Vitreous Fluorophotometry: Mathematical Analysis of the Effect of Peripheral Leakage on Axial Scans

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Current instrumentation in vitreous fluorophotometry allows the determination of a fluorescein concentration profile along the optical axis of the eye. Based on an assumption of a uniform blood–retinal barrier permeability, several methods have been used for the determination of the permeability from an axial scan. The assumption of a uniform permeability is not realistic and it has been unknown to what extent the calculated common permeability reflects the local permeability in different areas of the retina. Using a mathematical model for a nonuniform permeability, we have investigated the effect of localized leakage on the axial concentrations and thereby on the calculated common permeability under the assumption of free diffusion in the vitreous body. It turns out that leakage outside the large temporal vessels has to be extremely strong to have a noticeable impact on 60 min axial scans. A 100-fold increase of the permeability in the region more than 30° (central angle) from the optical center of the eye leads to just a 2-fold increase of the apparent common permeability. Thus, axial vitreous fluorophotometry almost exclusively measures the condition of the retina in the vicinity of the optical center. Invest Ophthalmol Vis Sci 30:1522–1526, 1989

The blood–retinal barrier consists of the pigment epithelium and the endothelial linings of the retinal vessels. The barrier is normally almost impermeable to all but a few water-soluble substances necessary for the metabolism of the retina (glucose and certain amino acids). The faint leakage can, however, become highly increased under pathological conditions (notably diabetic retinopathy).

Vitreous fluorophotometry aims at quantifying such leakage. A water-soluble fluorescent substance (sodium fluorescein) is injected intravenously and during its circulation in the bloodstream, it permeates the blood–retinal barrier and diffuses into the vitreous body. An optical technique exists for measuring the concentration of fluorescein in small volumes of the vitreous body. Current equipment allows concentration scans to be performed along the optical axis of the eye. During an examination, the concentration of fluorescein in the bloodstream is monitored by analyzing blood samples taken 5, 15, 30, 60 and 120 min after the injection.

To relate fluorophotometric scans to the condition of the blood–retinal barrier, a method for the estimation of the barrier permeability has previously been developed. In this method—as well as in other similar methods—the barrier is assumed to have a uniform permeability.

In diseased eyes this assumption does not hold, as witnessed by fluorescein angiography, where leakage is typically seen to be concentrated in small areas. Even the normal barrier is probably not completely homogeneous, but in pathological circumstances the assumption of homogeneity becomes clearly invalid. It has been unknown to what extent such inhomogeneity affects the determination of permeability by current methods. In particular, it is important to know how far from the optical axis a leakage spot can be located before it no longer affects the axial measurements.

The purpose of the current study is to propose a mathematical model for the diffusion across an inhomogeneous blood–retinal barrier, so that it will be possible to calculate the contribution of a point source to axial measurements. The equations of the model are solved using a numerical method and the results are used to investigate the effect on the permeability values obtained from current methods when the point source is located at different distances from the optical axis. The same method allows for the cal-
culation of the effect of a highly increased permeability in the entire peripheral region.

Materials and Methods

Larsen et al.4 formulated a system of differential equations describing diffusion into the eye through a homogeneous barrier. The model below is an extension of that model, accommodating an inhomogeneous barrier.

The equation for passive diffusion in a homogeneous region of space is7

\[ \frac{\partial c}{\partial t} = D \Delta c \]  

where \( \Delta \) (the Laplacian) can be written in spherical coordinates as

\[ \Delta = \frac{\partial^2}{\partial r^2} + \frac{2}{r} \frac{\partial}{\partial r} + \frac{1}{r^2} \left[ \frac{\partial^2}{\partial \theta^2} + \cot \theta \frac{\partial}{\partial \theta} + \frac{1}{\sin^2 \theta} \frac{\partial^2}{\partial \phi^2} \right] \]  

where \( c = c(r, \theta, \phi; t) \) is the concentration, \( D \) is the diffusion coefficient, \( t \) is time, \( r \) is the distance from the center of the eye, and where \( \phi \) and \( \theta \) give the direction in terms of longitude and colatitude, respectively.

Introducing an inhomogeneous barrier, the boundary condition is

\[ D \frac{\partial c}{\partial r}(R, \theta, \phi; t) = P(\theta, \phi)(c_+(t) - c(R, \theta, \phi; t)) \]  

where \( R \) is the radius of the eye, \( c_+ \) is the plasma concentration and \( P(\theta, \phi) \) is the local permeability. The condition states that the flux per unit area through the barrier at \( (R, \theta, \phi) \) is proportional to the difference between the plasma concentration and the concentration immediately inside the barrier.

Finally, the initial condition is that the fluorescein concentration is zero throughout the eye before the injection of fluorescein:

\[ c(r, \theta, \phi; 0) = 0 \]  

We have only considered cases where \( P \) does not depend on \( \phi \). The model is then essentially two-dimensional and can be solved numerically using an adaptation to spherical coordinates of the ADI (Alternating Direction Implicit) method.8,9 The procedure is outlined in the Appendix.

Regarding the specific choices of permeability functions, it was of primary interest to investigate the solution corresponding to a permeability concentrated in a small area, ideally in a single point. However, the numerical method required a reasonably smooth permeability function; therefore, a compromise had to be made. We have used the following type of functions:

\[ P(\theta) = \begin{cases} 1 & (\theta < 0.1) \\ 1 - \frac{\theta}{0.1} & (0.1 \leq \theta < 1) \\ 0 & (\theta \geq 1) \end{cases} \]  

This models a point source at the optical center of the eye, results for sources at other locations being obtained by a rotation of the solution. In equation (5), \( \theta \) is measured in radians. When \( R \) is 12 mm, 0.1 radians correspond to increased leakage in an approximately plane area with a diameter of 2.4 mm; however, since the permeability decreases from the center towards the edge of the point source, the strength of the leakage is equivalent to a value of \( P_{\text{peak}} \) throughout an area with a diameter of 1.4 mm.

We have also worked with permeability functions where a background permeability was assigned to the central region and a larger permeability was assigned to the entire peripheral region, leading to the following expression:

\[ P(\theta) = \begin{cases} 1 & (\theta < 0.01) \\ (1 - \frac{\theta}{0.01}) & (0.01 \leq \theta < 1) \\ 0 & (\theta \geq 1) \end{cases} \]  

We have assumed the standard value \((6 \times 10^{-6} \text{ cm}^2/\text{sec})\) for the diffusion coefficient \( D \). The radius of the eye, \( R \), was set to 12 mm. The plasma curve was chosen to be the one published by Lund-Andersen et al.3

The numerical simulation enabled us to calculate the concentration profiles one would obtain in an axial scan if the point source was situated in a given position. For these simulated scans, we calculated the apparent permeability by using them as input to our program for determination of homogeneous \( P \)-values from axial scans. Similarly, we could calculate the increase in apparent permeability in the presence of heavy peripheral leakage.

Results

In this and the following section, angular measures are given as degrees in order to facilitate the interpretation of the results.

For a pure point source \((P_{\text{background}} = 0 \text{ cm/sec}; P_{\text{peak}} = 5 \times 10^{-6} \text{ cm/sec})\), a contour plot of the resulting 60 min concentration distribution is shown in Figure 1. The concentration is seen to decay rapidly away from the point source.

Figure 2 shows the apparent permeability calculated from simulated measurements of the fluorescein concentration in the vitreous body along the optical axis of the eye. The curves show the results obtained for two point sources of different strengths, added to a uniform background permeability and placed at varying distances from the optical axis.

For reference, curve 1 shows results for a constant...
In the mathematical simulations, the eye is modeled as a sphere. The figure shows a cross-section of the sphere with curves of equal concentration, 60 min after injection of fluorescein, when the permeability is large in a small area around 0° and zero elsewhere.

Curve 1 shows how the apparent permeability is increased when a point source (P_{peak} = 5 \times 10^{-6} \text{ cm/sec}) is added at various distances from the axis where measurements are taken. It is also seen that the increase disappears quickly as the point source is moved away from the axis. At 20° from the axis, the contribution is less than 10%.

Curve 3, which arises from a much stronger point source (P_{peak} = 25 \times 10^{-6} \text{ cm/sec}), displays the same features as curve 2. It is seen that even though the apparent permeability is increased by a factor of 18 if the point source is close to the optical axis, the increase is reduced to less than 15% when the point source is located 30° from the axis.

Figure 3 shows the result when strong peripheral leakage is present in the entire region outside 30°. Here, the data are presented in terms of the calculated concentration scans. The lower curve shows a scan corresponding to a uniform permeability of 10^{-7} \text{ cm/sec}. The upper curve shows a scan when the leakage outside 30° is increased to 10^{-5} \text{ cm/sec}. The apparent permeability corresponding to the latter curve is only 1.93 \times 10^{-7} \text{ cm/sec}.

Discussion

We have developed a model, enabling us to study the sensitivity of axial fluorophotometry to inhomogeneity of the blood-retinal barrier permeability.

This has been done for point sources located at varying distances from the axis as well as for a uniformly increased permeability in the periphery.

The model shows that a leakage spot about the size of the optic nerve head, having a permeability 250 times larger than the rest of the retina, has very little influence on the axially measured concentration profile if it is located more than 30° (central angle) from the posterior pole. Even a 100-fold increase of the permeability in the entire region outside 30° from the posterior pole yields only a doubling of the apparent permeability.

These results indicate that axial fluorophotometry can be interpreted as an expression of the permeability in the area within the large temporal vessels.

We know from angiograms of diabetic retinopathy that there can be substantial inhomogeneity of the leakage and that leakage spots can show strong hyperfluorescence in the region outside the temporal vessels. Only if the permeability in these areas is 250 times larger than in the macular region will the axially measured concentration (and thereby the permeability calculation) be affected. At present, it is unknown how large the permeability is in these localized leakage spots, but preliminary results indicate...
that it is considerably less than 250 times the permeability in the macular region. However, further research in the determination of the local permeability is necessary to determine whether peripheral leakage, as observed clinically, can affect axial fluorophotometry. This work is in progress.

In the model, it is assumed that the vitreous body is a homogeneous gel in which only passive diffusion takes place. In case of the collapse of the vitreous body, which can occur following intracapsular cataract extraction or related to trauma, aging, myopia, diabetes and retinitis pigmentosa, the convective forces contribute to a much faster distribution of fluorescein in the vitreous body, so that the axial fluorescein concentration reflects the condition of the entire retina, including the anterior part. Therefore, an evaluation of the condition of the vitreous body by slitlamp examination and by inspection of the fluorescein concentration profile is necessary in order to use the present results in practice. Also, convective forces in a seemingly intact vitreous gel will interfere with the conclusions. Thus, the model calculations have their limitations. However, the model calculations can also be used to study deviations from simple diffusion kinetics and thereby provide information on basic physiological and pathological transport processes within the eye.

Key words: vitreous fluorophotometry, blood–retinal barrier, spatial sensitivity, diffusion, mathematical model

References


Appendix

This section gives the details of the adaptation to spherical coordinates of the ADI method.

We use the transformation \( u = r \xi \), whereby the condition of a continuous solution across the origin is replaced by the more tractable \( u = 0 \). An approximate solution of the differential equation is obtained at the gridpoints \( (r_i, \xi_i) \), \( r_i = \Delta r, \xi_i = j \Delta \xi, \xi_i = k \Delta t \) where \( \Delta r = R/N, \Delta \xi = \pi/M, \Delta t = T/K \). The value of the approximate solution at \( (r_i, \xi_i) \) in the \( k \)-th time step is denoted \( u_{ij}^{(k)} \). The vectors of values corresponding to fixed \( i \) or \( j \) are denoted \( u_i^{(k)} \) and \( u_j^{(k)} \), please note that these are all column vectors.

The ADI method consists of alternatingly solving two sets of tridiagonal linear systems:

\[
A_i^j u_i^{(k+1/2)} = z_i^{(k+1/2)}, \quad j = 0, \ldots, M
\]

and

\[
A_j^i u_j^{(k+1)} = z_j^{(k+1)}, \quad i = 1, \ldots, N
\]
The right-hand sides of these equations are given by the following recurrence relation:

\[ x^{(k+1/2)} = 2u^{(k)} - x^{(k)} + \frac{\Delta t}{2} b^{(k+1/2)} \]

Using the convention that a tridiagonal matrix is specified by calling the nonzero elements of the p-th row \( \alpha(p) \), \( \beta(p) \) and \( \gamma(p) \) (the first \( \alpha \) and the last \( \gamma \) being undefined) and letting \( \rho_r = D \frac{\Delta t}{\Delta r^2} \) and \( \rho_s = D \frac{\Delta t}{r^2 \Delta \theta^2} \), the coefficient matrices \( \Lambda_r \) and \( \Lambda_s \) are:

\[
\begin{align*}
\beta_r(1) &= 1 + \rho_r \\
\gamma_r(1) &= -\rho_r/2 \\
\alpha_r(i) &= -\rho_r/2
\end{align*}
\]

\[
\begin{align*}
\beta_s(0) &= 1 + 2\rho_s \\
\gamma_s(0) &= -2\rho_s \\
\alpha_s(j) &= -\rho_s/2 \left( 1 + \frac{\Delta \theta}{2} \cot \theta \right)
\end{align*}
\]

\[
\begin{align*}
\beta_r(N) &= 1 + \rho_r \\
\gamma_r(j) &= -\rho_r/2 \\
\alpha_r(M) &= -\rho_r
\end{align*}
\]

\[
\begin{align*}
\beta_s(N) &= 1 + \rho_s \\
\gamma_s(0) &= -\rho_s/2 \left( 1 + \frac{\Delta \theta}{2} \cot \theta \right) \\
\alpha_s(i) &= -\rho_s/2 \left( 1 + \frac{\Delta \theta}{2} \cot \theta \right)
\end{align*}
\]

\[
\begin{align*}
\beta_s(M) &= 1 + 2\rho_s \\
\gamma_s(j) &= -2\rho_s \\
\alpha_s(i) &= -\rho_s/2 \left( 1 + \frac{\Delta \theta}{2} \cot \theta \right)
\end{align*}
\]

Finally, the specification for \( b^{(k)} \) is:

\[
\begin{align*}
b_r^{(k)} &= \frac{2}{\Delta r} P(\theta) R_c(t_i), \quad i = N \\
b_s^{(k)} &= \frac{2}{\Delta \theta} P(\theta) R_c(t_i), \quad i < N
\end{align*}
\]

For point sources, the resolution employed by the procedure was \( (N = 50, M = 500, K = 50) \). For the central/peripheral type of permeability function M was reduced to 200.