Mathematical Model of Hyperbaric Oxygen Therapy Applied to Chronic Diabetic Wounds

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Abstract  The failure of certain wounds to heal (including diabetic foot ulcers) is a significant socioeconomic issue for countries worldwide. There is much debate about the best way to treat these wounds and one approach that is shrouded with controversy is hyperbaric oxygen therapy (HBOT), a technique that can reduce the risk of amputation in diabetic patients.

In this paper, we develop a six species mathematical model of wound healing angiogenesis and use it to investigate the effectiveness of HBOT, compare the response to different HBOT protocols and study the effect of HBOT on the healing of diabetic wounds that fail to heal for a variety of reasons. We vary the pressure level (1 atm–3 atm), percentage of oxygen inspired by the patient (21%–100%), session duration (0–180 minutes) and frequency (twice per day–once per week) and compare the simulated wound areas associated with different protocols after three weeks of treatment.

We consider a variety of etiologies of wound chronicity and show that HBOT is only effective in treating certain causes of chronic wounds. For a wound that fails to heal due to excessive, oxygen-consuming bacteria, we show that intermittent HBOT can accelerate the healing of a chronic wound but that sessions should be continued until complete healing is observed. Importantly, we also demonstrate that normobaric oxygen is not a replacement for HBOT and supernormal healing is not an expected outcome. Our simulations illustrate that HBOT has little benefit for treating normal wounds, and that exposing a patient to fewer, longer sessions of oxygen is not an appropriate treatment option.

Keywords  Hyperbaric oxygen · Optimal protocol · Chronic wound · Mathematical modelling · Diabetes

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1. Introduction

A chronic wound is one that does not progress through the stages of wound healing that normally lead to a successful outcome. Often chronic wounds are a surface manifestation of an underlying disease such as diabetes mellitus, arterial disease, and vascular insufficiency (Mathieu, 2002). The treatment of such wounds is expensive since the patients often require ongoing regular care or hospitalisation. Among people with diabetes, approximately 15% will suffer from a foot ulcer and up to 24% of those with a foot ulcer will require amputation of a limb (Anonymous, 1999). A recent estimate suggests that it costs the US health care system up to US$25 billion annually to treat patients with nonhealing wounds (Sen et al., 2009). Grey and Harding (2006) have recently edited an excellent series of papers that provide a comprehensive review of wound healing and current standard treatments.

1.1. Wound healing and hyperbaric oxygen therapy

A normal healing wound is thought to progress through four stages; haemostasis, inflammation, cell proliferation, and tissue remodelling (Thackham et al., 2008), although these processes are interconnected and overlapping. During haemostasis, which lasts for several hours, the blood flow is halted. The inflammation phase lasts for approximately one week and sees the production of chemoattractants that stimulate the migration of fibroblasts into the wound. Fibroblasts are the dominant cell type during the proliferative stage of healing, which lasts several weeks. These cells produce collagen, the main component of the extracellular matrix (ECM). The cocktail of chemoattractants also stimulate the systematic rearrangement of endothelial cells (ECs) from neighbouring blood vessels (Diegelmann and Evans, 2004). Capillary sprout extension is facilitated by EC proliferation and directed migration toward the chemical attractant. The fusion of two capillary sprouts within a healing wound forms a loop through which blood can flow. Additional new sprouts develop from this looped vessel, thus propagating angiogenesis. The final stage of healing, tissue remodelling, can last for several months or even years.

The role of oxygen in wound healing is complex. Hypoxia (low oxygen) is required to initiate angiogenesis (Gordillo and Sen, 2003). However, if the oxygen level is not corrected and hypoxia persists, a chronic wound may form (Gordillo and Sen, 2003). It has been said “although hypoxia can initiate neovascularisation by inducing angiogenic factor expression, it cannot sustain it” (Gordillo et al., 2008). Hyperbaric oxygen therapy (HBOT) is a treatment aimed at raising the oxygen levels within the wound bed which