Glaucoma

A Theoretical Model to Allow Prediction of the CSF Pressure From Observations of the Retinal Venous Pulse

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PURPOSE. There is no easy way to estimate the intracranial pressure (ICP) noninvasively. The retinal vein can exhibit large amplitude oscillations at the level of the lamina cribrosa under certain circumstances. The aims of this study were to develop a theoretical understanding of the conditions required to establish this vigorous oscillatory behavior and to determine whether observations of it could lead to a noninvasive estimate of the ICP.

METHODS. A mathematical model was constructed in which the central retinal vein was modeled as 2 Starling resistors in series, 1 located in the eye and the other in the cerebrospinal fluid (CSF) space, separated by a region where it was not collapsible, corresponding to its course within the optic nerve itself. Intraocular pressure (IOP) and ICP were modeled as sinusoidal wave forms.

RESULTS. The model predicted an approximately linear relationship between the IOP and the ICP at the point of onset of oscillatory behavior. The predicted onset IOP also depended weakly on the retinal blood flow rate and on vein diameter and was only mildly sensitive to the phase difference between the two pressure waveforms. The predicted onset curve showed encouraging agreement with measurements in canines.

CONCLUSIONS. The model suggested that it may be possible to estimate the ICP from observations of the retinal venous pulse by using a modified form of ophthalmodynamometry.

Keywords: cerebrospinal fluid pressure, glaucoma, retinal venous pulse

The mechanism of disease in glaucoma is postulated to be damage to the optic nerve generated by increased intraocular pressure (IOP). However, it is well known that, in ocular hypertension, some individuals can exhibit raised IOP and yet not develop glaucoma, whereas other individuals develop glaucoma despite having IOP within the normal range. While it is easy to measure a person’s blood pressure, there is no accepted way to measure a person’s CSF pressure noninvasively, despite a number of attempts including transcranial Doppler ultrasonography, tympanic membrane displacement, optic nerve sheath diameter, and magnetic resonance imaging or computed tomography imaging. However, none of these methods was considered accurate or reliable enough for routine clinical use. There was a report of a strong correlation between CSF pressure and IOP, but that finding has not been confirmed by others.

In this study, we hypothesized that retinal venous pulsation (RVP) could be used as a novel method to estimate ICP noninvasively. The retinal venous pulse was first observed by Coccius in 1855 and is present in 90% of healthy subjects. This pulsation has long been noted to be absent in cases of raised intracranial hypertension and disappearing at an ICP of 19 cm H2O; the retinal venous pulse is also reduced by a reduction in IOP.10 Correlations between retinal venous collapse,10,11 retinal venous outflow pressure,10,11 and decreased pulsatility11 and ICP have all been observed.

This study developed a theoretical model for the onset of RVP by using the theoretical model of Levine12 as a starting point, which is based on constant in-flow and variable out-flow. Key assumptions in Levine’s model were that IOP was always higher than ICP and that the two were always in phase, allowing the author to neglect changes in the retinal vein as it crossed the CSF space. Levine’s model predicted that collapse of the retinal vein correlates with the peak IOP rather than the trough.13 However, recent clinical observations indicate that RVP is, instead, in phase with the pulse pressure in the CSF,14 undermining the assumption that fluctuations in the ICP can be ignored. Accordingly, the model developed herein took both compartments into account. It describes blood flow through the central retinal vein, accounting for changes in IOP and ICP independently, allowing examination of how the onset of RVP is modified by these two pressures. Importantly, the model also accounts for the spatial distribution of the flow, allowing prediction of the shape of the vessel wall and the blood flow profile along the vein; these quantities can only be approximated using more traditional models of the retinal vasculature.15 The model predicted that for fixed (mean) ICP, increasing the IOP through a threshold results in the flow...
Mean vein diameter 152.8 μm to understand the onset of RVP.

Phase difference between IOP and ICP Variable

Flow rate into the vein 44 L min⁻¹

Density of blood 1 g/cm³

Viscosity of blood 0.004 Pa s

Parameter Values Used in the Mathematical Model*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Typical Value</th>
<th>Study Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>Viscosity of blood</td>
<td>0.004 Pa s</td>
<td>22</td>
</tr>
<tr>
<td>ρ</td>
<td>Density of blood</td>
<td>1 g/cm³</td>
<td>22</td>
</tr>
<tr>
<td>L₁</td>
<td>Length of compartment I</td>
<td>1 mm</td>
<td>26</td>
</tr>
<tr>
<td>L₁₁</td>
<td>Length of compartment I</td>
<td>10 mm</td>
<td>27</td>
</tr>
<tr>
<td>L₁III</td>
<td>Length of compartment III</td>
<td>1 mm</td>
<td>28</td>
</tr>
<tr>
<td>L₁IV</td>
<td>Length of compartment IV</td>
<td>10 mm</td>
<td></td>
</tr>
<tr>
<td>T₁</td>
<td>Venous wall tension in compartment I</td>
<td>0.112 Pa m⁻¹</td>
<td></td>
</tr>
<tr>
<td>T₁III</td>
<td>Venous wall tension in compartment III</td>
<td>0.112 Pa m⁻¹</td>
<td></td>
</tr>
<tr>
<td>Pₒ</td>
<td>Outlet pressure</td>
<td>0 mm Hg</td>
<td></td>
</tr>
<tr>
<td>P₁</td>
<td>Mean intra-ocular pressure</td>
<td>15–35 mm Hg</td>
<td></td>
</tr>
<tr>
<td>A₁</td>
<td>Amplitude of the intra-ocular pressure</td>
<td>2 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Pᵦᵣ</td>
<td>Mean cerebrospinal fluid pressure</td>
<td>~5 to 20 mm Hg</td>
<td></td>
</tr>
<tr>
<td>τ</td>
<td>Phase difference between IOP and ICP</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Ω</td>
<td>Frequency of arterial pulsations</td>
<td>0.75 Hz</td>
<td></td>
</tr>
<tr>
<td>Q</td>
<td>Flow rate into the vein</td>
<td>44 L min⁻¹ (40–60 L min⁻¹)</td>
<td>29</td>
</tr>
<tr>
<td>d</td>
<td>Mean vein diameter</td>
<td>152.8 μm (150–225 μm)</td>
<td>29, 30</td>
</tr>
<tr>
<td>Aᵦᵣ</td>
<td>CSF pressure amplitude</td>
<td>2 mm Hg</td>
<td>31, 32</td>
</tr>
</tbody>
</table>

* The method for estimating the mean vein diameter is described in the Supplementary Material.
transition to RVP in the normally observed physiological range. In practice, the vessel wall tension will be a patient-specific parameter. Given measurements of ICP and IOP, this parameter can be inferred for an individual patient by using the results presented in Supplementary Figure S2. This value of the vessel tension can then be used to estimate the ICP noninvasively at a later date, although it is expected that the elastic properties of the vein wall will change gradually due to aging.

### RESULTS

For constant IOP (setting $A_1 = 0$ mm Hg), the model prediction of the channel constriction in the eye compartment (region I) is illustrated as the solid line in Figure 2a as a function of time over a complete period of ICP oscillation (Fig. 2a, dashed line), with a mean IOP of $P_I = 18.0$ mm Hg and a mean ICP of $P_{II} = 0$ mm Hg. For these parameter values, the wall of the vessel in compartment I exhibited a small amplitude oscillation of a frequency identical to that of the ICP but a quarter cycle out of phase (Fig. 2a, dashed line). However, when the mean IOP was increased to $P_I = 18.5$ mm Hg, the vessel wall in compartment I exhibited a transient violent oscillation of much higher frequency than that of the ICP pulsation (Fig. 2b), consistent with the onset of RVP in the vein at the optic disc. The critical value of IOP where onset was observed is a function of ICP but also the RBF $Q$, the vein diameter $d$ and the vessel tension $T$. The dependency on each of these parameters is explored in the Supplementary Material. Briefly, in the range of $Q$, considered the onset, IOP varied by approximately 3.8 mm Hg; in the range of $d$, the onset IOP varied by approximately 6 mm Hg. In the examples shown in Figure 2, the vessel wall in compartment III oscillated with small amplitude in phase with the arterial pulsation, whereas the oscillations in IOP are offset by a constant phase shift, $\tau$. This simple sinusoidal model of ICP and IOP is sufficient to explain the mechanisms generating RVP.

The blood flow along the vein is calculated subject to these boundary conditions by solving the Navier-Stokes equations along the region of interest, representing conservation of mass and conservation of momentum in the fluid; the model is considerably simplified by assuming that the length of each compartment is significantly greater than the diameter of the vessel; the resulting system of equations is closed by assuming that the flow profile is locally parabolic and was solved in MATLAB software (MathWorks, Natick, MA, USA) by using a numerical method previously described and used.$^{18}$ The model predicted the flow rate of the blood along the vein, $q$, the blood pressure along the vein, $p$, and the shape of the flexible wall in the two compliant compartments, denoted $d_I$ and $d_{II}$ respectively, each as a function of the distance $x$ along the vein measured from the optic disc and time $t$. These model outputs are summarized in Table 2, and the full equations solved are presented in equation 8 (a–g) in the Supplementary Material.

The values chosen for the model parameters are listed in Table 1. All these values can be estimated reliably apart from the vessel tension $T$ in the vein wall. The simulations below used a reasonable value for which the system exhibited vigorous oscillations reported using similar models.$^{19,20}$ Where the vein becomes highly constricted at one or more points over a period, but the walls are prevented from making contact due to the inertia of the flow in the downstream segments.

The dependency of the threshold mean IOP value $P_I$ on the mean ICP $P_{II}$ is illustrated in Figure 3. In the region above and to the left of the curve formed by open circles and solid lines (Fig. 3), the model predicts RVP. The model predicts a clear demarcation between weak pulsation and RVP. For mean ICP values less than 5 mm Hg, the onset IOP is constant.

### Table 2. Variables Used in the Mathematical Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t$</td>
<td>Time</td>
</tr>
<tr>
<td>$x$</td>
<td>Distance along the vein from the optic disc</td>
</tr>
<tr>
<td>$U_0$</td>
<td>Mean flow velocity along the vein</td>
</tr>
<tr>
<td>$q(x,t)$</td>
<td>Flow rate along the vein</td>
</tr>
<tr>
<td>IOP$(t)$</td>
<td>Intraocular pressure</td>
</tr>
<tr>
<td>ICP$(t)$</td>
<td>Intracranial pressure</td>
</tr>
<tr>
<td>$p(x,t)$</td>
<td>Blood pressure along the vein</td>
</tr>
<tr>
<td>$d_I(x,t)$</td>
<td>Constriction of the vein in compartment I</td>
</tr>
<tr>
<td>$d_{II}(x,t)$</td>
<td>Constriction of the vein in compartment III</td>
</tr>
</tbody>
</table>

 prescribed at the outlet of compartment IV, denoted $P_0$, where the central retinal vein joins the ophthalmic vein.

In the model, both IOP and ICP are assumed to oscillate with a simple sinusoidal waveform around a known mean with constant frequency, $\Omega$. The mean IOP is denoted $P_I$, and the amplitude of the IOP oscillation is denoted $A_I$. Similarly, the mean ICP is denoted $P_{II}$, and the amplitude of oscillation is denoted $A_{II}$; oscillations in ICP are assumed to be in phase with the arterial pulsation, whereas the oscillations in IOP are offset by a constant phase shift, $\tau$. This simple sinusoidal model of ICP and IOP is sufficient to explain the mechanisms generating RVP.

The blood flow along the vein is calculated subject to these boundary conditions by solving the Navier-Stokes equations along the region of interest, representing conservation of mass and conservation of momentum in the fluid; the model is considerably simplified by assuming that the length of each compartment is significantly greater than the diameter of the vessel; the resulting system of equations is closed by assuming that the flow profile is locally parabolic and was solved in MATLAB software (MathWorks, Natick, MA, USA) by using a numerical method previously described and used.$^{18}$ The model predicted the flow rate of the blood along the vein, $q$, the blood pressure along the vein, $p$, and the shape of the flexible wall in the two compliant compartments, denoted $d_I$ and $d_{II}$ respectively, each as a function of the distance $x$ along the vein measured from the optic disc and time $t$. These model outputs are summarized in Table 2, and the full equations solved are presented in equation 8 (a–g) in the Supplementary Material.

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**FIGURE 3.** Threshold IOP for transition from weak pulsation to RVP for a range of ICP for constant IOP (solid line and open circles) and oscillatory IOP (dashed line and crosses) for a phase shift of half a cycle. Other parameters are listed in Table 1. Also included are the canine measurements of Morgan et al.23 for the “venous pulse pressure.”

approximately 18.5 mm Hg for these parameter values. For larger values of mean ICP (greater than 5 mm Hg), the onset IOP increases approximately linearly. This onset curve is in clear qualitative agreement with the canine measurements of “venous pulse pressure” reported by Morgan et al.,23 and their lines of best fit are shown in Figure 3 (filled circles and dotted lines). The onset curve is also qualitatively consistent with earlier experimental work correlating CSF pressure with venous pressure at the head of the optic nerve24 or the onset of RVP.25 Examining the minimal construction of the vein in compartments I and III for ICP values less than 5 mm Hg, the vein wall was inflated in compartment III, whereas for ICP values greater than 5 mm Hg, the vein was collapsed in compartment III for at least some interval of a period of oscillation (see Supplementary Material). Hence, the kink in the onset curve for RVP in Figure 3, and as evident in the canine data,25 is hypothesized to be driven by collapse of the vein in the nerve sheath. Generally both the IOP and ICP are oscillatory functions of time separated by a constant phase shift, τ. Simulations of the model for various τ values indicated that the qualitative behavior of the system was similar to the simplified system outlined above, where the wall of the vein at the rear of the eye exhibited a transition from small amplitude oscillation to RVP when the mean IOP exceeded a threshold. This threshold intraocular pressure depends on the phase shift, varying over a range of approximately 1.5 mm Hg for mean ICP of 0 mm Hg (see Supplementary Material). As in the simplified case, the critical mean IOP for the onset of high-frequency oscillations in compartment I is illustrated as a function of the mean ICP in Figure 3, as the curve formed by crosses and dashed lines, for an illustrative phase shift of half a cycle; this curve again exhibits a plateau for low mean ICP and a linear increase for large ICP.

**DISCUSSION**

RVP can be striking, with localized violent oscillations of the segment of vessel where it exits the eye. This is a distinct phenomenon from the small amplitude pulsations that can affect a much larger extent of the vascular tree.

In this study a mathematical model was constructed to understand the onset of RVP as a function of the IOP and ICP, predicting a clear demarcation line (Fig. 3) separating small-amplitude oscillations from vigorous large-amplitude oscillations, consistent with RVP; these violent oscillations exhibited features similar to the “slamming” oscillations described in theoretical models of flow through flexible-walled channels.19,20

Two encouraging features emerge from this model. First, the threshold for the onset of large amplitude oscillations appears to be an approximately linear relationship between the IOP and the CSF pressure over a significant range, consistent with measurements in canines22; second, our predictions show only a modest dependency on the phase shift between the IOP and the ICP oscillations, for the model parameters chosen, the maximal difference in the predicted onset IOP was 1.5 mm Hg across the range of phase shift. This finding was of practical importance as there is no simple way to observe the phase shift.

The model uses parameter values obtained from the literature (Table 1) and considers IOP and ICP in the typical physiological range. However, it contains one free parameter that could not be reliably estimated, the vessel tension in the wall of the retinal vein (this parameter can only be estimated in vivo). This study used a reasonable value such that the model exhibited transition to RVP in the physiological range. In practice, this parameter will be patient-specific and can be estimated using other methods for ICP measurement.

It is possible to vary the IOP while observing the behavior of the retinal blood vessels at the optic disc by ophthalmodynamometry. Thus, it may be possible to obtain a reasonable estimate of the ICP by noting the IOP at which the onset of RVP is observed to occur and by using the results from relationships such as that shown in Figure 3.

This model suggested that one can estimate the CSF pressure by observations of the retinal venous pulse in a noninvasive manner. There are a number of potential clinical applications, including the possibility of large scale observational studies which are required to help distinguish between some of the competing hypotheses for the mechanism of optic nerve damage in glaucoma.

The model described herein is presented as a proof of concept, providing a rational mechanical basis for the possibility of using the onset of RVP as a noninvasive method to estimate ICP. However, the model uses an idealized representation of the elastic vessel wall (neglecting bending stiffness), assumes simple sinusoidal waveforms for the ICP and IOP and neglects pulsatility in the inlet flow into the vein. The model also assumes that the diameter of the vein is constant along its length and ignores bifurcations. The proposed mathematical model will require refinement to address these issues before the results can be used clinically. Nonetheless, the model predictions show excellent qualitative agreement with canine measurements and form a useful basis for further studies. In addition, the model elucidated the pressure gradient along the entire course of the central retinal vein; this could be incorporated into a spatial model to predict the retrolaminar tissue pressure and its correlation with IOP (measured by Morgan et al.25). However, this is deferred for future work.

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**References**

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