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Original article

Theoretical predictions of metabolic flow regulation in the retina

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Abstract

Purpose: This study uses a theoretical model to investigate the response of retinal blood flow to changes in tissue oxygen demand. The study is motivated by the need for a better understanding of metabolic flow regulation mechanisms in health and disease.
Methods: A mathematical model is used to calculate retinal blood flow for different levels of tissue oxygen demand in the presence or absence of regulatory mechanisms. The model combines a compartmental view of the retinal vasculature and a Krogh cylinder description for oxygen delivery to retinal tissue.
Results: The model predicts asymmetric behavior in response to changes in tissue oxygen demand. When all regulatory mechanisms are active, the model predicts a 6% decrease in perfusion when tissue oxygen demand is decreased by 50% and a 23% increase in perfusion when tissue oxygen demand is increased by 50%. In the absence of metabolic and carbon dioxide responses, the model predicts a constant level of blood flow that does not respond to changes in oxygen demand, suggesting the importance of these two response mechanisms. The model is not able to replicate the increase in oxygen venous saturation that has been observed in some flicker stimulation studies.
Conclusions: The increase in blood flow predicted by the model due to an increase in oxygen demand is not in the same proportion as the change in blood flow observed with the same decrease in oxygen demand, suggesting that vascular regulatory

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mechanisms may respond differently to different levels of oxygen demand. These results might be useful for interpreting clinical and experimental findings in health and disease.

Keywords: flicker stimulation, light-dark adaptation, mathematical model, metabolic flow regulation, retina

1. Introduction

Impaired retinal perfusion is associated with many ocular and systemic diseases such as glaucoma, age-related macular degeneration, and diabetes. Under healthy conditions, the retina is able to adjust perfusion in response to alterations in tissue oxygen demand (metabolic flow regulation) or blood pressure (autoregulation). This change in perfusion is achieved through vascular responses to mechanisms including myogenic, shear-dependent, metabolic, and carbon dioxide responses. It is hypothesized that in disease states some of these mechanisms are impaired, compromising the oxygenation of the retina. Mathematical modeling has been used previously[1,2] to investigate the roles of these mechanisms in achieving autoregulation. Here, these mathematical models are used to investigate the response of retinal blood flow to changes in tissue oxygen demand.

There is inconsistency in the scientific literature regarding the vascular response to changes in oxygen demand, as observed in flicker stimulation studies and light-dark adaptation studies. In particular:

- Flicker stimulation causes an increase in retinal oxygen demand, triggering an increase in blood flow;[6] changes in vessel diameter appear to depend on the frequency and/or exposure time of the flicker stimulation.[5,6,7,11,14]
- Retinal oxygen consumption differs with light, dark, and flicker stimulation.[12,16,18]
- Venous oxygen saturation is observed to increase in cases of flicker stimulation and dark as compared to adaptations to light in humans.[11,12]
- Changes in metabolism in the retina are not the same in the inner and outer retina, likely due to differences in vascularization.[12,16]
- Adaptation studies to light-dark and flicker stimulation differ by species, as shown in Table 1.

In this study, the response of the retinal vasculature to changes in oxygen demand is modeled using a compartmental model of the retinal vasculature and a Krogh cylinder model for oxygen delivery to retinal tissue.[2] The model results are consistent with some clinical observations[6] but do not replicate the behavior observed in other studies, suggesting the need for an improved description of retinal geometry and oxygen delivery.

2. Methods

In this study, the retinal vasculature is modeled as a series of lumped compartments, representing the central retinal artery (CRA), large arterioles (LA), small arterioles (SA), capillaries (C), small venules (SV), large venules (LV) and the central retinal vein (CRV) (Fig. 1). Analogous to an electric circuit in which the potential difference drives the electric current, the pressure difference between the inlet and outlet nodes of the model ($\Delta P = P_{in} - P_{out}$) drives the blood flow (Q) through the system according to Ohm's Law: $Q = \Delta P/R$, where R represents the total vascular resistance to blood flow offered by the retinal vasculature.

The variable resistances, indicated by an arrow in Figure 1, modulate the level of blood flow in the system accounting for passive (pressure-related) and active (vascular regulation-related) changes in the diameter of the representative vessel. The balance between internal pressure and intraocular pressure (IOP) leads to passive changes of resistances $R_{1,IOP}$ and $R_{5,IOP}$. The balance between internal pressure and the mechanical stress exerted by the lamina cribrosa (LC), resulting

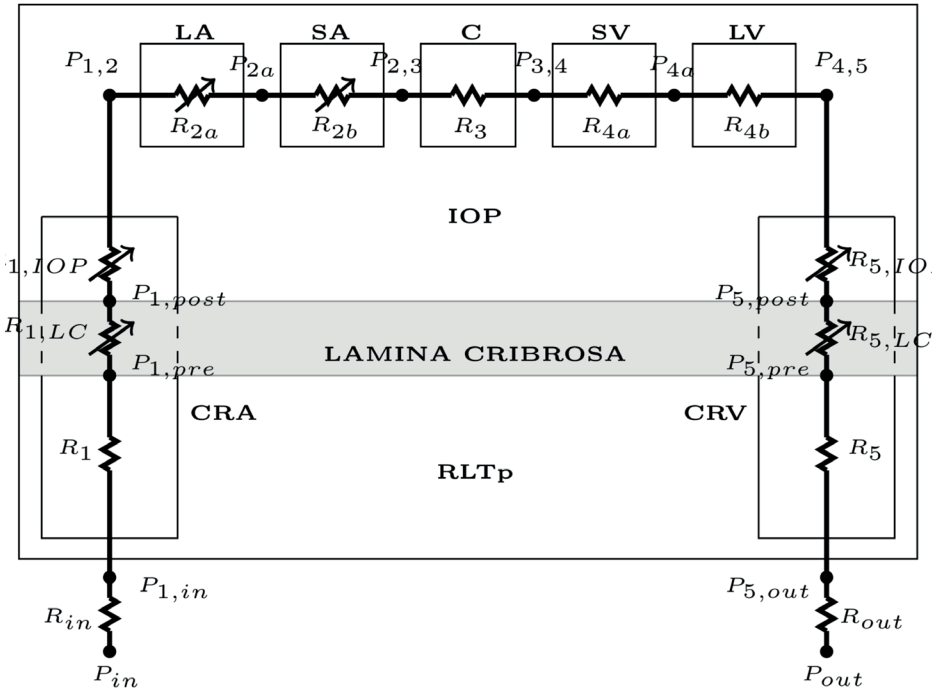

Fig. 1. Retinal vasculature represented by the following compartments: the central retinal artery (CRA), large arterioles (LA), small arterioles (SA), capillaries (C), small venules (SV), large venules (LV), and the central retinal vein (CRV).

from the combined effect of IOP, retrolaminar tissue pressure (RLTp) and scleral tension,[2,9,10] leads to passive changes of resistances $R_{1,LC}$ and $R_{5,LC}$. The changes in the variable resistances of the CRA and CRV follow the Law of Laplace.[2,10] Active changes in resistances R_{2a} and R_{2b} are achieved via four regulatory mechanisms that respond to changes in (a) systemic pressure (myogenic response); (b) arteriolar shear stress (shear stress response); (c) ATP concentration (metabolic response); and (d) carbon dioxide concentration (carbon dioxide response).

A dynamic (ODE) representation of the vessel response to diameter and vascular smooth muscle tone is used to approach the steady state conditions in the LA and SA; the resulting values of vascular resistance are computed using Poiseuille's law. The conservation of blood flow in the network leads to a nonlinear system of equations which is solved to obtain the pressure distribution at the nodes of the network and the level of blood flow as oxygen demand (M_0) is varied.[2] The value of blood oxygen saturation in the system is predicted using a Krogh cylinder model in which the CRA, LA, SA and C compartments are assumed to deliver oxygen to a surrounding cylinder of tissue. A more detailed description of the model, including equations and parameter values, can be found in Cassani *et al.*[2]

3. Results

Table 1 provides a summary of the observed effects of flicker stimulation and light-dark studies on retinal blood flow, blood oxygen saturation, and vessel diameter in multiple species (humans, rats, cats, and bullfrogs). These studies do not translate the degree of flicker stimulation or exposure to light into a quantifiable level of oxygen demand in the retina. In addition, the observed hemodynamic changes are not the same across species or for similar flicker stimulation frequencies or light exposure time. Because of these aspects, these data provide mathematical modelers with a unique challenge of capturing the various responses according to the geometric and mechanistic assumptions built into their models.

Figure 2 provides a first attempt of using a mathematical model to predict the change in perfusion when tissue oxygen demand is varied between 1 and 5 cm^3 O_2/100 cm^3/min. The effects of different response mechanisms (myogenic, shear, metabolic, and carbon dioxide) are evaluated by running multiple model simulations with some of the mechanisms active and some inactive. The model predicts asymmetric behavior in response to changes in tissue oxygen demand. For example, when all mechanisms are active, the model predicts a 6% decrease in perfusion when tissue oxygen demand is decreased by 50% and a 23% increase in perfusion when tissue oxygen demand is increased by 50%. If both the metabolic and carbon dioxide responses are impaired (light blue line), the model predicts a constant level of blood flow that does not respond to changes in oxygen demand, suggesting the importance of these two response mechanisms.

Table 1. Summary of vascular response to flicker stimulation and light-dark adaptation studies.

Study	Species	Results	Source
Flicker light stimulation	humans	Retinal arterial and venous blood flow increases during flicker stimulation. Major retinal arterial and venous diameter increases during flicker stimulation.	[6]
Flicker light stimulation	humans	Retinal venous oxygen saturation is higher during flicker stimulation than in light adaptation. Major retinal arterial and venous diameter increase during flicker stimulation.	[11]
Flicker light stimulation	rats	Retinal venous oxygen saturation is lower during flicker stimulation than in light adaptation.	[17]
Light-dark adaptation	humans	Retinal arterial and venous oxygen saturation is higher during dark than in light adaptation (in humans). Oxygen consumption in the outer retina is higher in dark than light adaptation (in cats). Oxygen consumption in the inner retina is similar in dark and light adaptation (in cats).	[12]
Light-dark adaptation	cats	Outer retina tissue oxygen partial pressure is lower in dark than light adaptation (in cats). Inner retina tissue oxygen partial pressure is higher in dark than light adaptation (in cats). Retinal oxygen consumption is higher in dark than in light adaptation (in bullfrogs).	[18]
Light-dark adaptation and flicker light stimulation	rats	Oxygen consumption in the outer retina is higher in dark than in light adaptation. Inner retina activity is lower in dark than in light adaptation. Retinal blood flow is higher in light adaptation and during flicker stimulation than in dark adaptation.	[16]

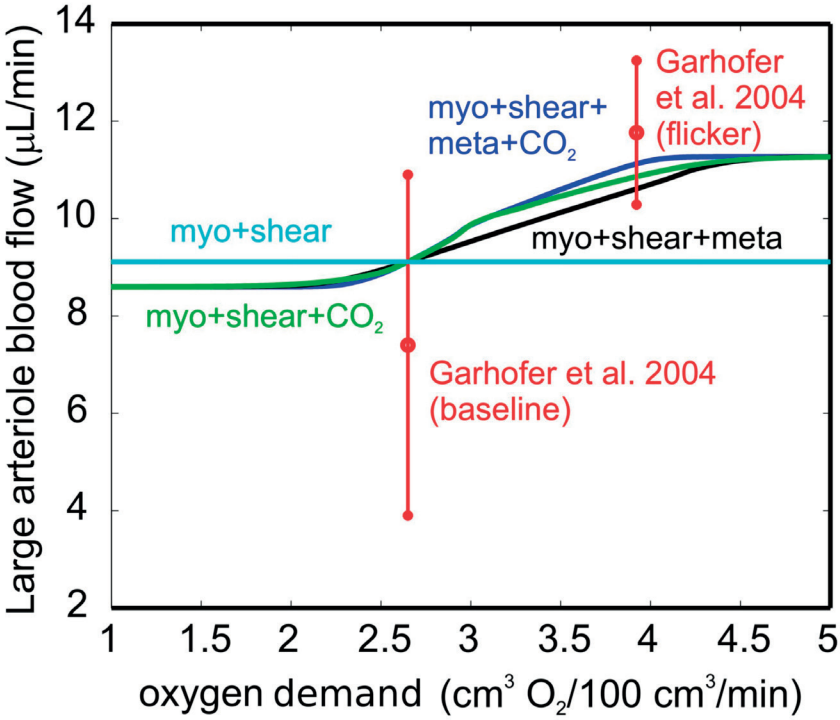

Fig. 2. Large arteriole blood flow vs. oxygen demand. The model predictions for different autoregulation mechanisms are compared with clinical data[6] at baseline and during flicker stimulation.

The predictions of blood flow through a large arteriole are also compared with data from a study on flicker stimulation in healthy individuals[6] in Figure 2. The clinical study measures: (i) the average value of blood flow in one large retinal arteriole of 7.4 ± 3.5 *μl/min* in light adapted conditions; and (ii) a 59% increase in blood flow with flicker stimulation. In the model, a baseline value for oxygen demand is chosen to be M_0 = 2.65 cm^3 O_2/100 cm^3/min in order to yield the experimentally observed value of venous blood oxygen saturation of 60%.[11] The M_0 value corresponding to flicker stimulation is obtained from a study showing that flicker stimulation induces a 48% increase in oxygen demand.[17] Using these clinical data points, Figure 2 shows that the model predictions are in good agreement with clinical data.

The model predicted value of oxygen saturation in the large venules is also compared with data from a clinical study on flicker stimulation.[11] The clinical study measures an increase in venous saturation from 60% ± 5.7% to 64% ± 5.9% with flicker stimulation, while the model predictions show a decrease in venous saturation with flicker stimulation from 60% to 52%.

Discussion

The increase in blood flow predicted by the model due to an increase in oxygen demand is not in the same proportion as the change in blood flow observed with the same decrease in oxygen demand, suggesting that vascular regulatory mechanisms may respond differently to different levels of oxygen demand. In addition, the model is used to quantify the relevance of the different regulatory mechanisms, suggesting that metabolic and carbon dioxide responses play a major role in achieving vascular regulation. While the model is able to quantify the average retinal response to changes in oxygen demand, it cannot differentiate between the contributions of the inner and the outer retina. In the current model, variations in the tissue oxygen demand M_0 have a global effect on the retina; the separate contributions of the inner and outer retina, which would yield local changes in metabolic activity, are not included. This could explain the difference between the model-predicted levels of oxygen saturation and the saturation levels observed in flicker stimulation and light-dark adaptation studies cited in this work. In addition, modeling the SV and LV as Starling resistors[10] would alter the venous resistance in response to changes in the transmural pressure difference and thereby alter the levels of retinal blood flow and oxygen saturation predicted in the system. Overall, the preliminary results of this model give important insight into metabolic flow regulation; however, the inability to capture all of the *in vivo* observations listed in Table 1[11,12,16,18] suggests a need for more realistic descriptions of the retinal geometry and oxygen delivery to explain the response of blood flow to changes in retinal oxygen demand.

To represent the retinal geometry more accurately, the model can be adapted to account for the multiple layers (vascular and avascular) of the retina, as depicted in Figure 3. In this updated geometry, oxygen will be assumed to diffuse from retinal capillaries and the choroid into the various retinal tissue layers.

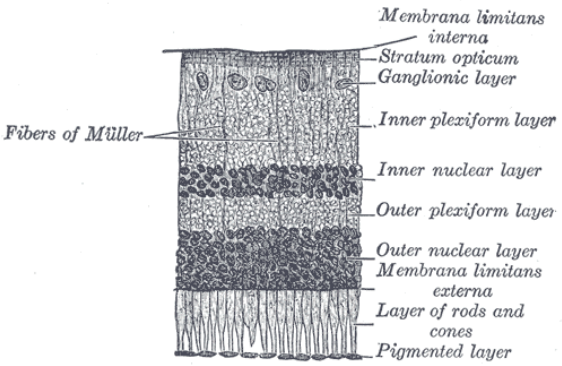

Fig. 3. Tissue layers of the retina, Henry Vandyke Carter [Public domain], via Wikimedia Commons from Gray.[8]

Previous works have been developed to predict the hemodynamics in the retina[10,13] or oxygen distribution in the multiple layers of the retina.[4,15,18] Causin *et al.*[3] modeled retinal flow and oxygenation in a realistic geometry but did not include the effect of vascular regulation. Extending the current study to combine more realistic descriptions of retinal geometry, oxygen delivery, and vascular regulation should improve the predictive ability of this mathematical model to describe the experimental observations summarized in Table 1. The development of such a model will involve non−trivial mathematical challenges related to mass conservation and approximation techniques but will ultimately yield a model that can better explain the retinal response to different metabolic conditions.

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