Idiopathic intracranial hypertension and transverse sinus stenosis: a modelling study

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Idiopathic intracranial hypertension (IIH) is a syndrome of unknown etiology characterized by elevated intracranial pressure (ICP). Although a stenosis of the transverse sinus has been observed in many IIH patients, the role this feature plays in IIH is in dispute. In this paper, a lumped-parameter model is developed for the purpose of analytically investigating the elevated pressures associated with IIH and a collapsible transverse sinus. This analysis yields practical predictions regarding the degree of elevated ICPs and the effectiveness of various treatment methods. Results suggest that IIH may be caused by a sufficiently collapsible transverse sinus, but it is also possible that a stenosed sinus may persist following resolution of significant intracranial hypertension.

Keywords: lumped-parameter model; intracranial pressure; idiopathic intracranial hypertension; cerebrospinal fluid; venous sinus.

1. Introduction

Idiopathic intracranial hypertension (IIH), also called pseudotumour cerebri and benign intracranial hypertension, is a syndrome of unknown cause characterized by elevated intracranial pressure (ICP) without evidence of ventricular dilatation, mass lesion, cerebrospinal fluid (CSF) abnormality or dural sinus thrombosis. It presents with symptoms of headache, nausea, vomiting, papilledema and visual obscurations (Binder et al., 2004). In many patients suffering from IIH, a stenosis or tapering of the

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transverse sinuses is observed by magnetic resonance venography or retrograde catheter venography (Farb et al., 2003; Higgins & Pickard, 2004; King et al., 2002). The role played by transverse sinus stenosis in the etiology of IIH has been a matter of some dispute.

Bateman (2004) has suggested that a compressible transverse sinus is associated with the development of IIH and proposed that the syndrome develops as the result of an unstable pressure spiral initiated by a precipitating event. Several reported studies involving a small number of patients in which venous stenting resolved IIH lend further support to the hypothesis that a stenosis plays a role in the development of IIH (Higgins et al., 2003; Owler et al., 2003). However, King et al. (2002) report the disappearance of the pressure gradient across the transverse sinus and resolution of the stenosis with CSF drainage. As a result, they inferred that sinus stenosis was not the cause of IIH, but a secondary phenomenon or an exacerbating factor which may be caused by the hypertension. King’s findings have been confirmed by others who have reported the disappearance of the stenosis on imaging after CSF drainage or diversion procedures (Baryshnik & Farb, 2004; Higgins & Pickard, 2004; McGonigal et al., 2004). More recently, Bono et al. (2005) report that the transverse sinus stenosis in their study persists even after CSF pressure has been normalized in all patients who presented with a stenosis. They conclude that there is no direct relationship between the degree of transverse sinus stenosis and CSF pressure.

A recent modelling study by Stevens et al. (2005b) suggests that the observed tapering of the sinus and the persistent hypertension of IIH may be a physiological manifestation of a stable steady state of elevated pressures predicted, by the model, to exist when the transverse sinus is sufficiently collapsible rather than rigid. In that study, a collapsible transverse sinus was represented by a downstream Starling resistor in a lumped-parameter model of the intracranial system and the elevated steady state came into existence by means of a saddle-node bifurcation in the parameter domain. Due to the complexity of their model, explicit descriptions of the steady-state solutions were not attainable. The model developed here is a simplified version of their model and is designed to focus on the relationship between CSF and venous sinus pressures in the presence of a collapsible drainage pathway. In consideration of this refined focus, the current model retains the relevant features of the previous model. Specifically, (1) a variably compressible transverse sinus is represented by a downstream Starling-like resistor, (2) a stable steady state of elevated CSF pressures is created by a saddle-node bifurcation in the parameter domain and (3) model simulations can predict CSF and venous sinus pressure responses to various stimuli.

The current model is simple enough to allow for explicit analysis of the steady-state solutions. This analysis focuses on the ICP levels associated with the stable elevated pressure state. Treatment methods for IIH are simulated as a step towards determining optimal interventions. Results also indicate that under certain conditions, the transverse sinus stenosis may persist, even after CSF pressure has been normalized. This theoretical result reproduces and helps explain the clinical results of Bono as well as those presented by King et al.

Lumped-parameter models are generally analogous to electrical models, and the one presented here is analogous to a nonlinear resistor–capacitor circuit with voltage-sensitive resistors and capacitors. While a considerable body of literature exists regarding the bifurcation theory of nonlinear electrical models (see, e.g. Ajjarapu & Lee, 1992; Canizares, 1995), very little exists for lumped-parameter models of intracranial fluid dynamics. This is because previous mathematical models have considered the sinuses rigid (Sorek et al., 1988; Stevens & Lakin, 2001; Stevens et al., 2005a; Ursino, 1988), and collapsible veins were modelled with ‘upstream’ Starling-like resistors (Ursino, 1988; Czosnyka et al., 1997b; Piechnik et al., 2001). Under these conditions, multiple steady-state solutions are not obtained, and thus bifurcation theory does not apply. However, the model presented here does have multiple steady-state solutions. So, in addition to analysing the extent of the elevated pressure steady state, special attention is also paid to the bifurcations that create and destroy the steady-state solutions.
2. The model

The lumped-parameter model developed for this study is a simplified version of the model formulated by Stevens et al. (2005b) to study IIH. While retaining the relevant features of that model, the present simplifications allow steady-state solutions for the pressure fields to be explicitly expressed in terms of the various model parameters.

In the present lumped-parameter model, consistent with previous models of this type (Karni et al., 1987; Sorek et al., 1988; Stevens et al., 2005a), the intracranial region is divided into interacting subunits termed ‘compartments’. For this study, the intracranial region is divided into the four compartments depicted in Fig. 1. Compartment C consists of the intracranial arteries and capillaries. This vasculature leads into the veins and sagittal sinus which are represented by compartment S. Blood then drains through the transverse sinuses and into the jugular veins in compartment V. Brain tissue and the associated intra- and extracellular fluid are combined with the CSF to form compartment F. The present model contains one extracranial compartment, namely, the thoracic space, which is represented by compartment Y.

![Diagram of the lumped-parameter model](image-url)

**Fig. 1.** A diagram of the lumped-parameter model. Compartment labels are indicated in parentheses. The dark line represents the rigid cranial wall and thin lines separate compartments. \( Q_{ij} \) represents fluid flow from compartment \( i \) to compartment \( j \). Arrows indicate the customary direction of flow. \( Q_{inf} \) represents an infusion rate of CSF. The normal resting pressure of each compartment is represented by the number in brackets. The flows \( Q_{FS} \) and \( Q_{FV} \) are initially set at 75 and 25% of CSF production, respectively.
Clinically, the term ICP is used to describe both the CSF and brain pressures, which are nearly equal in healthy physiology (Stevens et al., 2005a). Hence, the term ICP will refer here to the CSF/brain pressure from both the clinical and current modelling perspective.

Pressure in each compartment $i$ is given in millimetres of mercury and denoted by $P_i$. For example, $P_F$ will denote the spatially averaged pressure in the brain/CSF compartment. Fluid flow or filtration from compartment $i$ to compartment $j$ is given in millilitres per minute and denoted by $Q_{ij}$. For example, $Q_{CS}$ represents the flow of blood from the capillaries into the veins. Likewise, $Q_{CF}$ represents fluid filtration from the capillaries and choroid plexuses into the brain and CSF system.

2.1 Model assumptions

The following basic assumptions lead to the time-dependent model’s differential equations that govern the pressure dynamics of this system:

1. All fluids are considered incompressible and isothermal.
2. The regulation of cerebral blood flow ($Q_{CS}$) and CSF production by the choroid plexus ($Q_{CF}$) over a full range of ICPs is described by Lakin et al. (2003). For the pressure ranges considered here, these regulatory mechanisms remain robust. Hence, for simplicity, constant rates will be assumed for both $Q_{CS}$ and $Q_{CF}$.
3. All other flows are related to pressure differences by the hydrodynamic version of Ohm’s law:

$$Q_{ij} = \frac{P_i - P_j}{R_{ij}} = Z_{ij}(P_i - P_j) = Z_{ij}P_{ij}, \quad (1)$$

where $Q_{ij}$ is the flow from compartment $i$ to compartment $j$, $P_i$ and $P_j$ are the spatially averaged pressures of compartments $i$ and $j$, respectively, $P_{ij} = P_i - P_j$, $R_{ij}$ is the lumped resistance and $Z_{ij}$ is the fluidity (inverse of $R_{ij}$).
4. Absorption of CSF via the arachnoid villi is considered unidirectional (Guyton & Hall, 2000; Welch & Friedman, 1960). This is achieved in the model by defining the fluidity $Z_{FS}$ through the relationship

$$Z_{FS} = \begin{cases} \bar{Z}_{FS}, & \text{if } P_F > P_S, \\ 0, & \text{if } P_F \leq P_S, \end{cases} \quad (2)$$

where $\bar{Z}_{FS}$ is constant to be determined in Section 2.3. A similar definition of $Z_{FV}$ assures that this parameter will also describe a one-way absorption route.

It has been previously argued that a portion of CSF absorption is via the extracranial lymphatic system (Boulton et al., 1998a,b; Bozanovic-Sosic et al., 2001). If this is indeed the case, then this drainage will eventually be deposited in the central veins and will also be unidirectional. Therefore, CSF absorption, as modelled here, will be indicative of flow either across the arachnoid villi or through the extracranial lymphatics.
5. A downstream Starling resistor has been placed between compartments S and V to allow a partially collapsible drainage route at the level of the transverse sinuses (Stevens et al., 2005b). In particular, the fluidity term $Z_{SV}$ will be allowed to fluctuate depending on the negative of the transmural pressure difference $P_F - P_V$. As the normal value of transmural pressure is negative at this location, the normal value of $P_F - P_V$ will be positive, and $Z_{SV}$ will decrease (increasing
resistance) as this pressure difference increases. In particular, the Starling-like fluidity $Z_{SV}$ will be defined here by

$$Z_{SV} = \max\{\overline{Z}_{SV}(1 - m(P_{FV} - \overline{P}_{FV})), p\overline{Z}_{SV}\}, \quad \text{where } 0 \leq p \leq 1 \text{ and } m \geq 0. \quad (3)$$

In (3), $P_{FV}$ and $\overline{Z}_{SV}$ represent the normal resting values of the pressure difference $P_{FV}$ and the fluidity $Z_{SV}$, respectively. A sample graph of the relationship between $Z_{SV}$ and $P_{FV}$ is shown in Fig. 2. A large value of $m$ represents a sinus that is initially very collapsible and a small value of $p$ represents sinuses which can collapse almost completely. In the normal healthy state, where the sinus is fully rigid, the parameters in (3) take the values $p = 1$ and/or $m = 0$.

6. The deformation of the membrane between adjacent compartments is a function of the change in the pressure difference between these compartments. That is,

$$\frac{dV_{ij}}{dt} = C_{ij} \frac{d}{dt}[P_i - P_j] = C_{ij} \dot{P}_{ij}, \quad (4)$$

where $V_{ij}$ denotes the volume of the ‘cup’ formed at the interface of compartments $i$ and $j$, and $\dot{P}_{ij}$ represents the time derivative of the pressure difference $P_{ij}$. Here, $C_{ij} = C_{ji}$ denotes the local compliance (Stevens & Lakin, 2001) between the two compartments.

7. Compartmental pressures are considered to be temporally averaged over one cardiac cycle, but the resulting compartmental variables are otherwise fully time dependent. The focus of this study is on the pressures $P_F$ and $P_S$. The hypothesis presented here is that IIH is a result of an abnormally collapsible transverse sinus and no other pathologies need exist in order for the symptoms to develop. Therefore, the pressure in compartments A, V and Y will be assumed constant and held at normal values.

![Fig. 2. A graph of the downstream Starling-like resistor in terms of the fluidity $Z_{SV}$ described by (3) when $m = 0.08$ and $p = 0.1$. The large dot indicates $(Z_{SV}, P_{FV})$ with a linearly decreasing portion of slope $-mZ_{SV}$. The minimum value of the fluidity is given by $pZ_{SV}$ and is represented by the horizontal portion of the curve.](image-url)
2.2 Governing equations

The model’s governing differential equations are obtained by imposing conservation of mass in each compartment. As the fluid is considered incompressible, this requirement is equivalent to a conservation of volume equation of the form

\[ \text{flow rate in} - \text{flow rate out} = \text{rate of volume change}. \]  

(5)

Imposing this constraint in compartments F and S results in the equations

\[ Q_{CF} + Q_{\text{inf}} - Q_{FS} - Q_{FV} = C_{FS} \dot{P}_{FS} + C_{FV} \dot{P}_{FV} + C_{CF} \dot{P}_{FC} + C_{FY} \dot{P}_{FY} \]  

(6)

and

\[ Q_{CS} + Q_{FS} - Q_{SV} = C_{FS} \dot{P}_{SF}, \]  

(7)

respectively. The \( Q_{\text{inf}} \) term has been included in (6) to allow for simulations of clinical CSF infusion tests. Applying Assumptions 2, 3 and 7, the model’s governing equations now become

\[ Q_{CF} + Q_{\text{inf}} - Z_{FS} P_{FS} - Z_{FV} P_{FV} = C_{FS} \dot{P}_{FS} + (C_{FV} + C_{CF} + C_{FY}) \dot{P}_{F}, \]  

(8)

\[ Q_{CS} + Z_{FS} P_{FS} - Z_{SV} P_{SV} = C_{FS} \dot{P}_{SF}. \]  

(9)

2.3 Parameter identification

Before analysing changes from a base state due to various stimuli, it is necessary to characterize this base state in terms of initial values for the variables and parameters involved in the model. These starting values have been obtained from available clinical data and will be referred to throughout this study as ‘base values’.

2.3.1 Base values for pressures, flows and fluidities. Base values for fluidities are determined by solving (1) for \( Z_{ij} \) given prescribed base pressures and flows. That is,

\[ Z_{ij} = \frac{O_{ij}}{P_{i} - P_{j}}. \]  

(10)

Consequently, we will first consider determination of base values for the mean flows \( \overline{O}_{ij} \) and pressures \( \overline{P}_{ij} \).

Calculations of the base-state blood pressures and flows begin with the cerebral blood flow \( \overline{Q}_{CS} \). This flow is considered to be 15% of total cardiac output (Guyton & Hall, 2000), which will be assigned a value of 6900 ml/min (Murgo et al., 1980). Intracranial artery pressure is assigned a value of 80 mmHg (Joshi et al., 1997; Olufson et al., 2004). Transverse sinus and jugular pressure will be assigned a base-state value of 5.4 mmHg (Katkov & Chestukhin, 1980; King et al., 2002). The base-state thoracic space compartmental pressure is irrelevant in the current study as only the derivative of the pressure in this compartment is required for the current simulations. The base state for the brain/CSF compartment is set at 11.00 mmHg (Albeck et al., 1991; Stevens et al., 2005a), and that of the veins and sagittal sinus is set at 7.82 mmHg (Stevens et al., 2005a). The value for normal CSF production \( \overline{Q}_{CF} \) is set at 0.43 ml/min (Friden & Ekstedt, 1983). Values for CSF absorption are based on the finding that 25% of
CSF absorption is via the spinal subarachnoid space in sheep (Bozanovic-Sosic et al., 2001). Therefore, $Q_{FV}$ is 25% and $Q_{FS}$ is 75% of the total CSF absorption, which in the steady state is the same as CSF production. A summary of these base-state parameters is included in Fig. 1. In this figure, base-state pressures ($P_i$) are given in brackets, and the base-state flows ($Q_{ij}$) are adjacent to each flow term. Each base-state fluidity is now determined by (1).

2.3.2 Compliances. The present pressure-dependent compliances in (4) are extensions of the compliance functions previously developed by Stevens & Lakin (2001). Their model consisted of four compartments: CSF (f), intracranial arteries (a), intracranial veins (b) and a 'rest-of-body' compartment (g). Lower-case compartmental designations were used in their presentation and will be retained here to differentiate between their compliances and those developed for the current model. There were three compliance terms in that model: $C_{af}$ (CSF/artery), $C_{fv}$ (CSF/vein) and $C_{fg}$ (CSF/rest-of-body). Of these, the first two were considered pressure-difference dependent and the last was considered constant. The pressure-difference-dependent compliance terms, which have a maximum when adjacent compartments have equal pressures and decrease as the magnitude of the pressure difference increases, were of the general form

$$C_{af}(P_{af}) = C^o_{af}e^{-r_{af}|P_{af}|\gamma_{af}},$$

$$C_{fv}(P_{fv}) = C^o_{fv}e^{-r_{fv}|P_{fv}|\gamma_{fv}}.$$  

Here, $C^o$ indicates the peak compliance value when pressure difference is zero. Stevens & Lakin (2001) performed infusion simulations and, by comparing results to clinical data, approximated parameter values in (11) and (12) to be

$$C^o_{fv} = 6.53, \quad r_{fv} = 0.63, \quad \gamma_{fv} = 0.60,$$

$$C^o_{af} = 1.83, \quad r_{af} = 0.82, \quad \gamma_{af} = 0.87.$$  

The constant compliance term was estimated by a similar process to be

$$C_{fg} = 0.13.$$  

This feature allowed inclusion of the interface between extracranial CSF in the spinal theca and the rest of the body outside of the confined intracranial space.

The compliance terms developed by Stevens & Lakin (2001) and described by (11)–(15) fit well in the present model as the compartmental structure in Fig. 1 is nearly identical to the model which led to these equations. Thus, reference values for compliances in the present model will be defined by

$$C_{CF} = C_{af}(P_{CF}),$$

$$C_{FS} = C_{fv}(P_{FS}),$$

$$C_{FV} + C_{FY} = C_{fg}.$$  

With the determination of these compliance terms, all required values and functions for model parameters have now been determined, and simulations predicting changes from the base state can be performed.
2.4 Model validation

Two sets of simulations were performed and compared to measured clinical data to validate the current model. In the first set, healthy physiology was assumed, and a steady-state infusion of CSF was simulated. The comparison quantity in these tests of model predictions is the conductance of CSF outflow, $C_{out}$, defined as

$$C_{out} = \frac{\text{the change in CSF absorption}}{\text{the change in CSF pressure}}.$$

In clinical determinations of $C_{out}$, a change in CSF absorption or pressure is induced by various constant rate or constant pressure CSF infusions. After each such infusion, sufficient time is allowed for CSF pressure to reach a steady state, and the CSF absorption is then estimated. The slope of the least-squares line to the pressure-absorption data points determines the resulting clinical value of CSF conductance. Various sources calculate this parameter in healthy humans to be between 0.10 and 0.17 (ml/min)/mmHg (Albeck et al., 1991; Ekstedt, 1978; Sullivan & Allison, 1985).

To simulate clinical infusion tests with that model, a nonzero value was assigned to the flow $Q_{\text{inf}}$ in (8). In the steady state, the resulting change in CSF absorption will be simply $Q_{\text{inf}}$ itself as CSF production is assumed constant and there is zero volume change in such a state. Since, to accord with clinical measurements, this simulation assumes healthy physiology, the transverse sinus is taken as totally rigid ($m = 0$ and/or $p = 1$) and $Z_{SV}$ is set equal to $\overline{Z}_{SV}$ throughout the simulation. Solving (8) and (9) with the derivative terms set to zero now yields a calculated model conductance to CSF outflow of

$$\frac{Z_{FS} \overline{Z}_{SV} + Z_{FV} \overline{Z}_{FS} + Z_{FV} \overline{Z}_{SV}}{Z_{FS} + \overline{Z}_{SV}} = 0.12 \text{ (ml/min)}/\text{mmHg}. \quad (19)$$

This predicted value is in agreement with the average value of 0.12 ((ml/min)/mmHg) observed by Albeck et al. (1991).

The second set of validation simulations involved determination in healthy physiology of the bulk pressure–volume relationship within the intracranial system, and specifically that of the CSF and brain. Clinically, this relationship is determined by measurements taken from lumbar CSF space in the supine position (Friden & Ekstedt, 1983). In this position, lumbar pressure is assumed equivalent to the intracranial CSF and brain pressures. Infusions or withdrawals of CSF are performed, and the resulting pressures are recorded. Depending on the infusion rate, it may be necessary to estimate changes in CSF absorption in order to calculate volume changes (Friden & Ekstedt, 1983; Sullivan & Allison, 1985).

Physiologically, pressure–volume buffering occurs primarily between the CSF and vascular components of body. At lower pressures, this buffering is associated with a lower pressure plateau in the neighbourhood of resting pressure. On this lower plateau, the CSF system has a high compliance, and changes in CSF volume are easily accommodated by expansions or contractions of the venous system. Consequently, a small CSF volume change in this lower pressure regime will produce only a small change in ICP. As the CSF volume increases and venous blood volume decreases, it becomes increasingly difficult to expel the remaining venous blood. Compliance of the CSF system drops, small CSF volume changes produce increasingly large relative changes in ICP and the steepness of the pressure–volume curve increases. Above the 30- to 40-mmHg range, and in particular as the CSF pressure approaches the intracranial artery pressure, ICP is sufficiently high that arterial blood volume can be affected. With the introduction of this additional means of compensation for added CSF volume, the pressure–volume curve becomes less steep at higher pressures, changes concavity and smoothly goes to an upper pressure
plateau. Beyond the upper pressure plateau, the intracranial system contains no additional compensatory features to buffer additional volume increases. Hence, the pressure–volume curve rises steeply, and the compliance of the CSF system falls to zero. For the case of CSF withdrawals, the relationship remains in the high compliance lower plateau region over a much greater range in CSF volume changes. However, after a significant volume of 25–40 ml of fluid has been removed, compliance drops and the curve becomes steeper (Friden & Ekstedt, 1983). At this point, there is very little CSF remaining in the system and clinical trials stop.

Simulating these clinical measurements with the model is again achieved by introducing positive and negative values for $Q_{\text{inf}}$ in the governing equation (8). Because this is again a simulation of healthy physiology, the transverse sinus is taken to be totally rigid and $Z_{\text{SV}}$ is set equal to $\overline{Z}_{\text{SV}}$ throughout the simulation. The simulated pressure response is determined by numerically solving (8) and (9) for $P_F$ and $P_S$. Note, both sides of these equations represent the time derivative of compartmental volume. Therefore, once the compartmental pressures are known, compartmental volume changes are determined by integrating either side of (8) and (9) from time zero to the end of the simulation. The pressure–volume relationship is then depicted as a parametric plot between pressure and volume as functions of time. The resulting pressure–volume curve is depicted in Fig. 3. The present simulation results produce a curve that matches, in both shape and magnitude, the pressure–volume relationship obtained clinically (Friden & Ekstedt, 1983; Sullivan & Allison, 1985).

2.5 The steady-state equations

The first step in a steady-state analysis of the current model is to set the time derivative terms in the governing equations (8) and (9) to zero. The CSF infusion term $Q_{\text{inf}}$ will also be set equal to zero as it will not be needed in the following analysis. The resulting system of algebraic equations for the steady state now becomes

\[ \overline{Q}_{\text{CF}} - Z_{FS} P_{FS} - Z_{FV} P_{FV} = 0, \]  \hspace{1cm} (20)

\[ \overline{Q}_{\text{CS}} + Z_{FS} P_{FS} - Z_{SV} P_{SV} = 0. \]  \hspace{1cm} (21)
Here, in accordance with Assumption 2, cerebral blood flow \( (Q_{CS}) \) and CSF production \( (Q_{CF}) \) have been assigned constant values \( Q_{CS} \) and \( Q_{CF} \), respectively.

As described in Section 2.3, the fluidity calibration process ensures that the set of normal pressures \( P_F = \bar{P}_F \) and \( P_S = \bar{P}_S \) will satisfy the steady-state equations. Hence, the ordered pair \( (\bar{P}_F, \bar{P}_S) \) will be referred to as the 'base-value' steady-state solution of the system described by (20) and (21). It is convenient at this point to perform a transformation of variables

\[
x = P_F - \bar{P}_F, \\
y = P_S - \bar{P}_S,
\]

so that the origin \( (0, 0) \) now corresponds to the base-value steady state and \( (x, y) \) represents changes from the base-value state. Applying this transformation and by Assumption 7 setting \( P_V = \bar{P}_V \), (20) and (21) become

\[
f(x, y) = Q_{CF} - Z_{FS}[(x - y) + \bar{P}_{FS}] - Z_{FV}(x + \bar{P}_{FV}) = 0, \tag{24}
g(x, y) = Q_{CS} + Z_{FS}[(x - y) + \bar{P}_{FS}] - Z_{SV}(y + \bar{P}_{SV}) = 0. \tag{25}
\]

In terms of \( x \) and \( y \), the downstream Starling resistor in (3) now has the representation

\[
Z_{SV} = \begin{cases} 
Z_{SV}(1 - mx), & \text{for } x \leq \frac{1-p}{m}, \\
pZ_{SV}, & \text{for } x \geq \frac{1-p}{m}, 
\end{cases} \tag{26}
\]

and the one-way CSF drainage valves become

\[
Z_{FS} = \begin{cases} 
Z_{FS}, & \text{when } x > y - \bar{P}_{FS}, \\
0, & \text{when } x \leq y - \bar{P}_{FS}, 
\end{cases} \tag{27}
\]

and

\[
Z_{FV} = \begin{cases} 
Z_{FV}, & \text{when } x > \bar{P}_{VF}, \\
0, & \text{when } x \leq \bar{P}_{VF}. 
\end{cases} \tag{28}
\]

Equations (24)–(28) will govern the steady-state solutions. By considering the various domains associated with (26)–(28), it is possible to solve (24) and (25) explicitly for the various steady states predicted by the model.

### 2.6 Stability analysis

When the fully time-dependent system of differential equations (8) and (9) are expressed in terms of the transformed variables \( x \) and \( y \), the result can be put into matrix form as

\[
\begin{pmatrix} C_{FS} + C_{FY} + C_{CF} + C_{FV} - C_{FS} \\ -C_{FS} \\ C_{FS} \end{pmatrix} \begin{pmatrix} \dot{x} \\ \dot{y} \end{pmatrix} = \begin{pmatrix} f(x, y) \\ g(x, y) \end{pmatrix}. \tag{29}
\]

Here, the arguments of the compliance terms must be expressed in terms of \( x \) and \( y \), and the functions \( f(x, y) \) and \( g(x, y) \) are defined in the steady-state equations (24) and (25). Note that since \( C_{FS} \) is positive, the compliance matrix on the far left of (29) is nonsingular, and System (29) can be expressed...
explicitly as
\[
\begin{pmatrix}
\dot{x} \\
\dot{y}
\end{pmatrix} = C^{-1} \begin{pmatrix}
f(x, y) \\
g(x, y)
\end{pmatrix} = \begin{pmatrix}
F(x, y) \\
G(x, y)
\end{pmatrix},
\]
(30)
where
\[
C = \begin{pmatrix}
C_{FS} + C_{FY} + C_{CF} + C_{FV} & -C_{FS} \\
-C_{FS} & C_{FS}
\end{pmatrix}.
\]
(31)

Now the stability properties of various steady-state solutions can be determined by the eigenvalues of the Jacobian matrix \( J(x, y) \) of partial derivatives, defined by
\[
J(x, y) = \begin{pmatrix}
F_x(x, y) & F_y(x, y) \\
G_x(x, y) & G_y(x, y)
\end{pmatrix},
\]
(32)
where \( F \) and \( G \) are defined in (30). The process of determining stability properties from the eigenvalues of the Jacobian matrix is described in most texts on differential equations and nonlinear dynamics. See, e.g. Strogatz (1994).

3. Results

The results presented here are based on explicitly solving (24) and (25) for all steady-state solutions under various conditions and determining the stability properties of each. The algebra involved in solving (24) and (25) is straightforward but very tedious and time-consuming due to the piecewise nature of the fluidity terms. Additionally, the inherent complexity of the Jacobian matrix in (32) precludes explicit derivation of its eigenvalues in terms of the model parameters. Therefore, these eigenvalues will be determined with numerical values assigned to these parameters. As such, the stability and bifurcation classifications described here are based on these numerical results.

3.1 Steady-state analysis

The values of the two rigidity parameters \( m \) and \( p \) in (26) that describes the downstream Starling resistor located at the transverse sinus determine the extent to which these vessels are capable of some degree of collapse. If \( p \) is close to unity and/or \( m \) is small, the transverse sinuses are more rigid, and they are fully rigid if \( p = 1 \) and/or \( m = 0 \). If \( p \) is small and/or \( m \) is large, the sinuses are less rigid and are capable of a greater degree of collapse. The steady-state and bifurcation analysis presented here is with respect to these two parameters. For all values of \( m \) and \( p \), there exists the steady-state solution \((0, 0)\) in terms of \((x, y)\). Since this solution represents the normal ICPs: \( P_F = \overline{P}_F \) and \( P_S = \overline{P}_S \), it is termed the ‘base-value’ steady state in \( x \) and \( y \). Provided \( m < M \), where
\[
M = \frac{\overline{Z}_{FS}Z_{SV} + \overline{Z}_{FV}Z_{FS} + \overline{Z}_{SV}Z_{FV}}{\overline{Q}_{SV}Z_{FS}},
\]
(33)
the base-value steady state is stable. In this case, the eigenvalues of the Jacobian matrix evaluated at \((0, 0)\) are both real and negative, making the base-value state a stable node. When \( m = M \), one of the eigenvalues is zero, and when \( m > M \) this eigenvalue becomes positive and the base-value state becomes an unstable saddle point. This occurs via a transcritical bifurcation at \( m = M \).
The parameter plane $\{(p, m)\}$ is separated into a ‘more-rigid’ region and a ‘less-rigid’ region by a curve of the form $m = B(p)$, depicted in Fig. 4, where

$$B(p) = \begin{cases} \frac{Z_{FV}(1-p)}{Q_{FS}}, & \text{if } p \leq p^*, \\ \frac{aZ_{SV}}{Z_{FS}} p + \frac{Z_{FV}}{Q_{SV}}, & \text{if } p > p^* \end{cases}$$

(34)

and

$$p^* = \frac{Z_{FV}Q_{CS}}{Z_{SV}Q_{CF}}$$

(35)

$$\alpha = \frac{Z_{FS} + Z_{FV}}{Z_{FS}}.$$  

(36)

When model parameters are assigned their normal base values, $p^*$ and $\alpha$ in (34) have the approximate values 0.108 and 1.189, respectively.

The number and stability of steady-state solutions are determined by whether the parameter pair $(p, m)$ lies below or above the curve $m = B(p)$. In the more-rigid sinus region of the $(p, m)$-plane ($m < B(p)$), only the base-value steady state exists and it is globally stable. For values of $(p, m)$ in the less-rigid sinus region ($m > B(p)$), the base-value state remains but two additional steady states are also present. One is the unstable saddle point $(x_m, y_m)$ defined by

$$x_m = \frac{aZ_{SV} + Z_{FV} - mQ_{SV}}{\alpha m Z_{SV}},$$

(37)

$$y_m = \alpha x_m,$$

(38)
and the other is stable node \((x^*, y^*)\) defined by

\[
x^* = \begin{cases} 
\frac{\mathcal{Q}_{FS}}{Z_{SV}}, & \text{if } p \leq p^*, \\
\frac{(1-p)\mathcal{Q}_{SV}}{apZ_{SV} + Z_{SV}}, & \text{if } p > p^*,
\end{cases}
\] 

\[\tag{39}\]

\[
y^* = \begin{cases} 
\frac{\mathcal{Q}_{CS} - p\mathcal{Q}_{SV}}{pZ_{SV}}, & \text{if } p \leq p^*, \\
ax^*, & \text{if } p > p^*.
\end{cases}
\] 

\[\tag{40}\]

Therefore, the curve \(m = B(p)\) defined by (34) and depicted in Fig. 4 represents a bifurcation curve above which there is an additional stable equilibrium solution. The stable node \((x^*, y^*)\) represents this solution and is a state of elevated ICPs. This state will be referred to as the ‘elevated steady state’. It is hypothesized that this state represents the elevated ICP and sagittal sinus pressures associated with IIH. The value of \(p^*\) in (34) has a physiological interpretation in terms of this elevated state. It represents the value of \(p\) below which the elevated steady state occurs with the one-way valve represented by \(Z_{FS}\) closed. In this scenario, the model shows that the elevated state occurs with \(P_S\) exceeding \(P_F\) as observed clinically by King et al. (2002) in some IIH patients.

Figure 5 displays two bifurcation diagrams which illustrate the types of bifurcations possible in this system. Both of these diagrams depict the steady-state solutions of \(x\) in terms of one parameter with the other held constant. In Fig. 5(A), the parameter \(m\) is held constant at 0.25 and \(p\) is allowed to vary over its complete range of values between 0 and 1. In this diagram, a saddle-node bifurcation occurs as

![Bifurcation diagrams](image)

**Fig. 5.** Bifurcation diagrams of the steady-state solutions in \(x\) with respect to \(p\) and with respect to \(m\). Solid curves represent stable nodes, while the dashed curves represent unstable saddle points.
$p$ decreases across the curve $m = B(p)$. In Fig. 5(B), the parameter $p$ is held constant at 0.2 and $m$ is allowed to vary over a feasible region. This diagram also demonstrates the saddle-node bifurcation, this time as $m$ crosses $B(p)$. Furthermore, Fig. 5(B) illustrates the transcritical bifurcation that occurs when $m$ crosses the critical value $M$. In this case, the elevated state remains stable but the base-value state, upon which the model parameters are based, becomes unstable. On physiological grounds, this possibility must be precluded. Therefore, it must be assumed that the base-value steady state always remains stable, and $m$ will be restricted between 0 and $M$.

The relationship between $p$, $m$ and various possible steady states is clarified in the phase portrait shown in Fig. 6. Here, the bifurcation occurs along a 1D subspace of the $(x, y)$-plane. In this figure, the values chosen for $p$ and $m$ lie in the three steady-state domain. The three steady states depicted here all lie on the line $y = \alpha x$, where $\alpha$ is defined in (36), denoted by the dashed curve. As $m$ increases, the saddle point moves along this line towards $(0, 0)$. When $m = M$, the saddle point coincides with the base-value state, a transcritical bifurcation occurs and the stability properties switch. On the other hand, as $m$ decreases, the saddle moves towards the elevated state and both vanish after the intersection occurs. As $p \rightarrow 1$, the elevated state $(x^*, y^*)$ approaches $(0, 0)$ along the dashed line. At some point, the stable elevated state will coincide with the saddle point, a saddle-node bifurcation occurs and again both elevated states vanish. As $p \rightarrow 0$, the elevated state moves away from $(0, 0)$. However, it now remains on the common line only for $p \geq p^*$. As $p$ decreases below $p^*$, $x^*$ remains constant, but $y^* \rightarrow \infty$.

Figure 6 also demonstrates the effect of the parameter $m$ on the likelihood of transitioning from the base-value state to the elevated state. The separatrix denoted by the solid curve in this figure delineates between trajectories that eventually lead to the base-value state and those that lead to the elevated state. This curve was generated numerically and approximates the only two trajectories in the plane that lead to the unstable saddle point. As $m$ increases, the saddle point and the associated separatrix move towards $(0, 0)$. This implies that for increasing $m$, smaller perturbations from the base-value state are required.
to cause a permanent transition to the elevated state. In this sense, \( m \) represents the tendency for small disturbance to cause permanent transitions to the elevated state when an elevated state exists.

While the existence of a stable elevated steady state depends on the values of both \( m \) and \( p \), (39) and (40) show that the magnitude of this state, when it exists, depends on \( p \) exclusively. This dependency is illustrated in Fig. 7 which shows that \((x^*, y^*) \to (0, 0)\) as \( p \to 1 \). Conversely, as \( p \to 0 \), \( y^* \to \infty \) while \( x^* \) remains bounded.

An important implication of (39) is that an elevated state can only be realized in conjunction with a maximally collapsed sinus. This conclusion can be more formally stated as follows:

**Claim 1:** If the elevated steady state defined by (39) and (40) is realized, then the fluidity term \( Z_{SV} \) is at its minimum value of \( pZ_{SV} \).

**Proof.** If an elevated stable steady state exists, then it is necessary that \( m > B(p) \), where \( B(p) \) is defined in (34). Therefore, if \( p \leq p^* \), then

\[
m > \frac{Z_{FV}(1 - p)}{Q_{FS}} = \frac{1 - p}{x^*}
\]  

and if \( p \geq p^* \), then

\[
m > \frac{apZ_{SV} + Z_{FV}}{Q_{SV}} = \frac{1 - p}{x^*}
\]  

In both cases, \( x^* > (1 - p)/m \) and, by the definition of \( Z_{SV} \) in (26), \( Z_{SV}(x^*) = pZ_{SV} \) which is its minimum value.

The importance of Claim 1 lies in its requirement that the elevated pressure state and the collapsed sinus must exist simultaneously. One does not necessarily cause the other, but one does not exist without

![Fig. 7. The transformed pressures \( x^* \) (solid curve) and \( y^* \) (dashed curve) of the stable, elevated, steady state as functions of the rigidity parameter \( p \).](image)
the other. Indeed, it is the existence of a sufficiently collapsible sinus that allows such an elevated pressure state to exist and possibly be realized.

3.2 Treatment simulations

Two treatment methods have been simulated using the present model to predict their effect on the elevated stable steady-state pressures that can exist for a less-rigid transverse sinus. The first of these simulations considers the effect of acetazolamide (ACTZ), which has been shown to reduce CSF production. The second investigates the effect of a surgically implanted CSF shunt, which provides an additional drainage route for CSF.

3.2.1 Acetazolamide. ACTZ, which has been shown to reduce CSF production by nearly 50%, is a medication often prescribed for patients suffering from IIH (Schoeman, 1994; Sorenson et al., 1988) and other disorders involving elevated CSF pressures or volumes (Carrion et al., 2001). The effect of ACTZ is simulated here by reducing the CSF production term \( Q_{\text{CF}} \) in the model by a factor of \( a \).

Therefore, to simulate treatment involving ACTZ, CSF production in the model will be governed by

\[
Q_{\text{CF}} = aQ_{\text{CF}}, \quad \text{where } 0.5 \leq a \leq 1.
\]

The domain restriction on the parameter \( a \) is based on the clinical observations that ACTZ can reduce CSF production by 50% or less (Schoeman, 1994; Sorenson et al., 1988). With CSF production now a function of \( a \), the critical value \( p^* \) will be a function of \( a \) as well. It will be denoted by \( p^*_\text{ACTZ} \) and is given by

\[
p^*_\text{ACTZ} = \frac{Z_{FS}Q_{CS}}{aZ_{SV}Q_{CF}}.
\]

As a reference point, if \( a = 0.5 \) (representing the maximum efficacy of ACTZ), then \( p^*_\text{ACTZ} \approx 0.216 \), or about twice the value of \( p^* \) in the absence of this intervention.

The bifurcation curve depicted in Fig. 4 will also be a function of \( a \) for ACTZ-reduced CSF production. The resulting bifurcation curve with ACTZ in the \((p, m)\)-plane will be denoted by \( m = B_{\text{ACTZ}}(p) \) and is given by

\[
B_{\text{ACTZ}}(p) = \begin{cases} 
\frac{Z_{FS}(1-p)}{Q_{FS}-(1-a)Q_{CF}}, & \text{if } p \leq p^*_\text{ACTZ}, \\
\frac{(1-p)(pZ_{FS}Z_{SV}+Z_{FS}(Z_{FS}+pZ_{SV}))}{(1-p)Z_{SV}Z_{FS}-(1-a)Q_{CF}(Z_{FS}+pZ_{SV})}, & \text{if } p > p^*_\text{ACTZ}.
\end{cases}
\]

For \( a = 0.5 \), \( B_{\text{ACTZ}} \) is displayed as the lower dashed curve in Fig. 8. Comparing the lower dashed and solid (no treatment) curves in this figure, model simulations predict that treatment with ACTZ is capable of reducing the region in the \((p, m)\)-plane where an elevated steady state can exist.

The curve \( m = B_{\text{ACTZ}}(p) \) will have a vertical asymptote at

\[
p = p_{\text{vert}} = \frac{Z_{FS}((a-1)Q_{CF}+Q_{SV})}{Q_{SV}Z_{FS}+(1-a)Q_{CF}Z_{SV}}.
\]

For \( a = 0.5 \), this asymptote occurs at \( p_{\text{vert}} \approx 0.533 \). However, this vertical asymptote is not relevant for the present physiological application as \( m \) will reach its maximum allowed value well before \( p \) reaches the value of \( p_{\text{vert}} \).
FIG. 8. The bifurcation curves in the \((p, m)\)-plane without treatment (solid), with ACTZ for \(a = 0.5\) (lower dashed curve), and with a shunt installed with \(Z_{sh} = 0.02\) (upper dashed curve). A stable, elevated, steady state exists for ordered pairs of parameter values that lie above these curves.

For values of \(m\) and \(p\) such that \(B_{ACTZ}(p) < m < M\), there exists a stable elevated state \((x^*_{ACTZ}, y^*_{ACTZ})\), which depends on both \(a\) and \(p\), defined by

\[
x^*_{ACTZ} = \begin{cases} 
\frac{\overline{Q}_{FS} - (1-a)\overline{Q}_{CF}}{Z_{FV}}, & \text{if } p \leq p^*_{ACTZ}, \\
\frac{(1-p)\overline{Q}_{SV}Z_{FS} - (1-a)\overline{Q}_{CF}Z_{FS} + pZ_{SV}}{pZ_{FV}Z_{SV} + Z_{FS}(Z_{FV} + pZ_{SV})}, & \text{if } p > p^*_{ACTZ},
\end{cases}
\]  

(46)

and

\[
y^*_{ACTZ} = \begin{cases} 
\frac{(1-p)\overline{Q}_{SV} - \overline{Q}_{FS}}{pZ_{SV}}, & \text{if } p \leq p^*_{ACTZ}, \\
\frac{(1-p)\overline{Q}_{SV}(Z_{FS} + Z_{FV}) - (1-a)\overline{Q}_{CF}Z_{FS}}{pZ_{FV}Z_{SV} + Z_{FS}(Z_{FV} + pZ_{SV})}, & \text{if } p > p^*_{ACTZ}.
\end{cases}
\]  

(47)

These transformed pressures with ACTZ treatment are depicted in Fig. 9 for \(a = 0.5\). In this figure, it appears possible for the elevated state to become negative if \(p\) is sufficiently large. However, this appearance is misleading since, as is clear from Fig. 8, at these large values of \(p\) an elevated pressure state will not exist. It should also be pointed out that if an elevated steady state of \(y^*\) still exists after ACTZ treatment, i.e. the elevated steady state is not completely eliminated by this treatment method, the model suggests that the magnitude of the sinus pressure may be essentially unaffected, but the level of \(x^*\) can be reduced by as much as 50%. Even if this is the case, the statement made in Claim 1 will still hold as the elevated state with ACTZ treatment still occurs simultaneously with the maximally collapsed sinus.

3.2.2 Ventriculoperitoneal shunt. CSF diversion procedures provide an alternate treatment method for those IIH patients who do not respond well to ACTZ prescription (Garton, 2004). The CSF diversion modelled in this study is an idealized version of a ventriculoperitoneal (VP) shunt where the resistance is constant after the valve opens. The effect of such a shunt is simulated by introducing an additional
FIG. 9. The solutions $x^*$ (solid curves) and $y^*$ (dashed curve) in the stable, elevated, steady states with and without treatment. Treatment does not affect $y^*$. The upper solid curve is the solution $x^*$ with no treatment. ACTZ treatment with $a = 0.5$ is represented by the middle solid curve and treatment through shunting by the lowest solid curve.

A one-way drainage route ($Q_{sh}$) from the CSF/brain compartment defined by

$$Q_{sh} = Z_{sh}P_F,$$

where $Z_{sh} = \begin{cases} 
Z_{sh}, & \text{if } P_F > P_{close}, \\
0, & \text{if } P_F \leq P_{close}.
\end{cases}$ \hspace{1cm} (48)

In this application, the opening and closing pressure values of the shunt valve are considered to be equal and are set at the base steady-state value for $P_F$. In this way, additional steady-state solutions of the model equations are not created. In terms of the steady-state parameter $x$, (48) becomes

$$Q_{sh} = Z_{sh}(x + P_F),$$

where $Z_{sh} = \begin{cases} 
Z_{sh}, & \text{if } x > 0, \\
0, & \text{if } x \leq 0.
\end{cases}$ \hspace{1cm} (49)

This term is now subtracted from the left side of (24) to produce the new steady-state equation for $x$.

Analysis of the model with CSF diversion now follows a route similar to that predicting the efficacy of treatment with ACTZ. With $Q_{sh}$ included in the model equations, this analysis indicates that if an elevated state persists despite treatment with an implanted shunt, the shunt fluidity $Z_{sh}$ in (49) must be restricted to the range

$$0 < Z_{sh} < \frac{Q_{FS}}{P_F} \approx 0.029 \text{ (ml/min)/mmHg}. \hspace{1cm} (50)$$

Beyond this range, an elevated state would involve a negative value for the pressure $x$, and for elevated states to be relevant in the present context, both $x$ and $y$ must be positive. The fluidity range (50) is associated with a shunt that has a greater resistance $R_{sh} = 1/Z_{sh}$ than many high-resistance shunts in clinical use (Czosnyka et al., 1997a). However, shunts in vivo often have a greater resistance than that determined in vitro (Czosnyka et al., 1997a), and increased resistance can also result from a partial blockage. Therefore, it is quite possible that a surgically implanted shunt will have a fluidity value in the range given by (50), and even with treatment, pressures can still be elevated above normal. If $Z_{sh}$ lies above the range defined in (50) (reflecting a shunt that works perfectly, does not obstruct, and has an
in vivo resistance less than \( \frac{Q_{FS}}{P_F} \), the model predicts that treatment involving CSF diversion will completely eliminate the elevated state.

With a shunt included in the model, the critical value of \( p \) becomes a function of \( Z_{sh} \) that will be denoted by \( p_{sh}^* \) and is given by

\[
p_{sh}^* = \frac{Q_{CS}(Z_{FV} + Z_{sh})}{Z_{SV}(Q_{CF} - Z_{sh}P_V)}. \tag{51}
\]

As reference points, when the fluidity \( Z_{sh} \) of the shunt is 0.02, then \( p_{sh}^* \approx 0.30 \), and when \( Z_{sh} = 0.01 \), \( p_{sh}^* \approx 0.19 \). The bifurcation curve depicted in Fig. 4 also becomes a function of \( Z_{sh} \) as well as a function of \( p \). The resulting bifurcation curve with shunting in the \((p, m)\)-plane will be denoted by \( m = B_{sh}(p) \) and is given by

\[
B_{sh}(p) = \begin{cases} 
\frac{(Z_{sh}+Z_{FV})(1-p)}{Q_{FS} - Z_{sh}P_F}, & \text{if } p \leq p_{sh}^*, \\
\frac{(1-p)[pZ_{SV}(Z_{sh}+Z_{FV}+Z_{FS})+Z_{FS}(Z_{sh}+Z_{FV})]}{Z_{FS}(Q_{SV}-Z_{sh}P_F)-p(Z_{FS}Q_{SV}+Z_{SV}Z_{sh}P_F)}, & \text{if } p > p_{sh}^*. 
\end{cases}
\tag{52}
\]

The upper dashed curve in Fig. 8 displays the bifurcation curve for \( Z_{sh} = 0.02 \). In general, the curve \( m = B_{sh}(p) \) will have a vertical asymptote at

\[
p_{vert} = \frac{Z_{FS}(Q_{SV} - Z_{sh}P_F)}{Z_{FS}Q_{SV} + Z_{SV}Z_{sh}P_F}. \tag{53}
\]

When the fluidity \( Z_{sh} \) is 0.02, this asymptote occurs at \( p_{vert} \approx 0.526 \). When \( Z_{sh} = 0.01 \), this asymptote occurs at \( p \approx 0.689 \).

With shunting, a stable elevated state \((x_{sh}^*, y_{sh}^*)\) will exist for values of \( m \) and \( p \) such that \( B_{sh}(p) < m < M \). Both \( x_{sh}^* \) and \( y_{sh}^* \) are functions of \( Z_{sh} \) and \( p \) and are given in this case by the relations

\[
x_{sh}^* = \begin{cases} 
\frac{Q_{FS} - Z_{sh}P_F}{Z_{FV} + Z_{sh}}, & \text{if } p \leq p_{sh}^*, \\
\frac{Z_{FS}(Q_{SV} - Z_{sh}P_F) - p(Z_{FS}Q_{SV} + Z_{SV}Z_{sh}P_F)}{pZ_{SV}(Z_{sh} + Z_{FV} + Z_{FS}) + Z_{FS}(Z_{sh} + Z_{FV})}, & \text{if } p > p_{sh}^*, 
\end{cases}
\tag{54}
\]

and

\[
y_{sh}^* = \begin{cases} 
\frac{(1-p)Q_{SV} - Q_{FS}}{pZ_{SV}}, & \text{if } p \leq p_{sh}^*, \\
\frac{(1-p)Q_{SV}(Z_{sh} + Z_{FS} + Z_{FV}) - Z_{sh}P_FZ_{FS}}{pZ_{SV}(Z_{sh} + Z_{FS} + Z_{FV}) + Z_{FS}(Z_{sh} + Z_{FV})}, & \text{if } p > p_{sh}^*. 
\end{cases}
\tag{55}
\]

These solutions are depicted in Fig. 9 for \( Z_{sh} = 0.02 \). As is the case for treatment by AZCT, the solution \( x_{sh}^* \) in the elevated state with shunting will not become negative for large values of \( p \). This is because the elevated state will not exist for large values of \( p \), as indicated by Fig. 8. The behaviour of \( x_{sh}^* \) in the elevated state with shunting at the upper and lower bounds of the range in (50) may also be determined. As \( Z_{sh} \to 0 \), the solution curve \( x_{sh}^*(p) \) tends to the original (no treatment) curve in Fig. 9, and as \( Z_{sh} \to \frac{Q_{FS}}{P_F} \), this curve tends to the \( p \)-axis.

The same argument previously given to prove Claim 1 shows that again with shunting, if the elevated state is not completely eliminated by treatment, it occurs simultaneously with a maximally collapsed
sinus. In this case, as with ACTZ treatment, the ICP level of the elevated state may be reduced and not be considered hypertensive, but the degree of collapse can be quite severe.

4. Summary and conclusions

In many mathematical models of intracranial blood flow, a Starling resistor is assumed to exist at the location of a collapsible vein (Ursino, 1988; Czosnyka et al., 1997b; Piechnik et al., 2001; Pedley et al., 1996), where the normal transmural pressure is positive. For a traditional Starling resistor at such a location, if transmural pressure becomes negative or zero, the vessel is assumed to be fully collapsed and all flow is occluded. A traditional Starling resistor is thus not appropriate for use at the location of the transverse sinus, where the normal transmural pressure is negative. Consequently, these vessels have traditionally been considered rigid and modelled by assuming a constant resistance to flow. In healthy individuals, this is certainly a valid assumption. However, in order to accommodate the observed stenosis of these vessels in IIH (Farb et al., 2003; Higgins & Pickard, 2004; King et al., 2002), a downstream, pressure-dependent resistor may be introduced into an ICP and flow model to account for this phenomenon (Stevens et al., 2005b). The form of this resistor in the present model is given in terms of a fluidity defined by (3).

It has been shown (Heil, 1997) that a compliant tube with constant fluid flow subjected to a uniform external pressure demonstrates a lumped resistance which increases in response to an increasingly negative downstream transmural pressure. The fluidity described by (3) has this same behaviour prior to reaching a limiting value beyond which the fluidity can decrease (or resistance can increase) no further. This minimum on \( Z_{SV} \) in (3) has been imposed here for three reasons. First, fluidity cannot be negative. Second, even when ICP is equal to arterial pressure, the model presented by Tym et al. (1972) shows that there will be only an 80% reduction in cerebral blood flow. Finally, there may be other pathways for venous drainage (Bateman, 2002). Stevens et al. (2005b) demonstrated that the etiology and symptoms associated with IIH can be well described by a model with such a downstream resistor. However, the model developed in that work was too complicated to extract explicit analytic results. While retaining the relevant features of that model, the present simplified model allows explicit solutions to the steady-state equations to be obtained, validated and their responses to IIH treatment methods fully analysed.

The parameters \( p \) and \( m \), in (3), determine the collapsibility of the vessel. Specifically, \( p \) describes the maximal level of collapse and \( m \) determines the degree of collapsibility prior to reaching the maximal level of collapse. A healthy (rigid) state is described by \( p = 1 \) and/or \( m = 0 \), and the downstream Starling fluidity \( Z_{SV} \) becomes a constant for these parameter values. In this case, the model, as calibrated in Section 2.3, has exactly one steady-state solution with normal pressures and reproduces measured clinical results for both the conductance of CSF outflow and the bulk CSF pressure–volume relationship.

For cases where \( m > 0 \) and \( 0 < p < 1 \) in which some degree of collapse of the transverse sinus is allowed, the \((p, m)\)-plane can be divided into two regions; a region describing a more-rigid sinus and another describing a less-rigid sinus. In the more-rigid region, as in the fully rigid case, only one steady-state solution of the model equations exists, and it involves normal pressures. In the less-rigid region, three steady states are found to exist; one stable steady state of normal pressures, one unstable state of moderately elevated pressures and one stable state of elevated pressures. The curve \( m = B(p) \), depicted in Fig. 4, separates the less-rigid and more-rigid regions and represents a bifurcation curve in the \((p, m)\)-plane. \( B(p) \) has a discontinuous derivative at the critical value \( p^* \), which represents the value of \( p \) below which \( P_s \) in the elevated steady state is greater than \( P_F \) and the one-way valve represented by
ZFS is closed. It is hypothesized that IIH with its associated intracranial hypertension is a physiological manifestation of the stable elevated pressure state predicted by the model to exist in the less-rigid sinus region of the $(p, m)$-plane.

While the values of both $p$ and $m$ determine the existence of a stable elevated state, it is the value of $p$ which determines the magnitude of this state when it exists. This relationship is described by (39) and (40) and is depicted in Fig. 7. In these equations, $x^*$ and $y^*$ represent pressures in the elevated state in terms of changes from the base state (i.e. $P_F^* = P_F + x^*$ and $P_S^* = P_S + y^*$). The present analysis shows that elevated states occur simultaneously with a maximally collapsed sinus.

As $p \to 1$, representing a more-rigid sinus, both of the pressures $x^*$ and $y^*$ in the elevated state tend to the normal state. In particular, for the parameter ranges considered in this model, a $p$ value greater than approximately 0.2 produces a predicted steady state that, while elevated, would not qualify as hypertensive (Malm et al., 1992; Torbey et al., 2004). This result agrees with the data analysis performed by Stevens et al. (2005b) where patients with $p$ values estimated to be 0.125 and 0.034 had elevated states about 17 mmHg above normal, while the patient with a $p$ value estimated to be 0.643 had an elevated state only about 6 mmHg above normal. The resulting magnitude of the elevated states, as described by (39) and (40), depends on other parameters in addition to $p$, such as the central venous pressure, CSF production and the resistance to CSF absorption.

As $p \to 0$, the elevated state of $P_S$ tends to infinity. However, as the venous sinus pressure increases above normal capillary pressure, autoregulation of cerebral blood flow requires capillary pressure to increase, and eventually this can affect the production of CSF. Indeed, if sinus pressure increases excessively, then cerebral blood flow itself becomes impaired. Therefore, the results predicted by the present model are displayed only for values of $p$ greater than about 0.05 as predictions for $p$ below this value cannot be justified under the current assumptions.

As $p$ decreases below $p^*$ towards its minimum, sagittal sinus pressure continues to increase, but CSF/brain pressure stays at a maximum value achieved at $p = p^*$. This maximum is described by the first equation in (39). In terms of the original pressures, this maximum is given by

$$P_F^* = \frac{Q_{CF}}{Z_{FV}} + P_V,$$

which demonstrates a linear relationship between the maximum elevated steady state and downstream pressure $P_V$. Specifically, a decrease in $P_V$ results in an identical decrease in the CSF/brain pressure, i.e. in ICP. This result supports clinical observations that weight reduction and the resulting decrease in central venous pressure (Sugerman et al., 1997) are very effective in reducing the elevated ICP associated with IIH (Bono et al., 2005). Equation (56) further shows that it is possible for a reduction in $P_V$ caused by weight loss to reduce the level of $P_F^*$ to near-normal levels while the sinus remains in its maximally collapsed state. This situation can occur because the reduced, near-normal, elevated state and the maximally stenosed sinus will, by Claim 1, occur simultaneously, regardless of the magnitude of pressure elevation.

The phase portrait given in Fig. 6 depicts a typical case where three steady states exist. While $p \geq p^*$, the three points representing the steady states in the $(x, y)$-plane lie on a line. The stable elevated state is determined by $p$, and as $p$ increases this point moves towards the unstable saddle point until the two points collide and both vanish leaving only the stable base-value node. The locations of the saddle node and its associated separatrix are governed by the value of $m$, and as $m$ increases both features move towards the base-value node. Thus, a large value of $m$ suggests that the perturbation required to cause a transition from the base value to the elevated state can be small. On the other hand, as $m$ decreases the saddle node and separatrix move towards the elevated state suggesting that a larger
perturbation is required to escape the base-value state basin. As \( m \) decreases to zero, the saddle point and stable elevated node collide and then vanish in a saddle-node bifurcation.

Figure 6 provides information about precipitating events that may induce transitions between stable states. During a posture or position change, \( P_F \) and \( P_S \) change in a parallel manner (Stevens et al., 2005a). Therefore, a position change alone is unlikely to cause a transition between states because the resulting trajectory would follow a path nearly parallel to the separatrix. On the other hand, a CSF infusion or withdrawal effects CSF pressure to a much greater extent than sinus pressure. Therefore, such a procedure is likely to cause transitions from one stable state to the other because such a trajectory will cross the separatrix earlier than when both pressures change in tandem. For example, a CSF withdrawal could cause a permanent transition from the elevated state to the base-value state, which would explain why a temporary CSF drainage or ‘tap’ can cause long-term relief from IIH (Friedman & Rausch, 2002; Soler et al., 1998). In principle, any technique that temporarily drops CSF pressure can theoretically cause a similar long-term transition to the normal state. If such a transition can be instigated noninvasively, perhaps by hyperventilation, then repetition of such a manoeuvre may be tolerable as a regular temporary relief from symptoms of IIH.

In addition to weight loss and CSF taps, there are other options for IIH treatment. One such option is to surgically implant a stent at the location of the obstruction. A stent transforms a section of a collapsible sinus into a rigid section and is potentially the most effective treatment if the cause of the problem is local. However, this option is highly invasive and is still relatively experimental. Reports to date conclude that stenting ‘shows promise as an alternative treatment to neurosurgical intervention in intractable cases’ (Higgins et al., 2003), and ‘is a viable alternative for amenable lesions’ (Owler et al., 2003).

For other potential treatment methods, the model predicts that ACTZ is capable of eliminating the elevated state provided the point \((p, m)\) lies between the solid and lower dashed curves in Fig. 8. This treatment method is also capable of significantly reducing the magnitude of the elevated state in the CSF/brain compartment, as depicted by the middle solid curve in Fig. 9. When the elevated state is not completely eliminated by ACTZ, additional reductions in CSF/brain pressure can be achieved by weight loss, with its associated reduction in central venous pressure. From the first equation in (46), the maximum elevated pressure of \( P_F \) during ACTZ treatment can be expressed as

\[
P_{F_{ACTZ}}^* = \frac{Q_{CF}}{Z_{FV}} + P_V.
\] (57)

As is the case for the pressure \( P_F^* \) in (56) when no treatment is simulated, treatment with ACTZ combined with weight loss may now, by (57), result in a pressure state that, while elevated, is near-normal and is coincident with a maximally stenosed sinus.

CSF shunting is an important option in treating IIH and, with improved surgical methods, VP shunts are particularly appealing. However, even these shunts are subject to various complications such as over-draining and shunt obstruction or occlusion (Garton, 2004). As depicted in Figs 8 and 9, model simulations predict that even a shunt that has an unusually high resistance is capable of resolving or reducing the elevated ICP associated with IIH. As the shunt resistance increases, i.e. \( Z_{sh} \) decreases, the bifurcation curve in Fig. 8 moves towards the curve for the untreated case, as does the curve in Fig. 9 describing the level of elevation. Again, with treatment by a shunt, it is possible for the sinus to be in its maximally collapsed state while the level of CSF pressure in the elevated state is reduced to barely above that of the base value. This conclusion is supported by the analog of (56) and (57) obtained from
(54) for the maximum pressure $P_{sh}^*$. In particular,

$$ P_{sh}^* = \frac{Q_{CF} + Z_{FV} \bar{P}_V}{Z_{FV} + Z_{sh}}, \quad (58) $$

and CSF pressure in an elevated state will again be reduced by a decrease in $\bar{P}_V$. As the shunt resistance decreases, the bifurcation curve moves out of the feasible $p-m$ domain, and the elevated state no longer exists. This is the case when $Z_{sh} \geq \frac{Q_{FS}}{P_F}$.

The present model, though simple, provides a possible resolution of the dispute concerning the relationship between transverse sinus stenosis and the intracranial hypertension associated with IIH. Farb et al. (2003) show that 27 of 29 IIH patients and four of 59 control patients were judged to have substantial bilateral sinovenous stenosis. Therefore, it appears unlikely that a collapsible sinus is common in healthy physiology, but that this feature is quite prevalent in IIH patients. Bono et al. (2005) have shown that after ACTZ treatment and significant weight loss, the elevated ICP associated with IIH can be resolved while the sinus stenosis persists. The present model helps to explain why sinuses stenosis is predominantly associated with IIH patients and how the stenosis can persist even after the hypertension has been resolved. Simulations suggest that when the existence of the elevated state is not completely eliminated by treatment, the magnitude of pressures in the elevated state may be reduced to near-normal levels by ACTZ or shunt treatment (Fig. 9) and then reduced even further by a drop in $\bar{P}_V$ due to weight loss ((56)–(58)). Since Claim 1 applies to all the elevated states, regardless of the magnitude, even-pressure states no longer classified as hypertensive, can occur in conjunction with a maximally collapsed sinus. Therefore, in IIH cases where hypertension has been resolved by treatment and/or weight loss, the model predicts that a stenosed sinus may persist, but it was the sufficiently collapsible sinus that led to the hypertensive level of ICP observed upon diagnosis.

The theoretical efficacies predicted by this model cannot be directly translated into preferred clinically effective treatments for IIH. Safety issues may negate any theoretically predicted benefit, and judgements on the efficacies of specific clinical treatments will have to await the test of randomized, controlled clinical trials. However, the present simulations suggest that current treatment methods, such as ACTZ, CSF shunting and weight loss (alone or combined with ACTZ or shunting) provide promise for reducing the elevated pressure state in IIH, if not eliminating it completely.

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REFERENCES


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