

# The Critical Role of Nitric Oxide in Microvasculature Health

— Chris D. Meletis, ND

## Key Points

- Nitric Oxide (NO) bioavailability is critical for optimal microvascular function.
- NO plays an important role in both diabetic and non-diabetic wound healing as well as the healing of burn injuries.
- Coronary microvascular endothelial inflammation results in reduced NO bioavailability, which leads to heart failure over time.
- Peripheral artery disease (PAD) patients have lowered synthesis or function of NO, which leads to suppression of endothelium-dependent vasodilation.<sup>1</sup> Consequently, inorganic nitrate supplementation may have beneficial effects in patients with PAD.
- Replenishing nitrate levels can have beneficial effects on the retinal microvasculature.

The macrovascular system, which includes the body's larger arteries, tends to receive the lion's share of attention when addressing the health of patients. However, it is becoming increasingly clear that the microvascular system, which is composed of small blood vessels including arterioles, capillaries, and venules, is equally instrumental in driving many aspects of health. Impairments in the microvascular system are associated with improper wound healing, coronary microvascular disease, peripheral arterial disease, reduced healing from burn injuries, and declining retinal health.

A number of different factors can lead to a microvascular system that is not working optimally. Many of these risk factors are the same that can result in macrovascular problems. Smoking, high cholesterol, obesity, high blood pressure, not exercising, diabetes, insulin resistance, estrogen deficiency, polycystic ovary syndrome, age, and chronic inflammation can all adversely impact the microcirculation.<sup>2</sup>

An unhealthy diet, which predisposes to most of the aforementioned factors, can also contribute to microvascular problems. This was illustrated in a randomized, single-blind, crossover trial of healthy men, where drinking sugar sweetened beverages reduced both microvascular and macrovascular endothelial function and Nitric Oxide (NO) bioavailability.<sup>3</sup> Conversely, eating a diet rich in dietary nitrates or supplementing with NO donors can improve microvascular health. However, the drop in NO that occurs with aging and disease is extensive enough that eating a nitrate-rich diet of vegetables is not always sufficient enough



to compensate. Furthermore, few adults are eating the recommended 2 ½ to 3 cups servings of vegetables daily. This white paper will address the role of NO in microvascular health and the clinical usefulness of nitrate-rich supplements in a number of health concerns that involve the microcirculation.

## Nitric Oxide and wound healing

Between 2.4 and 4.5 million people in the United States suffer from chronic wounds such as pressure ulcers, vascular ulcers, and diabetic ulcers.<sup>4</sup> These type of wounds are notoriously challenging to treat. The systemic complications of diabetes such as tissue hypoxia, impaired inflammatory response, and decreased collagen production interfere with typical treatment strategies such as debridement of necrotic tissue, use of topical antibiotics, and application of a wound dressing as well as negative pressure therapy, hyperbaric oxygen therapy, or application of growth factors. In fact, chronic wounds are the primary cause of amputations due to diabetes.<sup>5</sup> Consequently, interest in NO as a potential therapeutic agent has increased.

NO plays an important role in both diabetic and non-diabetic wound healing. The mechanism by which hyperbaric oxygen therapy increases the healing rate of wounds is due to an increase in local wound levels of NO.<sup>6</sup> NO is an important regulator of normal tissue repair.<sup>7</sup> NO production and bioavailability govern several processes involved in normal wound repair including microvascular homeostasis, as well as angiogenesis (the growth of capillary-sized microvessels), epidermal migration, collagen deposition, and granulation tissue formation.<sup>6</sup> Many of these processes depend upon the microvasculature and its related cellular and metabolic components.<sup>8</sup> For example, angiogenesis relies upon microvascular remodeling.<sup>8</sup>

Further supporting the role of NO in wound healing is the relationship between impaired bioactivity of NO and slower diabetic wound healing due to reduced accumulation of collagen.<sup>9</sup> Additionally, NO regulates inflammation and has antibacterial properties, making it an ideal agent for wound healing.<sup>5</sup> Unfortunately, endogenous levels of NO are often low in diabetic patients.<sup>5</sup>

Furthermore, replenishing NO levels may have beneficial effects in repairing burn injuries. A rodent study found that giving an NO precursor to rats with burn injuries improved microcirculation in the animals and increased their survival time.<sup>10</sup>

## Coronary microvascular disease

Coronary microvascular disease, also referred to as small vessel disease or small artery disease, affects the endothelial lining of small coronary artery blood vessels. It has also been called cardiac syndrome X and nonobstructive coronary heart disease. It occurs more commonly in women, often at a younger age than macrovascular coronary heart disease, especially in women whose estrogen levels are lower than normal even before menopause or whose high systolic blood pressure precedes menopause. Risk factors include hypertension, high cholesterol, obesity, smoking, a sedentary lifestyle, aging, diabetes, and a family history of heart disease.<sup>2</sup> Symptoms of coronary microvascular disease include microvascular angina, shortness of breath, insomnia, and fatigue.<sup>2</sup>

It is estimated that 30% of people with angina also have coronary microvascular disease, which correlates with increased morbidity and mortality in this group of patients.<sup>11</sup> Additionally, a large study of 1,439 people found that two-thirds of patients who had chest pain without obstructive coronary artery disease had coronary microvascular disease.<sup>12</sup> Other data indicate that coronary microvascular disease was present in 42% of mostly obese patients who visited an emergency department with chest pain and who did not have a myocardial infarction (MI).<sup>13</sup> Coronary microvascular disease often occurs before the development of large artery atherosclerosis and can predict cardiovascular events in individuals with atherosclerotic cardiovascular disease or without.<sup>14</sup>



Low-grade vascular inflammation is involved in the pathogenesis of coronary microvascular disease, especially in people with diabetes, chronic inflammatory rheumatoid diseases, obesity, and heart failure with preserved ejection fraction.<sup>15-17</sup> It is thought that coronary microvascular endothelial inflammation leads to reduced Nitric Oxide bioavailability, which causes heart failure over time.<sup>17</sup> Furthermore, elevated homocysteine levels in people with coronary microvascular disease reduce NO activity and synthesis, which leads to endothelial dysfunction.<sup>18</sup>

## Peripheral Artery Disease

In peripheral artery disease (PAD), the arteries supplying the extremities undergo atherosclerotic stenosis, which correlates with an elevated risk of fatal cardiovascular events.<sup>19</sup> More than eight million Americans suffer from PAD.<sup>20</sup> Patients with PAD may have intermittent claudication and critical limb ischemia, which are linked to poor functional capacity that interferes with the ability to perform daily duties and exercise. This functional impairment may be related to atherosclerosis, but functional capacity is not restored even after revascularization.<sup>21</sup> Consequently, it is thought that the impaired functional capacity that occurs in PAD patients is related to microvascular dysfunction rather than the extent of atherosclerotic stenosis.<sup>20</sup>

Microvascular blood flow is governed by a complex relationship between vasodilatory and vasoconstrictor messaging.<sup>20</sup> In PAD patients, endothelium-dependent vasodilation is suppressed partly due to lowered synthesis or function of NO.<sup>1</sup> Consequently, inorganic nitrate supplementation may have beneficial effects in patients with PAD. This was shown in a study of inorganic nitrate given as a single dose, which enhanced exercise tolerance in a group of PAD patients.<sup>22</sup>


A study by Bock and colleagues of patients with PAD determined whether inorganic nitrate supplementation increases limb blood flow in the lower-limbs, and whether it could improve vasodilatory and functional capacities.<sup>20</sup> The researchers measured microvascular function in the forearm and calves of the patients with PAD. Supplementation with inorganic nitrate increased the total distance walked during a six-minute walk test. The improvement was likely due to the improvement in microvascular blood flow in the calves of the subjects and enhanced vasodilation that occurred after nitrate supplementation. The researchers concluded, "Given the prevalence of ischemia in patients with PAD and the low NO bioavailability in this patient population, supplementation of inorganic nitrate has significant potential to improve functional outcomes in patients with PAD." The researchers recommend using inorganic nitrate supplements together with exercise.

Confirming these results was another study by Woessner and associates where beetroot juice as a source of inorganic nitrate was more effective at enhancing exercise tolerance and blood flow in patients with PAD compared to exercise alone.<sup>23</sup> The study authors concluded, "Specifically, our data suggests that increasing plasma nitrite before exercise may allow PAD subjects to train with less pain, at higher workloads for longer durations at each training session, thereby maximizing the beneficial peripheral vascular and skeletal muscle adaptations."

## Retinal Health

Narrowing of retinal arterioles and widening of venular caliber are adverse alterations that occur in the retinal microvasculature.<sup>24</sup> These changes can be indicative of preclinical alterations that are occurring in the cerebral and coronary microcirculation and therefore correlate with an elevated risk of poor vascular outcomes.<sup>24</sup>

Replenishing nitrate levels can have beneficial effects on the retinal microvasculature. One



study assessed the relationship between intake of dietary nitrate from both vegetable and non-vegetable sources and the microvascular status of older adults (aged 49 or older).<sup>24</sup> Retinal arterioles were significantly narrower in participants who ate the lowest amount of vegetable nitrate. Higher intake of total nitrate and vegetable nitrate correlated with wider retinal arterioles. Eating more nitrate-rich vegetables was also associated with narrower retinal venules compared to people who ate less nitrate-rich vegetables.

## **Utilizing a nitrate-rich supplement to enhance microvascular health**

NO is clearly involved in the function of the microvasculature. Therefore, enhancing NO bioavailability with the use of a nitrate-rich supplement can be advantageous to patients who can benefit from improving their microcirculation. In addition to the human studies previously mentioned in this white paper, other studies have shown that enhancing nitrate through supplementation with beetroot can improve skeletal muscle microvascular oxygenation<sup>25</sup> and support healthy blood pressure and microvascular function.<sup>26,27</sup> Therefore, replenishing NO levels can be a viable strategy for optimizing the microvascular health of patients.



## References:

1. Allen JD, Miller EM, Schwark E, Robbins JL, Duscha BD, Annex BH. Plasma nitrite response and arterial reactivity differentiate vascular health and performance. *Nitric Oxide*. 2009;20(4):231–237.
2. Coronary Microvascular Disease. American Heart Association. <https://www.heart.org/en/health-topics/heart-attack/angina-chest-pain/coronary-microvascular-disease-m> vd Accessed May 6, 2021.
3. Loader J, Meziat C, Watts R, et al. Effects of Sugar-Sweetened Beverage Consumption on Microvascular and Macrovascular Function in a Healthy Population. *Arterioscler Thromb Vasc Biol*. 2017;37(6):1250–1260.
4. Does Bilayered Extracellular Matrix Technology Hasten Wound Healing in Venous Stasis Ulcers? A Retrospective Study. <https://www.woundsresearch.com/article/3755>. Published 2005. Accessed May 5, 2021.
5. Malone-Povolny MJ, Maloney SE, Schoenfisch MH. Nitric Oxide Therapy for Diabetic Wound Healing. *Adv Healthc Mater*. 2019;8(12):e1801210.
6. Boykin JV, Jr., Baylis C. Hyperbaric oxygen therapy mediates increased Nitric Oxide production associated with wound healing: a preliminary study. *Adv Skin Wound Care*. 2007;20(7):382–388.
7. Schwentker A, Billiar TR. Nitric Oxide and wound repair. *Surg Clin North Am*. 2003;83(3):521–530.
8. Dulmovits BM, Herman IM. Microvascular remodeling and wound healing: a role for pericytes. *Int J Biochem Cell Biol*. 2012;44(11):1800–1812.
9. Schäffer MR, Tantry U, Efron PA, Ahrendt GM, Thornton FJ, Barbul A. Diabetes-impaired healing and reduced wound Nitric Oxide synthesis: a possible pathophysiologic correlation. *Surgery*. 1997;121(5):513–519.
10. Shi S, Wu K. [Protective role of endogenous Nitric Oxide to microcirculation of rats during burn shock]. *Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi*. 1998;14(3):214–217.
11. Sinha A, Rahman H, Perera D. Coronary microvascular disease: current concepts of pathophysiology, diagnosis and management. *Cardiovasc Endocrinol Metab*. 2021;10(1):22–30.
12. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of Coronary Microvascular Dysfunction Among Patients With Chest Pain and Nonobstructive Coronary Artery Disease. *JACC Cardiovasc Interv*. 2015;8(11):1445–1453.
13. Safdar B, D'Onofrio G, Dziura J, Russell RR, Johnson C, Sinusas AJ. Prevalence and characteristics of coronary microvascular dysfunction among chest pain patients in the emergency department. *Eur Heart J Acute Cardiovasc Care*. 2020;9(1):5–13.
14. Katunaric B, Cohen KE, Beyer AM, Gutterman DD, Freed JK. Sweat the small stuff: The human microvasculature and heart disease. *Microcirculation*. 2021;28(3):e12658.
15. Hage C, Svedlund S, Saraste A, et al. Association of Coronary Microvascular Dysfunction With Heart Failure Hospitalizations and Mortality in Heart Failure With Preserved Ejection Fraction: A Follow-up in the PROMIS-HFpEF Study. *J Card Fail*. 2020;26(11):1016–1021.
16. Recio-Mayoral A, Mason JC, Kaski JC, Rubens MB, Harari OA, Camici PG. Chronic inflammation and coronary microvascular dysfunction in patients without risk factors for coronary artery disease. *Eur Heart J*. 2009;30(15):1837–1843.
17. Tona F, Montisci R, Iop L, Civieri G. Role of coronary microvascular dysfunction in heart failure with preserved ejection fraction. *Rev Cardiovasc Med*. 2021;22(1):97–104.
18. Ahmad A, Corban MT, Toya T, et al. Coronary Microvascular Endothelial Dysfunction in Patients With Angina and Nonobstructive Coronary Artery Disease Is Associated With Elevated Serum Homocysteine Levels. *J Am Heart Assoc*. 2020;9(19):e017746.
19. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992;326(6):381–386.
20. Bock JM, Treichler DP, Norton SL, Ueda K, Hughes WE, Casey DP. Inorganic nitrate supplementation enhances functional capacity and lower-limb microvascular reactivity in patients with peripheral artery disease. *Nitric Oxide*. 2018;80:45–51.
21. Regensteiner JG, Hargarten ME, Rutherford RB, Hiatt WR. Functional benefits of peripheral vascular bypass surgery for patients with intermittent claudication. *Angiology*. 1993;44(1):1–10.
22. Kenjale AA, Ham KL, Stabler T, et al. Dietary nitrate supplementation enhances exercise performance in peripheral arterial disease. *J Appl Physiol* (1985). 2011;110(6):1582–1591.
23. Woessner M, VanBruggen MD, Pieper CF, et al. Beet the Best? *Circ Res*. 2018;123(6):654–659.
24. Gopinath B, Liew G, Lewis JR, et al. Association of dietary nitrate intake with retinal microvascular structure in older adults. *Eur J Nutr*. 2020;59(5):2057–2063.
25. Barros-Santos E, de Oliveira GV, Volino-Souza M, Alvares TS. Dietary nitrate improves skeletal muscle microvascular oxygenation in HIV-infected patients receiving highly active antiretroviral therapy: a randomised, double-blind, cross-over, placebo-controlled study. *Br J Nutr*. 2020;124(12):1277–1284.
26. Zafeiridis A, Triantafyllou A, Papadopoulos S, et al. Dietary nitrate improves muscle microvascular reactivity and lowers blood pressure at rest and during isometric exercise in untreated hypertensives. *Microcirculation*. 2019;26(3):e12525.
27. Hobbs DA, Goulding MG, Nguyen A, et al. Acute ingestion of beetroot bread increases endothelium-independent vasodilation and lowers diastolic blood pressure in healthy men: a randomized controlled trial. 2013;143(9):1399–1405.