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Theoretical estimation of retinal oxygenation in chronic diabetic retinopathy

Q1 Jeffrey L. Olson [a,b], Masoud Asadi-Zeydabadi [c], Randall Tagg [c]

[a] University of Colorado Denver, Rocky Mountain Lions Eye Institute, Denver, CO, USA
[b] University of Colorado Denver, Department of Ophthalmology, Denver, CO, USA
Q2 [c] University of Colorado Denver, Department of Physics, Denver, CO, USA

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ABSTRACT

This paper uses computer modeling to estimate the progressive decline in oxygenation that occurs in the human diabetic retina after years of slowly progressive ischemic insult. An established model combines diffusion, saturable consumption, and blood capillary sources to determine the oxygen distribution across the retina. Incorporating long-term degradation of blood supply from the retinal capillaries into the model yields insight into the effects of progressive ischemia associated with prolonged hyperglycemia, suggesting time-scales over which therapeutic mitigation could have beneficial effect. A new extension of the model for oxygen distribution introduces a feedback mechanism for vasodilation and its potential to prolong healthy retinal function.

1. Introduction

Diabetic retinopathy is a leading cause of blindness in the industrialized world and results in a progressive loss of the capillary bed in the retina. This loss of blood supply in turn causes a shortage of oxygen critically needed by metabolically active retinal photoreceptors. In the face of this chronic anoxic challenge, retinal cells die and vision is progressively lost. Previous theoretical modeling of the retina has dealt with acute events, such as ophthalmic artery occlusion and retinal detachment. The aim of the present work is to develop a mathematical model of the retina under progressive and chronic ischemic conditions to study various aspects of retinal oxygenation.

Diabetes is a rapidly growing problem in the industrialized world – there are 18 million known diabetics in the United States, and 170 million worldwide [1,2]. For millions of diabetics, each day brings a further diminution of their vision. Despite recent technological and pharmacologic advances in medicine, the number of people losing sight continues to increase. In fact, diabetic retinopathy is the leading cause of blindness in adults aged 25–55 years old, and will blind over 25,000 Americans this year alone [3]. Often the vision loss is irreversible.

Vision loss carries profound impact for both the individual and society at large, and currently affects more people than ever. It has been noted that the population of those with visual impairment in the United States is expected to double over the next thirty years [4].

Diabetic retinopathy is characterized by progressive closure and loss of native blood vessels, usually on the anatomic level of the capillary, thought to be secondary to pericyte loss caused by chronic hyperglycemia. Over time, the loss of individual blood vessels results in decreased blood flow to the retinal tissue as a whole. This chronic, relentless loss of the capillary bed and tissue blood supply is fundamentally the same process that occurs in the kidney, heart, and peripheral nerves of the diabetic resulting in renal failure, cardiac disease, and neuropathy. The major difference between these diseases and retinopathy, is that the loss of capillaries can be visualized and photographed through the lens of the eye either non-invasively or minimally invasively via dye injection (Fig. 1).

The loss of blood supply that characterizes diabetes leads to the fundamental underlying problem associated with diabetic retinopathy: a chronic shortage of oxygen, along with other nutrients such as glucose. This decreased oxygen supply adversely affects retinal cells, which are some of the most metabolically active cells in the human body, with a concurrent high demand for oxygen [5].

With prolonged ischemia, these cells in the retina progressively lose their ability to function, and the patient suffers a progressive loss of vision [6]. While the current state of treatment using either lasers or injectable medication provides a means of slowing the rate of vision loss, it does not treat the underlying problem, i.e., a lack of tissue oxygen [7,8].

Conventionally, the retina is divided into two vascular zones: the inner vascularized retina and the outer avascular retina. The outer retina derives its oxygen by diffusion from the underlying choroid, which is a high flow network of interconnected channels not under metabolic regulation. The inner retina is nourished by an intrinsic vascular system under metabolic control. The watershed area between

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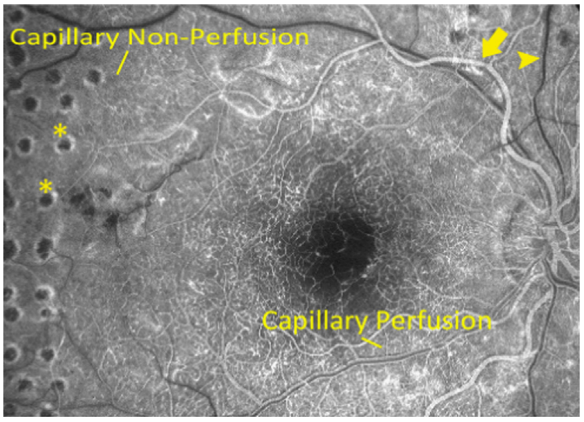

Fig. 1. Human retinal appearance, as photographed during fluorescein angiography. After injection of a fluorescent dye, blood flow can be imaged in the major retinal arterial (arrows) and venous (arrowheads) circulations. Further, capillary perfusion can be assessed. The areas where the capillaries have closed secondary to diabetic retinopathy are non-perfused. These areas of ischemia are treated with laser surgery (asterisks).

the two circulations typically occurs at the junction of the inner and outer retinal layers [9].

The rates of oxygen consumption in various levels of the retina have been determined by experimentation [10–12] and described by mathematical modeling [13,14]. Building upon these previous computer models, other researchers have used this dual domain blood flow concept to predict oxygen levels in different acute disease states such as retinal artery occlusion [15] and retinal detachment [16]. To date, there have been no computer models of chronic or progressive anoxic states in the retina to simulate diseases such as diabetic retinopathy, which may run their course over many decades. The prior models also did not include vasodilation as a possible feedback mechanism for compensating capillary loss in the inner retina.

It has been demonstrated that hyperoxia may provide some benefit in ameliorating the progressive of diabetic retinopathy by administering oxygen by nasal cannula [17]. Further, there is the possibility that moderate illumination may prevent progression of diabetic retinopathy by inhibiting the increase in photoreceptor oxygen demand that occurs during the dark cycle [9].

Attempts have been made to restore oxygen supply to the retina by means of oxygenated irrigating fluids [18], intraocular implants [19], and systemic oxygen delivery [17]. In theory, higher levels of oxygen delivered to the lungs results in higher oxygen levels carried by the blood to end organs. However, there are two factors which counteract this effect. First, increasing systemic arterial oxygen levels has differing effects on the two blood supplies of the eye: the choroidal supply increases dramatically with systemic hyperoxia, but the effect on the inner retinal is blunted dramatically secondary to autoregulation of retinal blood flow [20].

The second major obstacle in this treatment paradigm is the upper limit on oxygenation that occurs in the blood once hemoglobin is saturated, as defined by the oxyhemoglobin dissociation curve. For example, at an arterial partial pressure of oxygen of 90 mmHg, hemoglobin is about 97% saturated. Increasing the arterial pressure of oxygen to 100 mmHg increases the saturation of hemoglobin to 98% [21]. In short, there is not much room for physiologic improvement once the hemoglobin is saturated.

High levels of inhaled oxygen treatment have some serious drawbacks and side effects as well. The first and most obvious is the need to wear a nasal cannula and carry a continuous supply of oxygen. Second, high oxygen levels have been shown to induce hyperoxic lung damage through receptor mediated and mitochondrial cell death pathways [22].

In order to better frame the problem of maintaining adequate oxygen over many years of progressive decline of retinal capillary function, a model-based approach is explored. We first describe the mathematical representation of oxygen delivery, transport, and consumption, including numerical procedures used to calculate oxygen distributions from the model. Then we describe results both in terms of spatial distribution of oxygen in the retina and in terms of long-term effects of decreasing blood flow in the retina. The model is one-dimensional, capturing the dominant features of oxygen transport due to the thinness of the retina layer with the assumption that tissue parameters do not vary rapidly in the lateral directions at the 100 μm scale. While significant variation of parameters governing blood supply, diffusion and consumption can occur across the full spatial extent of the retinal layer and some highly localized regions of different structure exist (for example, the fovea centralis), we believe this 1-dimensional model permits primary understanding of long-term effects for a given location once local conditions are defined through the governing parameters. After exploring long-term effects within the established model, we add a new two-parameter extension of the model incorporating vasodilation to explore its potential mitigating effects over long times. Finally, we interpret the results to arrive at some conclusions to help guide future treatment.

2. Methods

2.1. The model

Histological and anatomical depictions of the retina are shown in Fig. 2. The total thickness of the retina has been measured histologically and in vivo by optical coherence tomography to be about 0.250 mm. To describe the distribution of oxygen within this tissue, we take as a starting point the model used by Roos [15,16]. In this one-dimensional model, the retinal structure is idealized as four distinct regions of oxygen shown schematically in Fig. 3. The outer retina, which is avascular and receives its oxygen supply from choroidal blood flow, is divided to regions 1–3. The delivery of oxygen in the outer retina depends on diffusion from choroid into the retina. Oxygen transport is modeled as pure diffusion across region 1, which includes Bruch's membrane, the pigmented epithelium, and the outer segmental layers of the rods and cones where light-transduction principally occurs. The majority of oxygen consumption in the outer retina occurs in region 2, the inner segmental layer of the retinal photoreceptors, which contain numerous mitochondria and are highly metabolically active with active transport of ions across membranes. Oxygen that is not consumed in this layer may further diffuse with assumed negligible consumption across region 3, consisting of the external limiting membrane and the outer nuclear layer. The thicknesses of layers 1–3 are taken to be 0.0375, 0.025, and 0.0625 mm, respectively, for a total of 0.125 mm which is half of the retinal thickness.

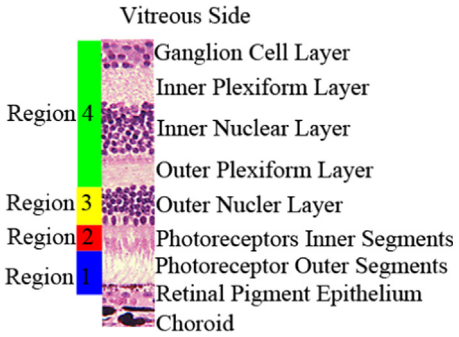

Fig. 2. Histological appearance of human retina. The cell layers are shown adjacent to the regions of oxygen consumption used in the mathematical model. (Histology microphotograph courtesy of Dr. Olson's lab).

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