Increasing Tissue Oxygenation for Diabetic Wound Healing

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Abstract

Adequate tissue oxygenation is an essential factor during wound healing. Diabetic foot ulcers almost always accompany vascular insufficiency. Unfortunately, recovery of vascular insufficiency is difficult in diabetic patients because of both macro- and micro-circulations. This article presents the author's methods or innovations developed to increase tissue oxygenation for diabetic wound healing. Normobaric hyperoxic (NBO) therapy, which requires increasing the fractional inspired oxygen to almost 100% at normobaric pressure, is a potentially attractive alternative to hyperbaric oxygen therapy because of its high availability, good patient compliance, cost-effectiveness, decreased complications, and few technical requirements. NBO significantly increases tissue oxygenation level of diabetic feet. The foot lowering, rather than elevation, also significantly augments tissue oxygenation level of diabetic foot ulcers. Based on experience of the author's group, percutaneous transluminal angioplasty (PTA) is efficient enough to increase tissue oxygenation even in severely ischemic feet. The most severely ischemic group shows the most dramatic increase of tissue oxygenation after PTA. Monochromatic infrared energy, ultrasound, and pain scrambler therapy can also be used as adjunctive to improve tissue oxygen level in diabetic foot ulcers.

Keywords: Diabetic wound, Tissue oxygenation

Introduction

Many wound specialists dedicate themselves to conducting studies about diabetic wounds although there are various types of chronic wounds including pressure ulcers, lower leg ulcers (arterial or venous ulcer), and radiation ulcers. Why is understanding a diabetic wound important? It can be explained with two reasons. First, there are a great number of diabetic patients and the number is increasing even at present. According to the World Health Organization, approximately 5-10% of adult patients are diabetic. Even in developed countries including the USA, where it has been known to have the most well managed diabetic patients, approximately 15-25% of diabetic patients develop diabetic foot (diabetic foot ulcers, diabetic wounds, or diabetic ulcers). Second, another reason that the diabetic wound has been of interest is that its pathophysiology, diagnosis, and treatment are not simple but rather complex because diabetic patients display a variety of diabetic complications. There is a complex pathophysiological connection between diabetes and wound healing impairment. Vascular, neurological, immunological and biochemical problems lead to the hindrance of tissue restoration.

Diabetic foot ulcers almost always accompany vascular insufficiency, polymicro-

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bial infection, and abnormal pressure distribution due to chronic neuropathy. Recovery of vascular insufficiency is difficult because of both macro- and micro-circulations. Adequate tissue oxygenation is an essential factor during diabetic wound healing.^{1,2} Increasing blood and tissue oxygen contents help maintain cellular integrity and function by acting as a substrate for ATP synthesis and a supply of metabolic energy. A recent study suggested that oxygen may support the differentiation of fibroblasts to myofibroblasts, which are responsible for wound contracture, by a variety of mechanisms.³ Increased wound oxygenation promotes the synthesis of collagen by fibroblasts, and its deposition provides tensile strength to the matrix for angiogenesis and tissue remodeling.^{4,6} Oxygen also reduces infection in chronic wounds because of an important mechanism by which polymorphonuclear leukocytes selectively kill bacteria that rely on oxygen.^{5,7,8}

During the past 17 years, the author has been interested in the development of new techniques and materials that can improve diabetic wound healing through a procedure of the least degree of invasiveness. The purpose of this article is to present the author's methods or innovations developed to increase tissue oxygenation for diabetic wound healing. The author would like to emphasize that the common subjects which have already been well dealt with elsewhere are only briefly in this article. Only those subjects regarding the technologies specifically used in the author's Diabetic Wound Center have been highlighted.

Measurement of Tissue Oxygenation

Unlike non-diabetic patients, microcirculation in diabetic patients is commonly compromised, regardless of the status of the macrocirculation.⁹ Multiple factors contribute to the differences noted in macrocirculation patency and tissue oxygenation in diabetic patients. For example, while the skin-capillary density of diabetics is similar to that of non-diabetic persons, the basement membrane of capillary walls is thicker.^{10,11} This is attributable to high hydrostatic pressure of the lower extremities resulting in damage to capillary endothelial cells. This process ultimately leads to basement membrane thickening and arteriole hyalinosis, which in turn leads to problems in capillary autoregulation and impaired vasodilatory function. Another factor contributing to impaired microcirculation is an increase in non-enzymatic advanced glycosylation end products (AGE) associated with hyperglycemia. Serum,

vessel wall, and extracellular matrix AGE levels are increased in persons with diabetes mellitus, and the accumulation of AGEs is hypothesized to contribute to microangiopathy with increased thickness and decreased permeability of capillary basement membranes, resulting in defects in vasodilatory function.¹² Hematologic changes in red blood cells (RBCs) are also postulated to contribute to microangiopathy. Hyperglycemia leads to non-enzymatic glycosylation of spectrin on the surface of RBCs, resulting in increased hemoagglutination and stiffening of the cellular surface.^{13,14} When passing through vessels with small diameters (such as lower extremity capillaries), the normally flexible RBCs crumple into flat-shaped structures. However, the increased stiffness of RBCs in persons with diabetes prevents this shape change, which inhibits RBC passage through capillaries or inflicts trauma on endothelial cells as the stiffer RBCs forcibly pass through lower extremity capillaries. Diabetic neuropathy can also contribute to decreased tissue oxygen perfusion by opening arteriovenous (AV) shunts between arterioles and venules. Normally, sympathetic nerves act to maintain the constrictive tone of these AV shunts, preserving capillary blood flow, but sympathetic denervation releases this tone, opening these shunts.^{14,15} These AV shunts then become circulatory bypasses, decreasing capillary blood flow.

Therefore, tissue oxygenation measurement is recommended when determining tissue viability and selecting amputation levels in patients with diabetic foot ulcers. The measurement of transcutaneous partial oxygen tension ($TcpO_2$) is a non-invasive, reproducible method which can detect if the peripheral arterial microcirculation is compromised.¹⁶⁻¹⁸ $TcpO_2$, which represents actual tissue oxygen perfusion, is widely acknowledged to be a reliable method for evaluating macro- and micro-circulations in diabetic patients.¹⁹ The technique of $TcpO_2$ measurement is dependent on oxygen diffusion across skin from dermal capillaries maximally dilated by heat. The diffused oxygen amount is dependent on capillary oxygen delivery as a function of arterial oxygen content and blood flow.¹⁶ Although opinions vary, minimal $TcpO_2$ values thought to be required for adequate wound healing lie between 25 and 40 mmHg.¹⁸⁻²¹

Normobaric Hyperoxic Therapy

Improving tissue oxygenation with hyperbaric oxygen (HBO) therapy has been a reasonable therapeutic strategy with a relatively low risk of complications.²²⁻²⁴ Current literature sug-

gests that HBO therapy is effective for increasing blood and tissue oxygenation in the management of diabetic foot ulcers. Increasing oxygen levels in hypoxic tissues may help maintain cellular function and integrity thereby contributing to wound healing.²⁵⁻²⁸ Therefore, HBO therapy is used as an adjunctive therapy to treat several clinical conditions associated with tissue hypoxia such as severe soft tissue infections and ischemic diabetic foot ulcers.²⁹ However, clinical applications of HBO therapy are limited by high-cost, low availability of HBO chambers, need for trained personnel to monitor patients, poor patient compliance because of headache and otalgia, and the possibility of high oxidative potential contributing to pulmonary edema and brain injury.³⁰ The occurrence of oxygen-toxic seizures after HBO therapy has also been reported.³¹ Cardiopulmonary, nephrologic, and neurologic comorbidities may be more frequent in patients with diabetic foot ulcers, who commonly have a poor general health condition. In addition, many patients with diabetic feet have difficulty moving to a HBO chamber or may have claustrophobia. For these reasons, the use of HBO therapy has been limited in patients with diabetic feet.

Normobaric hyperoxic (NBO) therapy, which requires increasing the fractional inspired oxygen to almost 100% at normobaric pressure, has gained great interest in the treatment of cerebral ischemia.³²⁻³⁵ Several animal and clinical studies on NBO therapy as adjuvant treatment to attenuate infarct volume after stroke and to improve functional outcomes after brain trauma have provided compelling evidence in past years. NBO therapy is a potentially attractive alternative to HBO therapy because of its high availability, good patient compliance, cost-effectiveness, decreased complications, and few technical requirements.

The author's group has performed a clinical study to evaluate the effect of NBO therapy on tissue oxygenation of diabetic feet since no reports regarding the effect of NBO therapy on its potential to contribute to wound healing had been published.³⁶ The study included 100 patients with diabetic foot ulcers. TcpO₂ values of diabetic feet were measured before, during, and after NBO therapy. The mean TcpO₂ values before, during, and after therapy were 46.6±21.5, 88.9±48.0, and 49.9±23.8 mmHg ($p<0.001$), respectively. The lower the initial TcpO₂ level, the more TcpO₂ increased. The results reveal that NBO therapy significantly increases tissue oxygenation level of diabetic feet.

Our patients with diabetic foot ulcers receives NBO therapy for 3-4 hours per day (1 hour per session and 3-4 sessions

per day). Up to now, hundreds of patients have been treated with this protocol in our center, and no patients have experienced any complications associated with the NBO therapy such as headache or otalgia. Another great advantage of NBO therapy is that patients are much more cooperative compared to that of HBO therapy. As patients can watch the increase in TcpO₂ on their feet when TcpO₂ is measured before and during the NBO therapy, they realize that the NBO therapy is very effective for elevating tissue oxygenation of the wound bed, which helps with their compliance with the therapy.

Foot Lowering

In managing diabetic foot ulcers, foot elevation has been generally recommended to reduce edema and prevent other sequential problems. Elevation decreases the local hydrostatic pressure and the superficial venous pressure, thereby reducing edema and the interstitial spillage of macromolecules. By decreasing the extravasation of macromolecules into the extravascular space, the inflammatory response is reduced. Stifling of the inflammatory response may limit the release of mediators detrimental to the process of wound healing.³ However, foot elevation may decrease tissue oxygenation of the foot more than the dependent position since the dependent position is known to increase blood flow within the arterial system.⁴⁻⁶ In addition, diabetic foot ulcers, which have peripheral vascular insufficiency, generally have less edema than other wounds. Therefore, the author's group argued that foot elevation might not be helpful for healing of vascularly-compromised diabetic foot ulcers.

The author's group carried out a study to evaluate the influence of foot height on tissue oxygenation and to determine optimal foot position to accelerate wound healing of diabetic foot ulcers.³⁷ The study included 122 cases of diabetic foot ulcer patients. TcpO₂ values of diabetic feet were measured before and after foot elevation. Elevation was achieved by placing a foot over four cushions. We also measured foot TcpO₂ values before and after lowering the feet. Feet were lowered to the patient's tibial height, approximately 30-35 cm, beside a bed handrail. Foot elevation lowered TcpO₂. Before elevation, the average TcpO₂ was 32.5±22.2 mmHg, but the TcpO₂ decreased to 23.8±23.1 mmHg after elevation, representing a decrease of 26.8%. In contrast, foot lowering had a positive effect on TcpO₂. The average baseline TcpO₂ was 44.6±23.8 mmHg and increased to 58.0±25.9 mmHg

after lowering; an increase of 30.1%. The lower the initial TcPO₂ level, the more the TcPO₂ level increased. The foot lowering, rather than elevation, significantly augments TcPO₂ and may stimulate healing of diabetic foot ulcers.

In the author's center, we obtain TcPO₂ measurements from all diabetic foot ulcer patients, and as became evident, if foot lowering is beneficial, we encourage the patients to lower their feet.

Percutaneous Transluminal Angioplasty

Bypass graft surgery and percutaneous transluminal angioplasty (PTA) are generally recommended to improve tissue oxygenation of the ischemic diabetic foot. Bypass graft surgery has been the mainstay of revascularization therapy for the ischemic foot. There are many reports showing the value of bypass surgery; however, the surgery is an invasive procedure associated with perioperative mortality and morbidity.³² In particular, patients with severe ischemia are at a higher risk of subsequent cardiovascular events, including myocardial infarction, stroke, and death.^{33,34} In addition, bypass surgery requires at least one patent artery and a good vein.

Alternatively, PTA has been used with increased frequency in recent years for treatment of the diabetic foot.^{35,36} PTA is a less invasive procedure than the bypass graft surgery and several studies have demonstrated good results for PTA in terms of patency and limb salvage.²⁷⁻³¹ In PTA, there is no need for general anesthesia and there are less associated wound problems. PTA allows for preservation of the saphenous vein and thus can be performed repeatedly. Furthermore, based on improved technical options for PTA, a significantly better outcome than before is now expected for the procedure. However, there are still concerns about the feasibility and effectiveness of PTA in severely ischemic feet. Even though certain recent studies suggested that PTA might be as effective as bypass surgery^{26,28,32} their conclusions were only based on clinical symptoms rather than objective setting. Thus, bypass graft surgery is still preferred for severely ischemic diabetic foot patients.³³⁻³⁵

In experience of the author's group, PTA was efficient enough to increase tissue oxygenation even in severely ischemic feet.³⁸ We have performed a study to objectively compare the outcomes of PTA according to the degree of ischemia in order to estimate the efficacy of PTA in severely ischemic diabetic feet. The results were that the most severely ischemic group had the most dramatic increase of tissue oxy-

genation after PTA. As such, PTA can be an effective method for increasing tissue oxygenation even in the severely ischemic diabetic feet. These days we do not use bypass graft surgery any more, but do PTA to increase tissue oxygenation on the wound area.

Adjunctive Therapy

Monochromatic infrared energy (MIRE) involves the delivery of near-infrared energy at 890 nm wavelength to the skin. MIRE modality increases nitric oxide (NO) in the blood and plasmas.³⁹ NO is a potent endogenous vasodilator that can be liberated from tightly bound hemoglobin on exposure to various wave lengths of energy. NO is thought to be the molecule that accounts for the increased wound healing of oral supplementation with L-arginine or topical nitroglycerin. An elevation in NO has been suggested to be the basis of improved rates and quality of wound healing during L-arginine or nitroglycerin therapy since dietary L-arginine is a source of NO. NO is bound to the cysteine of the beta chain of hemoglobin during the passage of red blood cells through the lungs. In addition to oxygen, hemoglobin also transports NO throughout the body. NO is thought to aid in vascular perfusion by dilatation of arterioles, thus enhancing tissue oxygenation, nutrient delivery, removal of waste products of metabolism, and successful wound healing. NO also has a powerful anabolic effect that manifests itself as improved tissue remodeling. The MIRE device was first cleared by the FDA in 1994 for the purpose of enhancing circulation and reducing pain. The treatment using the MIRE device is recommended for 30 minutes each day.

Ultrasound is defined as a mechanical vibration above the upper threshold of human hearing (>20 KHz).³⁹ Ultrasound therapy involves the application of high-frequency sound waves transmitted through water or gel to promote wound healing. Although the exact mechanism underlying its clinical effects is not known, therapeutic ultrasound has been shown to have a variety of effects at a cellular level including angiogenesis, leukocyte adhesion, growth factor and collagen production, and increases in macrophage responsiveness, fibrinolysis, and nitric oxide levels. There are two types of ultrasounds. High-frequency (MHz range: 1-3 MHz) ultrasounds enhance three phases of wound healing by creating local thermal effects. They increase angiogenesis as well as wound contraction, collagen deposition, granulation tissue formation, and scar pliability. Low-frequency (KHz) ultrasounds debride

necrotic tissue, reduce wound bioburden, and enhance wound healing.

Pain scrambler therapy (or Calmare pain therapy) can also help increase blood flow.³⁹ Many diabetic foot patients suffer from chronic pain on the lower extremity, some of which are very painful. These foot conditions should not be taken lightly. The condition results in vasoconstriction. Even though the pain is basically associated with peripheral neuropathy, successful pain management can enhance increase of blood flow.

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