On-Line Appendix

Mathematic Appendix

The aim of this Appendix is to provide a very brief introduction and overview of a recent mathematic model of intracranial pressure dynamics. This model, essentially based on a collapsible venous sinus, reproduces the clinical findings in a large percentage of patients with IIH and adds support to intracranial stent placement as a form of treatment. More extensive details are found in the literature.[1-4] We have reproduced and confirmed the findings from this model, and the images in this article are our results by using Mathematica (Wolfram Research, Champaign, Illinois) to perform the numeric integration.

The model under discussion here (Fig A1) consists of 5 compartments, each characterized by a pressure (P_i) and volume (V_i) given as functions of time—arteries/capillaries (C), veins/proximal venous sinuses (S), distal venous sinuses (V), brain/CSF (F), and thorax (Y). Intracranial pressure is taken as brain/CSF pressure.

Fluids are assumed to be incompressible and isothermal, and constant rates are assumed for cerebral blood flow (Q_{CS}) and CSF production (Q_{CF}). Fluid flows between compartments are otherwise driven by pressure differences:

$$Q_{ij} = \frac{1}{R_{ij}}(\dot{P}_i - \dot{P}_j) = Z_{ij}(P_i - P_j),$$

where Q_{ij} represents fluid flow from compartment i to j, R_{ij} represents the resistance to flow, and Z_{ij}, the fluidity (inverse of resistance). Flow from proximal to distal sinuses (Q_{SV}) is dependent on CSF pressure and is modeled by a Starling-like resistor, which models a collapsible venous sinus. As $P_F - P_V$ increases, Z_{SV} decreases down to some minimal value. Z_{SV} is a 2-parameter function, depending on sinus collapsibility and maximum collapsibility.

Compartmental volume changes are determined by the compliance ($Cij = C_{ji}$) of membranes between compartments:

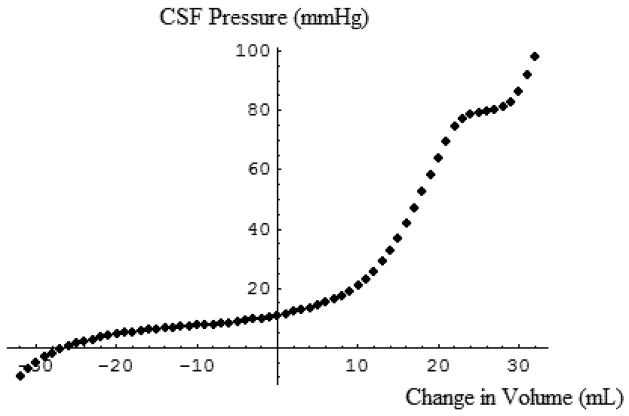

Fig A2. CSF pressure-volume curve obtained by simulated "infusion" or "withdrawal" of fluid from the CSF/brain compartment.

$$\frac{dv_1}{dt} = C_{ij}\frac{d}{dt}(P_i - P_j) = C_{ij}\dot{P}_{ij}.$$

Conservation of mass in each compartment then generates the differential equations governing the dynamics:

$$\text{Rate of Volume Change} = \text{Flow In} - \text{Flow Out}.$$

For compartments F (brain/CSF) and S (proximal venous sinuses), we thus have the following:

$$\frac{dV_F}{dt} = Q_{CF} + Q_{\text{inf}} - Q_{FS} - Q_{FV}$$

$$= C_{CF}\dot{P}_{FC} + C_{FX}\dot{P}_{FS} + C_{FV}\dot{P}_{FV} + C_{FY}\dot{P}_{FY}$$

and

$$\frac{dVs}{dt} = Q_{CS} + Q_{FS} - Q_{SV} = C_{FS}\dot{P}_{SF}.$$

Required physiologic parameters are taken from the literature, and the system of differential equations is integrated

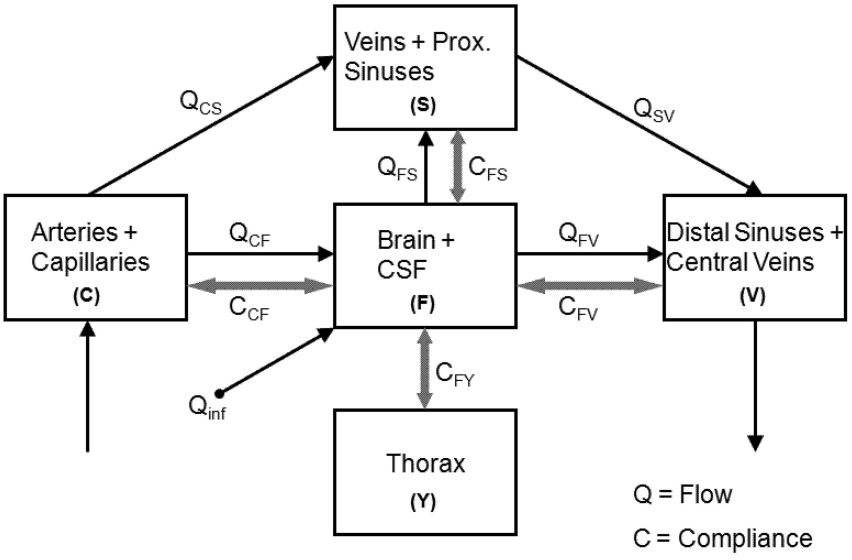

Fig A1. Compartmental model of intracranial pressure and volume dynamics. Flow rates between various compartments are represented by Q_{ij}, and compliance of membranes between compartments are represented by C_{ij}. The model includes a Starling-like resistor between compartments S and V, modeling a collapsible venous sinus, such that Q_{SV} also depends on CSF pressure.

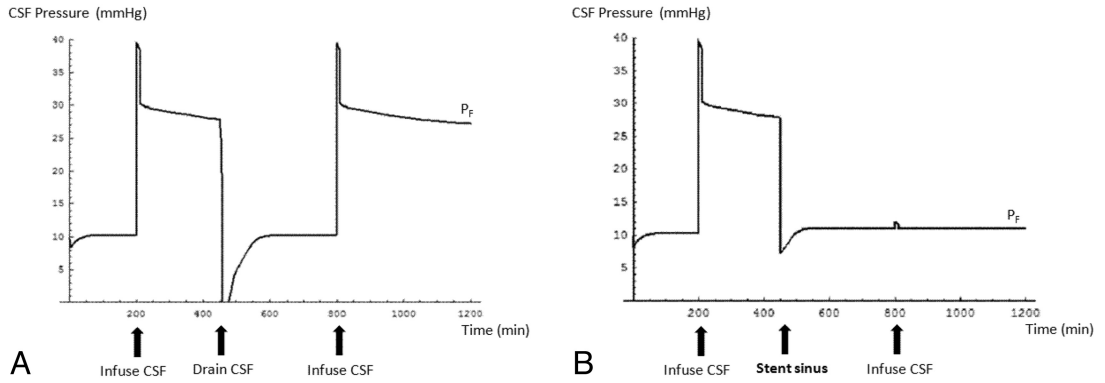

Fig A3. Model simulations demonstrating the change in CSF pressures (P_F) following infusion and withdrawal of CSF in a patient with IIH with a collapsible sinus and then the same patient (by using the same rate and volume) with the sinus stented. *A,* Collapsible sinus. *B,* Rigid sinus.

to examine the dynamics, allowing comparison with clinical observations.

A key finding of the mathematic analysis is that the inclusion of a Starling-like resistor, modeling a collapsible venous sinus, leads to 2 possible steady states—the normal-pressure steady state and an elevated-pressure steady state. The normal-pressure steady state is the only stable state in the presence of a noncollapsible sinus. Various perturbations, as shown in the example below, can cause the model to move from 1 steady state to the other.

Model Validation

Detailed results of validation simulations are given in Stevens et al.[2] For example, there is impressive agreement with experimental data concerning the global CSF pressure-volume relationship. To examine this in the model, varying volumes are "infused" into the CSF at various rates (too slow and normal arachnoid CSF drainage will maintain normal pressures) or "withdrawn," and the resulting pressures and volumes are measured. The CSF volume change is given by:

$$V_F(t) = \int_0^t Q_{\text{inf}} + Q_{CF} - Z_{FS}P_{FS}(\tau) - Z_{FV}P_{FV}(\tau)\ d\ \tau.$$

The result of these integrations is given in Fig A2. There is close agreement with experimental and clinical data over the entire range, as well as reproduction of the increase in compliance at the upper plateau due to alteration of interarterial blood volume as arterial blood pressures are reached.

Sample Simulation

A sample simulated patient is shown in Fig A3. Initially, with a collapsible sinus, infusion and withdrawal of CSF flips the patient between the normal- and high-pressure steady states as detailed in the "Discussion." Stent placement in the transverse sinus is equivalent to having a rigid sinus, and the patient returns to the single normal-pressure steady state. Further CSF infusion does not flip the patient into a higher steady state because this no longer exists and the pressure-volume relationship will follow that of a normal patient (Fig A2).

Appendix References

1. Stevens SA, Lakin WD. **Local compliance effects on the global pressure-volume relationship in models of intracranial pressure dynamics**. *Mathematical and Computer Modeling of Dynamical Systems* 2000; 6:445–65
2. Stevens SA, Previte M, Lakin WD, et al. **Idiopathic intracranial hypertension and transverse sinus stenosis: a modeling study.** *Math Med Bol* 2007;24:85–109. Epub 2006 Oct 27
3. Stevens SA, Thakore NJ, Lakin WD, et al. **A modeling study of idiopathic intracranial hypertension: etiology and diagnosis.** *Neurol Res* 2007;29:777–86
4. Stevens SA, Stimpson J, Lakin WD, et al. **A model for idiopathic intracranial hypertension and associated pathologic ICP wave-forms.** *IEEE Trans Biomed Eng* 2008;55(2 pt 1):388–98