

Nitric oxide and its role in health and diabetes.

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Part 10. Nitric Oxide (NO) and Its Role in Wound Prevention and Wound Healing

In previous articles we have alluded to the positive effects of NO on wound healing. In this article we address the overall implication of NO in wound prevention and wound healing.

Vasodilation:

By now, most readers will appreciate that the risk of developing a lower extremity ulcer in people with diabetes may be greatly reduced if loss of sensation due to peripheral neuropathy is either prevented or can be reversed. To do so, requires an improved blood flow. NO is a powerful regulator of acute vasodilation, both for arteries, veins, and lymphatics. The increase in blood flow fills capillaries that were underperfused bringing oxygen and nutrients to the peripheral nerves and tissue. In addition, the enhanced venous drainage as well as the increase in lymphatic motility helps to remove edematous fluid that accumulates in the wound area. The latter effects of NO allow more oxygen and nutrient delivery to the wound site and speeds the removal of metabolic waste products from the area. Simply put, hypoxia and ischemia are reversed.

Growth factors:

Increased circulation through NO also provides an increased delivery of platelets, the source of platelet-derived growth factor. Additionally, other growth factors and the cells that produce them will also have greater access to the wound area. Each of these growth factors is necessary for complete tissue remodeling in a healing wound. However, as Dr. Boykin pointed out, growth factors such as becaplermin, fail to achieve an acceleration of the wound healing process if the patient is deficient in NO. Elevation the concentration of NO locally, in addition to simple vasodilation, facilitates the action of all growth factors in speeding cell division to rapidly replace damaged tissue. Thus, local increase in NO near the wound site will cause initial cell proliferation and then differentiation. These cellular activities relate to all tissues involved including blood vessels (angiogenesis), lymph ducts (lymphogenesis), muscles, epithelial cells, and nerves.

Inflammation:

NO will down regulate the activity of iNOS, which produces large amount of peroxynitrite (ONOO). INOS activity is important to destroy injured cells, in order to prepare the site of injury for new cell growth. However, uncontrolled activity of iNOS

continues the inflammatory process and tissue destruction. Reducing iNOS activity with small, local amounts of NO will reduce shorten the inflammatory stage of wound healing and speed the repair process.

Immune Response:

It has been reported that dietary L-arginine will increase the concentration and activity of T-lymphocytes. This effect is likely mediated by NO itself rather than by L-arginine and thus NO is considered to be a powerful mediator of immune defenses. Therefore, in addition to NO mediated vasodilation that aids in the recruitment of white blood cells which defend against bacterial infections in non-healing ulcers, NO apparently strengthens the immune system, especially T-cells.

Skin flaps:

Wounds are often covered by grafts from other areas of the body. To survive, this viable tissue must be nourished with a good blood supply. We suspect that local elevations of NO for several days before as well as after surgery, in diabetic or other patients with reduced concentrations of NO in their circulation, would enhance the viability of these grafts. In fact, enhanced viability of skin grafts due to NO has been reported by Suzuki in *Plastic Reconstructive Surgery* (1998).

Cardiovascular integrity:

Diabetes is accompanied by serious cardiovascular disease. NO reduces platelet adhesion so in theory, there should be fewer atherosclerotic events. The ability of NO to grow new blood vessels reduces ischemia locally and removes edematous fluid in areas of low perfusion. Thus, the threat of clot formation, hypoxic or ischemic injury, and swelling of tissues are all minimized by elevations of NO toward normal.

Cumulative effect:

Continued elevation of local NO availability builds on the physiologic and biochemical effects, which were begun, with the first dose of NO. It is similar to starting up a staircase, where the first elevation of NO (first step) exerts positive effects on wound healing. Subsequent NO is important since the wound is never again as poor biochemically and physiologically as it was prior to the first increase in local NO. The first NO exposure stimulates acute angiogenesis, perhaps only one or two new capillaries. However, using the staircase analogy, subsequent NO delivery to the wound site will result in the progressive development of many new blood vessels. What starts as a modest acute vasodilation eventually results in a well perfused, well healed tissue bed, one in which a subsequent ulcer is very unlike to occur. This is not to say that an ulcer won't occur in another area of the body based on the underlying disease state.

Approaches to elevating NO:

There are caveats to the treatment of wounds with a source of NO. First, systemic administration of dietary supplements such as L-arginine must be able to reach the wound and if swelling, edema, and tissue damage impinge on the local blood supply, then dietary supplements will have little value. Furthermore, acidosis and low oxygen availability in the immediate wound area, compromise the ability of the enzyme NOS to make NO from L-arginine.

Adverse drug interactions:

Many diabetic patients receive diuretics for kidney or cardiovascular disease. Diuretics may cause problems with potassium and magnesium metabolism. Magnesium is a regulator of intracellular calcium which itself is a co-factor for NOS activity. Magnesium also helps regulate intracellular potassium content and the excretion of potassium by the kidney. Addressing these possible co-morbid factors in a diabetic ulcer, may speed the healing of an otherwise slow healing wound.

Importantly, potassium imbalance also affects transmembrane potential in nerves. Clearly, the sensation of pressure, temperature, balance, and pain can be adversely affected unless the possible effects of diuretic usage are considered by the healthcare professional in the overall approach to diabetic ulcer management.

In summary NO, by stimulating vasodilation and normal membrane potential, may reduce the likelihood of peripheral neuropathy and thereby the major risk factor for diabetic ulcers. NO also positively influences wound healing by increasing vasodilation, promoting cell division and proliferation, angiogenesis, collagen formation and collagen cross-linking. Since people with diabetes are often low in NO, localized increases in NO availability may speed the healing of refractory diabetic ulcers.

The next article will discuss our experience with the Anodyne Therapy System as an adjunctive modality in wound care.

Dr. Tom Burke received his PhD in Physiology from University of Houston, Post Doctoral Training at Duke Medical School, He was an Associate Professor of Medicine and Physiology at the University of Colorado Medical School. He has authored more than 70 published scientific clinical articles and has been a visiting scientist at the Mayo Clinic, Yale University, University of Alabama, and University of Florida. He is a recognized international lecturer on cell injury and nephrology.