Mean Pressures and Flows in the Human Intracranial System, Determined by Mathematical Simulations of a Steady-State Infusion Test *

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In order to understand the fluid dynamics within the human intracranial system, the relatively small flow of extracellular fluid into, and out of, the interstitial brain tissue must be determined. Due to the magnitude of these flows, it is difficult to measure them clinically. Through a steady-state infusion simulation run on a mathematical model, values for these small flows may be calculated based on clinical data regarding the conductance of CSF outflow. In this way, the mathematical model allows information to be obtained regarding these small mean flows, as well as the remaining mean flows and mean pressures throughout the intracranial space, with minimal reliance on data from intrusive procedures.

Key Words •intracranial •mean-pressure •mean-flow •cerebrospinal fluid (CSF) •steady state •conductance

1 Introduction

In determining physiological indications of abnormal intracranial fluid dynamics, a logical starting point is to determine what constitutes normal dynamics in the healthy human subject. The specific dynamics being studied here are the mean pressures in several subspaces of the intracranial system and the mean fluid flows between these subspaces. Here, a subspace is defined by constituent as opposed to physical location. These subspaces, referred to as compartments, fall into two categories; vascular and nonvascular. The vascular system is divided into five compartments: artery (a), capillary (c), vein (v), venous-sinus (s) and jugular (j), while the nonvascular system is composed of the CSF (f) and brain (b) compartments.

In terms of overall intracranial fluid flow, most of this consists of incoming arterial blood passing through the vascular system in sequence and exiting through the jugular bulb. Of the remainder, most of this is converted into CSF which passes through a series of canals and reservoirs and is then reabsorbed into the venous blood stream through the arachnoid villi. The smallest flows correspond to the extracellular fluid entering and exiting the interstitial brain

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tissue. In particular, these flows pose the greatest difficulty in terms of clinical measurement.

A mathematical model, similar to the one described by Karni *et al.*[5] and elaborated upon by Lakin *et al.*[7], is developed which allows simulations to be compared with the clinical results of the constant-pressure, constant-infusion-rate tests run by Albeck *et al.*[1] on healthy human subjects. Through these comparisons, estimations of model parameters are made. These parameters are the spatially averaged, mean pressures and mean flows throughout the intracranial system. Specifically, these include the smallest mean fluid flows which were not explicitly measured in the clinical experiments.

2 Methods

In clinical experiments, CSF absorption is determined to be linearly related to the CSF pressure increase[1,2,3,11], and the slope of this relationship is defined as the conductance of CSF outflow (C_{out}). The value of this term was calculated by Albeck, Gjerris and Sorenson[1](1991) using a constant-pressure, constant-infusion-rate test.

A mathematical method of modeling intracranial fluid dynamics is developed here that can simulate steady-state infusion tests. In this model, CSF absorption (and fluid flow in general) is linearly related to pressure differences between adjacent spaces. However, in the pressure/volume steady-state, CSF absorption is indeed linearly related to CSF pressure increase, with the slope defined as the 'model' conductance of CSF outflow (C^m_{out}).

2.1 Clinical Methods

In the experiments performed by Albeck *et al.*[1], each patient was placed in a lateral position to set the ventricular system and the lumbar subarachnoid space at the same level. A puncture was made in the lower lumbar space and two tubes were connected to the needle. Artificial CSF was delivered via one tube with a constant rate of infusion Q_{inf}. The outlet of the other tube was elevated in steps to increase the lumbar pressure. After equilibrium pressure was reached, a measurement of the outflow of the elevated tube, Q_{out}, was taken. The absorption rate was calculated by the formula:

$$Q_{abs} = Q_{inf} + Q_f - Q_{out},$$

where Q_f is the CSF production rate. The assumption involved in this formula is that once equilibrium pressure is reached, a constant volume of the CSF space is maintained. Corresponding values of equilibrium pressure and Q_{abs} were plotted and the linear regression line was calculated by the method of least squares. The slope of the regression line was then taken as the expression for C_{out}. The relationship between CSF absorption rate and CSF pressure increase can now be defined by

$$Q_{abs} = C_{out}(P^*_f - \bar{P}_f) + Q_f, \qquad (1)$$

where

$$\begin{aligned} Q_{abs} &= \text{CSF absorption rate} \\ P^*_f &= \text{CSF equilibrium pressure} \\ \bar{P}_f &= \text{CSF resting pressure} \\ Q_f &= \text{constant CSF formation rate} \\ C_{out} &= \text{conductance of CSF outflow.} \end{aligned}$$

2.2 The Mathematical Model

As in the model developed by Karni *et al.*[5], the intracranial space is divided into the seven compartments depicted in **Figure 1**. A term is added to represent an infusion rate of mock CSF into the CSF compartment (Q_{inf}). Furthermore, because CSF production is known to remain 'nearly' constant throughout a wide range

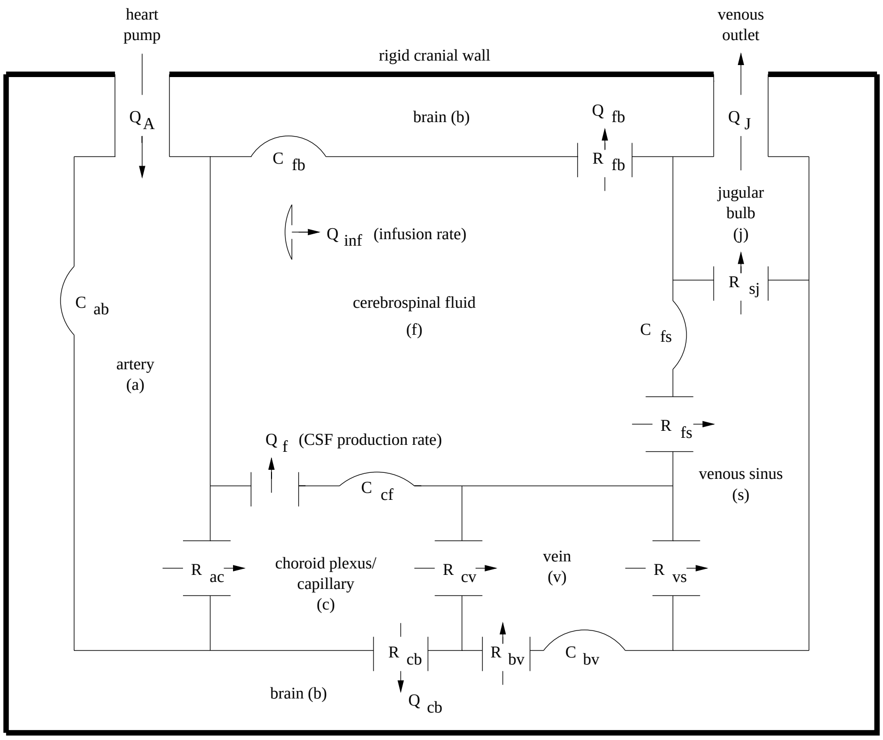

Figure 1: The seven compartment model

of intracranial pressures[1,4,11], this model introduces a constant CSF production term (Q_f).

The basic assumptions that lead to the equations describing the dynamics of this system are:

- Pressure driven flows are described by

$$Q_{ij} = \frac{P_i - P_j}{R_{ij}} = Z_{ij}(P_i - P_j) = Z_{ij}P_{ij}, \quad (2)$$

  where Q_{ij} is the flow from compartment i into compartment j, P_i is the spatially-averaged pressure of compartment i, R_{ij} is the resistance to flow between compartments i and j, Z_{ij} (fluidity) is the inverse of resistance and $P_{ij} = P_i - P_j$.

- The deformation of the membrane between adjacent compartments is a function of the change in pressure difference between these compartments;

$$\frac{dV_{ij}}{dt} = C_{ij}\frac{d(P_i - P_j)}{dt} = C_{ij}\frac{d(P_{ij})}{dt}, \quad (3)$$

  where V_{ij} denotes the volume of the 'cup' formed at the interface of compartments i and j. Here, C_{ij} denotes the compliance between these two compartments.

- The cranial volume is considered constant and the constituents considered incompressible. This implies that any input must be compensated by an equal output;

$$Q_A + Q_{inf} = Q_J. \quad (4)$$

  This is called the Kellie-Monro Doctrine[6,8].

Applying the law of conservation of mass in each compartment results in a set of seven differential equations. For example, in the CSF (f) compartment

$$Q_f + Q_{inf} - Z_{fs}P_{fs} - Z_{fb}P_{fb} = C_{fb}\frac{dP_{fb}}{dt} + C_{fs}\frac{dP_{fs}}{dt} - C_{cf}\frac{dP_{cf}}{dt}. \quad (5)$$

Because the jugular bulb is considered non-deformable, the equation for this compartment may be algebraically solved after the solution for P_s is obtained. Due to the Kellie-Monro doctrine, only five of the remaining six equations are independent. Therefore, considering arterial pressure as a known input, the system reduces to five linearly independent differential equations (see Lakin *et al.*[7]) described in matrix form by

$$C\frac{dP}{dt} + ZP = Q. \quad (6)$$

Here, P and Q are the five element vectors

$$\begin{aligned} P &= [P_s,\, P_v,\, P_c,\, P_f,\, P_b]^{tr} \\ Q &= [-(Q_A + Q_{inf}),\, 0,\, Q_f - Q_A, \\ &\quad Z_{ac}P_a - Q_A,\, C_{ab}\dot{P}_a + Z_{ac}P_a - Q_A]^{tr}. \end{aligned}$$

The compliance matrix (C) and fluidity matrix (Z) are explicitly defined in the appendix.

If the oscillatory nature of the forcing terms in Q is disregarded, the solution of (6) is a set of time-dependent mean pressures which correspond to those measured in clinical experiments. Due to the stability properties of the matrices involved, the solution of the time-averaged, linear problem tends to the steady-state defined by

$$P^* = Z^{-1}Q^* \quad (7)$$

where

$$\begin{aligned} Q^* &= [-(\overline{Q}_A + Q_{inf}),\, 0,\, Q_f - \overline{Q}_A, \\ &\quad Z_{ac}\overline{P}_a - \overline{Q}_A,\, Z_{ac}\overline{P}_a - \overline{Q}_A]^{tr}, \end{aligned}$$

In the case of zero infusion, equation (7) reduces to the form

$$\overline{P} = Z^{-1}\overline{Q} \quad (8)$$

where

$$\begin{aligned} \overline{Q} &= Q^* + Q_i \\ Q_i &= [Q_{inf},\, 0,\, 0,\, 0,\, 0]^{tr}. \end{aligned}$$

Here, the use of an overbar indicates the initial resting condition prior to the start of an infusion test.

Subtracting equation (8) from (7) yields

$$P^* - \overline{P} = -Z^{-1}Q_i. \quad (9)$$

Specifically, with regards to the CSF compartment, equation (9) implies

$$P_f^* - \overline{P}_f = -[Z^{-1}]_{(4,1)}Q_{inf}, \quad (10)$$

where $[Z^{-1}]_{(4,1)}$ is the fourth element in the first column of Z^{-1} and is explicitly defined in the appendix, equation (28).

As in the experiments, the model steady-state is achieved in the CSF compartment when CSF absorption is equal to the sum of CSF production and CSF infusion;

$$\begin{aligned} Q_{abs} &= Q_{inf} + Q_f \\ &= \frac{-1}{[Z^{-1}]_{(4,1)}}(P_f^* - \overline{P}_f) + Q_f \end{aligned}$$

where the second of these equalities is a result of equation (10).

Now, the model absorption rate is defined as a linear function of CSF pressure increase by

$$Q_{abs} = C_{out}^m(P_f^* - \overline{P}_f) + Q_f, \quad (11)$$

where

$$\begin{aligned} C_{out}^m &= \frac{-1}{[Z^{-1}]_{(4,1)}} \quad (12) \\ &= \text{model conductance of CSF outflow.} \end{aligned}$$

Note, equation (11) corresponds to the same relationship described experimentally by equation (1).

It can be seen that the model conductance of CSF outflow (12) is a function of the model fluidity values and each fluidity value is a function of mean pressures and flows from (2), defined by

$$Z_{ij} = \frac{\overline{Q}_{ij}}{\overline{P}_i - \overline{P}_j}. \tag{13}$$

The goal is to determine the mean flows and pressures which result in a calculated model conductance (C_{out}^m) that is in agreement with the clinical results of Albeck *et al.*[1].

If the mean pressures and $\overline{Q}_A$ are known, three additional mean flows must be determined in order to define all of the fluidity values. These must be chosen judiciously so that the remaining mean flows can all be defined in terms of these three and $\overline{Q}_A$. Choosing CSF production (Q_f), flow across the blood-brain barrier ($\overline{Q}_{cb}$), and flow across the CSF-brain barrier ($\overline{Q}_{fb}$) as the three additional mean flows, the remaining mean flows may then be determined by noting that each compartment maintains a constant volume in the resting steady-state, for example:

$$\overline{Q}_{ac} = \overline{Q}_A \tag{14}$$
$$\overline{Q}_{bv} = \overline{Q}_{fb} + \overline{Q}_{cb} \tag{15}$$
$$\overline{Q}_{fs} = Q_f - \overline{Q}_{fb} \tag{16}$$
$$\overline{Q}_{cv} = \overline{Q}_{ac} - Q_f - \overline{Q}_{cb} \tag{17}$$
$$\overline{Q}_{vs} = \overline{Q}_{cv} + \overline{Q}_{bv}. \tag{18}$$

Since valid estimations of mean arterial input ($\overline{Q}_A$) and mean CSF production (Q_f) are available, these will be considered 'known' flows. Therefore, $\overline{Q}_{fb}$ and $\overline{Q}_{cb}$ are considered the two 'unknown' flows. However, because the mean pressures are not necessarily available from the clinical experiments, some of these must be estimated from the available information.

The mean pressure framework of the compartmental model will be estimated by:

$$\overline{P}_a > \overline{P}_c > \overline{P}_f >\approx \overline{P}_b >\approx \overline{P}_v > \overline{P}_s, \tag{19}$$

where $\overline{P}_f$ will be taken from the clinical experiments. The above inequalities are necessary to ensure pressure driven flow between adjacent compartments. The inequality ($>\approx$) implies the difference is small but greater than zero. The use of this inequality above is based on two assumptions. First, brain and CSF have 'nearly' equal mean resting pressures[4]. Second, the mean venous pressure can never be 'significantly' lower than the mean CSF pressure, otherwise cerebral blood flow ceases[9].

An estimation for venous-sinus pressure is given by Davson[2] as

$$\overline{P}_s = \overline{P}_f - \frac{Q_f}{C_{out}}. \tag{20}$$

This is based on extending the linear regression line described by equation (1) to $Q_{abs} = 0$. It is assumed that the resulting value of P_f^* is equal to that of the resting saggital sinus pressure, or equivalently

$$Q_f = C_{out}(\overline{P}_f - \overline{P}_s). \tag{21}$$

This implies there is zero flow into the brain compartment in the resting steady state. In order to accommodate the notion that some CSF fluid is absorbed into the brain tissue[4,5,11] and that a pressure gradient of approximately 1.5 mmHg is necessary to initiate absorption across the arachnoid villi[4], equation (20) is reformulated to estimate the model mean venous-sinus pressure as

$$\overline{P}_s = \overline{P}_f - \frac{Q_f}{C_{out}^m} - 1.5\,. \tag{22}$$

At this point, the model conductance of CSF outflow is defined as a function of the 'unknown' flows $\overline{Q}_{fb}$ and $\overline{Q}_{cb}$ with the rest of the problem variables ($\overline{Q}_A$, Q_f and the mean pressures) considered 'known'. The use of the quotes here is to stress that the value of many of the 'known' variables are estimations based on available information. Furthermore, equation (22) now implies that the model conductance of CSF outflow is implicitly defined by equation (12). In this case, a unique explicit definition for model conductance in terms of the 'known' and 'unknown' variables does not exist. Therefore, equation (12) must be solved numerically. This requires assigning numerical values to the 'known' variables as described in the results.

3 Results

The model conductance (C_{out}^m) defined in equation (12) provides a term in the model which represents the identical term that is measured experimentally. Due to the complexity of the term C_{out}^m, numerical methods are required to obtain the mean pressures and flows necessary to reproduce experimental results regarding the conductance of CSF outflow. It is in this way that previously immeasurably small flows ($\overline{Q}_{fb}$ and $\overline{Q}_{cb}$), may be estimated through the mathematical model.

3.1 Clinical Results

Due to the nature of this method, it is seldomly performed on human subjects without suspicion of some form of altered intracranial hydrodynamics. Therefore, the sample size of healthy individuals studied by Albeck *et al.*[1] is relatively small. From the eight subjects tested, the following data was obtained: The mean ICP pressure was 11 ± 2 mmHg. A constant CSF formation rate, Q_f, was taken as 0.4 ml/min. It should be noted that this rate may be higher or lower but this would have no affect on the the slope of the regression line, C_{out}. All regression coefficients were greater than 0.95, suggesting a strong linear relationship between absorption rate and CSF pressure increase. This is also noted by Sullivan and Allison [11] where CSF conductance in humans is quoted as 'relatively' constant. A mean C_{out} of 0.11 ± 0.01 (ml/min)/mmHg was calculated with a 95% confidence interval of 0.10–0.13 (ml/min)/mmHg. This value was compared to similar tests from four other authors quoted by Albeck as having a range of 0.08 to 0.13 (ml/min)/mmHg.

3.2 Model Results

Assuming a mean arterial pressure of 100 mmHg and capillary pressure of 20 mmHg[5,10], a CSF pressure of 11 mmHg (from the Albeck experiments) and $Q_f = 0.35$ ml/min (this is an average of several estimations[1,3,4,5,10,11]), the remaining compartmental mean pressures may be estimated from (19) and (22) as

$$\begin{aligned} \overline{P}_b &= 10.5 \\ \overline{P}_v &= 10.0 \\ \overline{P}_s &= 11.0 - 0.35/C_{out}^m - 1.5 \\ &= 6.3 \qquad (\text{if } C_{out}^m = 0.11) \end{aligned}$$

where all pressures are measured in mmHg. Finally, assuming a mean arterial input ($\overline{Q}_A$) of 750 ml/min[4,5,10] completes the estimations of the 'known' variables, with C_{out}^m still undetermined.

Equation (12) may now be numerically solved to reveal the relationship between the unknown flows $\overline{Q}_{fb}$ and $\overline{Q}_{cb}$ necessary to achieve a model conductance of CSF outflow equal to 0.11 (ml/min)/mmHg as calculated by the Albeck experiments.

A new variable (p) is introduced to represent the portion of CSF absorbed into the venous-sinus compartment, $p = \overline{Q}_{fs}/Q_f$. This single variable replaces $\overline{Q}_{fs}$ and $\overline{Q}_{fb}$ by

$$\overline{Q}_{fs} = pQ_f, \tag{23}$$

$$\overline{Q}_{fb} = (1-p)Q_f, \quad (24)$$

where p is between zero and one.

It is now possible to assign values to $\overline{Q}_{cb}$ and p, and numerically solve equation (12) for the model conductance (C_{out}^m). **Figure 2** displays these results with $\overline{Q}_{cb}$ labeled Q_{cb}. Equivalently, assigning a value for $\overline{Q}_{cb}$ and requiring $C_{out}^m = 0.11$, the value for p is then fully determined. This can be seen by projecting the intersection of the curves in **Figure 2** to the p axis. By doing this it can be seen that p is between 0.87 and 0.945, regardless of the value assigned to $\overline{Q}_{cb}$. This agrees with the proposition that the saggital sinus is the 'main' recipient of CSF outflow[1,3,4,11].

As seen in **Figure 2**, if $\overline{Q}_{cb}$ is known, p can be determined, similarly if p is known, $\overline{Q}_{cb}$ can be determined. Unfortunately, very little conclusive data is available regarding the exact value of these terms. However, Sorek *et al.*[10] do provide a ratio (r) defined by

$$r = \overline{Q}_{cb}/\overline{Q}_{fb}. \quad (25)$$

Here, r is the ratio of flow across the blood-brain barrier to that across the CSF-brain barrier. Because these are the two smallest flows, it would seem reasonable that measuring the ratio of these two flows can be performed more accurately than measuring either of them individually.

It is now possible to numerically determine the relationship between r and p. This relationship is depicted in **Figure 3**. This shows the rapid increase of p to its limiting value ≈ 0.945.

An approximation of r is given by Sorek *et al.*[10] of 0.021. Using this value for r results in a numerically determined value for p of 0.874. At this point, $\overline{Q}_{fb}$ is determined from (24) and $\overline{Q}_{cb}$ is determined from (25) as

$$\overline{Q}_{fb} = 0.044 \text{ ml/min} \quad (26)$$

$$\overline{Q}_{cb} = 0.001 \text{ ml/min}, \quad (27)$$

with the remaining mean flows determined from equations (14) – (18).

4 Discussion

Using the model described in this paper and the results of clinical researchers, it is possible to extrapolate much of the information regarding normal fluid dynamics in the human intracranial system. In this study, experimental results regarding the conductance of CSF outflow (C_{out}) are incorporated into the mathematical model in order to determine intracranial mean pressures and flows that are not measured in these clinical tests. This is motivated by the lack of information regarding the small flow of extracellular fluid into the interstitial brain tissue. In attempting to determine these small mean flows, a mean pressure framework throughout the intracranial system is also estimated from available information.

If the mean pressures described above, as well as the mean arterial input and CSF production ($\overline{Q}_A = 750$ ml/min and $Q_f = 0.35$ ml/min respectively), are considered valid, then the range of possible values for the percentage of CSF outflow absorbed directly into the venous-sinus (p) can be estimated from the conductance of CSF outflow (**Figure 2**). For example, if the conductance of CSF outflow (C_{out}) is higher than the accepted value of 0.11 (ml/min)/mmHg, then the range of possible p values shifts to the left. This suggests that the flow of CSF into the interstitial brain tissue ($\overline{Q}_{fb}$) increases. While the larger value of CSF conductance prevents elevated intracranial pressures in the face of a CSF drainage blockage, the larger flow into the interstitial brain tissue could result in edema of the brain in such a case. Conversely, if C_{out} is below this value, this suggests that $\overline{Q}_{fb}$ decreases. In this case, patients with normal intracranial pres-

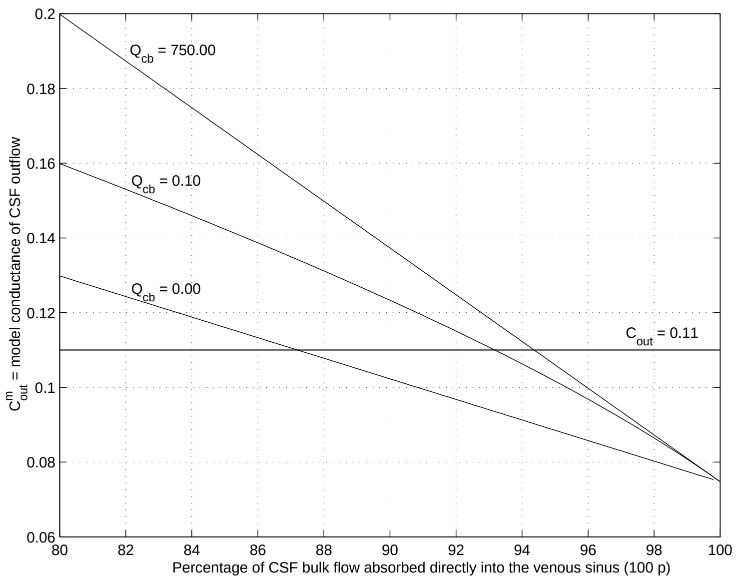

Figure 2: Model conductance of CSF outflow (C_{out}^{m}) as a function of p, where p is the portion of CSF outflow absorbed directly into the venous sinus ($p = \overline{Q}_{fs}\ /\ Q_f$). The horizontal line indicates the conductance as calculated from the Albeck experiments. Here, $\overline{Q}_{cb}$ is labeled Q_{cb}.

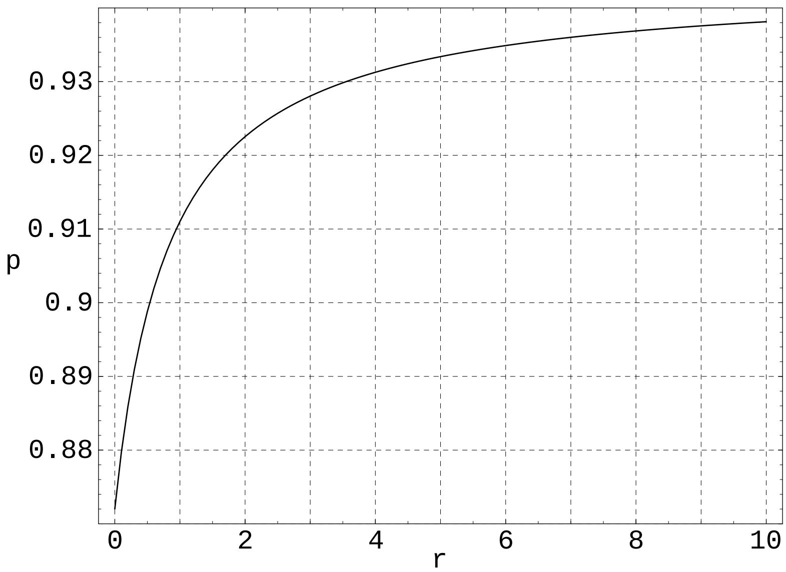

Figure 3: p as a function of r, when C_{out}^{m} is held constant at 0.11 (ml/min)/mmHg. p represents the portion of CSF outflow absorbed directly into the venous sinus ($p = \overline{Q}_{fs}\ /\ Q_f$), and r represents the ratio of extracellular fluid flow across the blood-brain barrier to that of the CSF-brain barrier, ($r = \overline{Q}_{cb}\ /\ \overline{Q}_{fb}$).

sures and a low conductance of CSF outflow are more likely to experience elevated CSF pressure when a blockage of the arachnoid villi occurs. This is due to the inability of the excess CSF to drain through alternate routes.

If, in addition, the value $C_{out} = 0.11$ (ml/min)/mmHg is considered indicative of normal human physiology, **Figure 3** reveals the relationship between p and the ratio of flow across the blood-brain barrier to that across the CSF-brain barrier ($r = \overline{Q}_{cb}/\overline{Q}_{fb}$). If future values of r differ from the suggested value of 0.021, the appropriate value of p can be determined from this graph and the values of $\overline{Q}_{fb}$ and $\overline{Q}_{cb}$ can be determined from equations (24) and (25) respectively. Similarly, if future values of p differ from the calculated value of 0.874, this same graph reveals the appropriate value for r.

Finally, if the suggested value of $r = 0.021$ is considered appropriate, then p is numerically determined to be 0.874 and the two smallest mean flows ($\overline{Q}_{fb}$ and $\overline{Q}_{cb}$) are calculated as 0.044 ml/min and 0.001 ml/min respectively. All of the other mean flows may then be calculated from equations (14) – (18).

While the mean intracranial pressures and flows developed in this paper are done with respect to the physiologically normal adult, the same methods may be employed in studying the intracranial fluid dynamics in persons with a variety of initial conditions, including physiological disorders. The benefit of using this mathematical model in conjunction with experimental results is that critical data, which may be difficult to obtain clinically, may be estimated with a minimal amount of intrusive procedures.

5 Appendix

The matrices in equation (6);

Z is the fluidity matrix

$$\begin{pmatrix} Z_{fs,vs} & -Z_{vs} & 0 & -Z_{fs} & 0 \\ -Z_{vs} & Z_{bv,cv,vs} & -Z_{cv} & 0 & -Z_{bv} \\ Z_{vs} & -Z_{vs} & 0 & Z_{fb} & -Z_{fb} \\ Z_{vs} & -Z_{cv,vs} & Z_{ac,cb,cv} & Z_{fb} & -Z_{cb,fb} \\ 0 & 0 & Z_{ac} & 0 & 0 \end{pmatrix}$$

and C is the compliance matrix

$$\begin{pmatrix} C_{fs} & 0 & 0 & -C_{fs} & 0 \\ 0 & C_{bv} & 0 & 0 & -C_{bv} \\ 0 & 0 & -C_{cf} & C_{cf,fb} & -C_{fb} \\ 0 & 0 & 0 & C_{fb} & -C_{fb} \\ 0 & 0 & 0 & 0 & C_{ab} \end{pmatrix}.$$

In these matrices, the repeated subscript ij, kl, .. has been used to denote the sum of the respective quanitities, e.g., $Z_{bv,cv,vs}$ represents $Z_{bv} + Z_{cv} + Z_{vs}$.

The fourth term in the first column of the inverse of Z (labelled $[Z^{-1}]_{(4,1)}$) introduced in equation (10) is defined in terms of fluidity values by:

$$\begin{aligned} &[Z^{-1}]_{(4,1)} = \\ &-\{Z_{vs}(Z_{bv}(Z_{cb}+Z_{cv})+Z_{cv}(Z_{cb}+Z_{fb}))\}/ \\ &\{Z_{cv}Z_{fb}Z_{fs}Z_{vs}+ \\ &\ Z_{bv}(Z_{cb}+Z_{cv})[Z_{fs}Z_{vs}+Z_{fb}(Z_{fs}+Z_{vs})]+ \\ &\ Z_{cb}[Z_{fb}Z_{fs}Z_{vs}+ \\ &\ Z_{cv}(Z_{fs}Z_{vs}+Z_{fb}(Z_{fs}+Z_{vs}))]\} \end{aligned} \tag{28}$$

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