

Nitric Oxide: Biofilms Beware!

BY
Catherine Harley

Chronic wounds of the lower extremity, as defined by showing no evidence of healing after a six- to 12-week period of best clinical practice,¹ are a challenge to both health-care professionals and patients. Several factors can impact the normal healing process, including infection, the presence of necrotic tissue, impaired tissue perfusion and the use of steroids.² Research has shown that the presence of bacterial biofilm or critical colonization—which is a complex, organized network of bacteria and tenacious film that is difficult to treat with conventional antibiotics³—can also disrupt the normal healing process. Sharp debridement and topical antimicrobials are often used to deal with these biofilms, but they are often ineffective.⁴ Introduced gaseous nitric oxide (gNO) may provide a new option for eradicating these biofilms.⁵

Nitric oxide (NO) is a very small free-radical gas that has now been identified as a key secondary messenger molecule for many basic biochemical reactions within body systems. NO, as a result of various stimuli, is regulated by three nitric oxide synthases (cNOS, iNOS and eNOS) that are each responsible for various concentrations and the duration of NO produced. NO is

synthesized in the presence of oxygen and calcium by cleaving a NO molecule off a precursor amino acid (L-arginine). The molecules of NO produced, because of their lipophilic nature and small size, readily pass through cell membranes. NO, acting as a secondary messenger molecule, reacts with chemical targets such as oxygen to form reactive oxygen/nitrogen species or enzymes containing heme or iron (Fe), resulting in the genesis of major cytokinetic activity.

For example, within the circulatory system, NO acts as a powerful and selective vasodilator by up-regulating cyclic guanosine monophosphate (cGMP), which prevents the influx of calcium ions that results in smooth muscle relaxation-vasodilatation. These characteristics of NO have led to extensive human studies with inhaled gaseous NO and its approval as a drug for reversing pulmonary vasoconstriction for treating “blue baby syndrome.” NO is also a neurotransmitter that helps in the processing of nerve signals as they cross synapses. Within the innate immune system, NO is produced by macrophages and neutrophils and plays a key role as a frontline non-specific antimicrobial agent against a wide variety of micro-organisms, including

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Catherine Harley, RN, IIWCC, is the Associate Editor of *Wound Care Canada* and Executive Director of the Canadian Association for Enterostomal Therapy.

Glossary of Terms

Angiogenesis: The growth of new blood vessels that restore blood flow to tissues after injury.

Amino Acids: Building blocks of proteins.

Biofilm: Micro-organisms that adhere to surfaces.

Guanosine monophosphate: A nucleotide found in RNA.

L-arginine: A protein amino acid present in the proteins of all living beings.

Lipophilic: Having the ability to dissolve, be dissolved in, or absorb lipids (fats).

Macrophage: A type of white blood cell that ingests foreign material and plays a major role in the immune response to foreign invaders such as infectious organisms.


Neutrophil: A type of white blood cell that helps to kill micro-organisms in the blood.

Proline: An amino acid.

bacteria and viruses. With so many roles, it is not surprising that NO is associated with the regulation of wound healing; in fact, when there is a lack of NO the normal wound-healing process is impaired.

The specific benefits of introduced nitric oxide gas in wound healing are associated with anti-microbial and anti-inflammation properties.^{6,7} Recently it has been suggested that availability of L-arginine resulting in NO synthesis is necessary for the proper cross-linking of collagen fibres to one another, via proline, to minimize scarring and maximize the tensile strength of healed tissue.⁸ Early research shows that NO may regulate gene expression, which can play an important role in the wound-healing process.⁹ At low levels, NO has an impact on keratinocyte proliferation, while at higher levels there is an inhibition of cellular proliferation and differentiation occurs. In addition to its antimicrobial properties, NO has been seen to play a role in angiogenesis (the formation of new blood vessels).¹⁰

Clinical case studies have shown that gaseous NO can be delivered nocturnally at home with good patient adherence. There have been no side effects noted for this treatment, and preliminary clinical studies demonstrate results that look promising. Clinical research with NO is in progress, and in the future you may see it as an adjunct therapy for non-healing, chronic wounds.

For further information on the use of nitric oxide in wound healing, visit www.baromedical.com/HBO2006/handouts/Boykin-HBO_Nitrix_Oxide.pdf. 

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