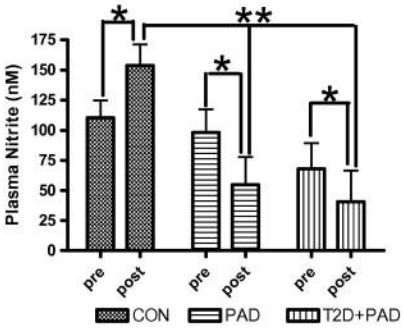

Fig. 3. Changes in circulating plasma NO_2^- prior to and following a maximal CPX. Samples were collected prior to (pre), and 10 min following (post) GXT. Data is represented as actual NO_2^- yield (nM) for each group. Values are statistically adjusted for differences between groups in age and VO_{2peak}. · = Significantly different within groups at the $p < 0.05$ level. ¨ = Significantly different between groups at the $p < 0.01$ level. CON = subjects with two or more risk factors for CVD but no clinical disease, PAD = subjects with diagnosed peripheral arterial disease, T2D + PAD = subjects with diagnosed PAD in the presence of Type II Diabetes Mellitus. Adapted from Allen et al. [37].

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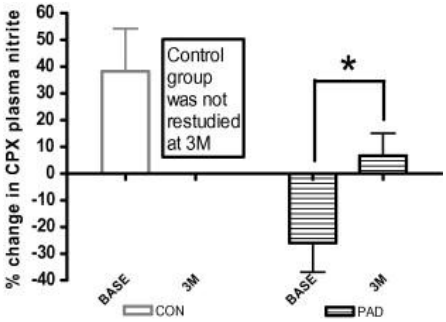

Fig. 4. Changes in plasma nitrite flux (% change in plasma nitrite concentration) pre to post Cardiopulmonary Exercise Testing (CPX) both baseline (Base) and 3 month (3 M-post exercise training) visits. Samples were collected prior to (Rest), and 10 min following CPX. · = Significantly different within groups at the $p < 0.05$ level. CON = subjects with two or more risk factors for CVD but no clinical disease, PAD = subjects with diagnosed peripheral arterial disease. Adapted from Allen et al. [60].

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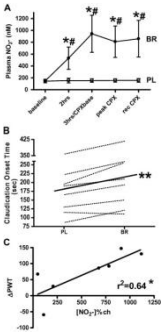

Fig. 5. Changes in (A) plasma nitrite (NO_2^-) concentration over time and (B) Claudication Onset Time (COT) prior to (baseline) and following consumption of a high nitrate (BR) or placebo (PL) beverage. (C) Shows the relationship between change in plasma nitrite [Onset Time] from baseline to 3 h following BR beverage and change in peak walk time (ΔPWT). 3 h/CPXbase indicates the time point 3 h following beverage consumption which was also just prior to commencement of the cardiopulmonary exercise test (CPX). Peak indicates immediately at time to exhaustion. Rec indicates 10 min after time to exhaustion. Values are group mean ± standard error. · = Significantly different from placebo group $p \leqslant 0.05$, ·· = significantly different from PL group $p \leqslant 0.01$, # = significantly different from baseline $p \leqslant 0.05$. Figs. 4a–c adapted from Kenjale et al [77].

Figure options

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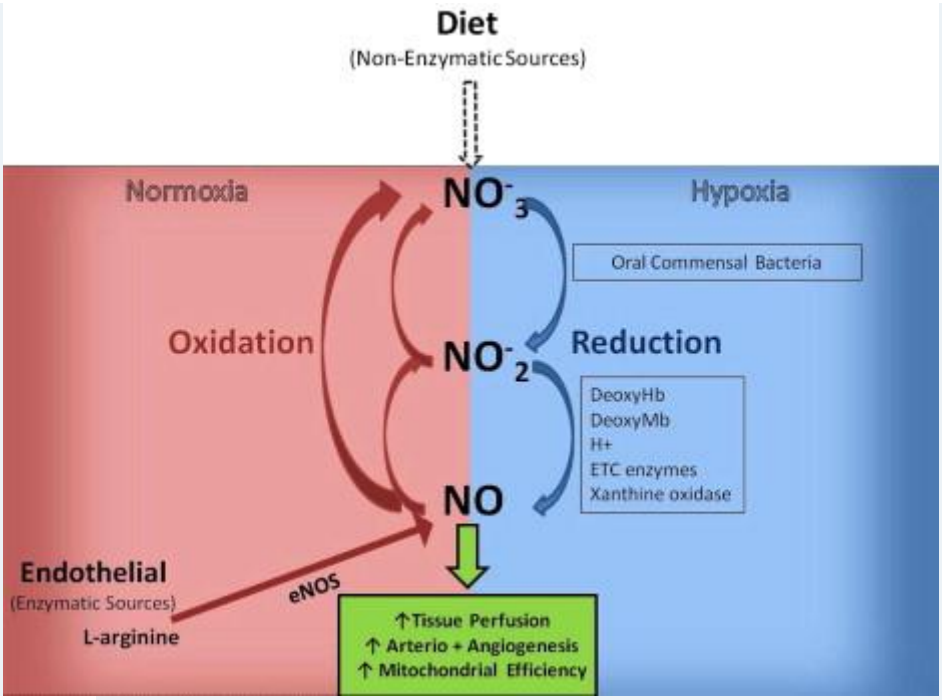

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