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A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics

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A mathematical model of the cerebrospinal fluid (CSF) system was developed to help clarify the kinetics of the intracranial pressure (ICP). A general equation predicting the time course of pressure was derived in terms of four parameters: the intracranial compliance, dural sinus pressure, resistance to absorption, and CSF formation. These parameters were measured in the adult cat, and the equation was tested by comparing experimental and calculated values of the time course of pressure in response to volume changes. The theoretical and experimental results were in close agreement, and the role of each parameter in governing the dynamic equilibrium of the ICP was determined. From this analysis, dynamic tests were developed for rapid measurement of CSF formation, absorption resistance, and the bulk intracranial compliance. These techniques are applicable to clinical settings, providing data that are useful in characterizing the physiological mechanisms responsible for raised ICP and assessing changes induced by therapy.

KEY WORDS • **intracranial pressure** • **compliance** • **mathematical model** • **cerebrospinal fluid system**

THE biological sequence of events leading to a relentless increase of intracranial pressure (ICP) and eventual neurological death are poorly understood. We know that if fluid is added to or withdrawn from the cerebrospinal fluid (CSF) space, pressure will change transiently from its initial value, followed by a gradual return to the predisturbance level. Ryder, *et al.*,[19] viewed this as a form of "dynamic control." They and other early workers recognized that the magnitude of pressure change and the overall stability of the system was somehow related to the intracranial elasticity and the "persistent seepage of fluid" into or out of the CSF space. However, the individual effects of these ongoing processes upon pressure are difficult to isolate by experimental means, since formation, absorption, and elasticity are mutually interactive and their combined effects upon the ICP are hydrodynamically complex.

The present work describes an analytical approach to the physics of the ICP with the objective of isolating those parameters leading to sustained elevation of the ICP. Using this approach, we developed a theory in the form of mathematical equations which explain how changes in volume (input) are related to changes in pressure (output). We tested the accuracy of the equations by applying this theory to the CSF dynamics of the ex-

perimental animal, and in this process isolated and studied four parameters that govern the ICP level and its rate of change.

Analytical Method

Mathematical Model

As a conceptual aid, we used an electrical model to approximate the hydrodynamics of the CSF system (Fig. 1). The fluid pump represents the combined action of elements responsible for the production of CSF. The newly formed fluid (I_f) is subdivided into two components (Equation 1). A portion (I_s) is retained within the CSF space, while the remainder (I_a) is eventually absorbed:

$$I_f = I_s + I_a. \quad (1)$$

Under normal physiological conditions, the rate of formation (I_f) is balanced by an equal rate of absorption (I_a). This condition of equilibrium results in no increase or decrease in the amount of volume stored ($I_s = 0$) and the initial resting volume as well as the CSF pressure (P) are maintained at a constant level. The rate of outflow (I_a) is given by the gradient of pressure between CSF space and the venous system of the dural sinus (P_d) divided by the resistance to absorption (R):

$$I_a = (P - P_d)/R. \quad (2)$$

The volume I_s that is not absorbed equals the time rate of change of stored volume (dV/dt). An increase in the volume stored raises the ICP. The amount of pressure rise will depend upon the intracranial compliance. By definition, the ratio of change in volume to change in pressure dV/dP equals the compliance (C) which can be obtained by measuring the slope of a volume-pressure curve of the system under study:

$$C = dV/dP. \quad (3)$$

For a straight-line relationship between pressure and volume, the rate of pressure change (dP/dt) would be directly proportional to the rate of volume change (dV/dt) and the constant compliance coefficient, as

$$dP/dt = C\,dV/dt. \quad (4)$$

However, it will be shown that because of an exponential PV curve, the intracranial compliance (C) is not a constant but decreases as pressure increases according to the following function:

$$C = 1/KP, \quad (5)$$

where the factor K is a mathematical constant describing the steepness of the curve. As a result, the time rate of pressure change (dP/dt) assumes exponential form, since it is not only a function of volume change as in Equation 4, but of pressure level as well.

$$dP/dt = K\,P\,dV/dt = K\,P\,I_s. \quad (6)$$

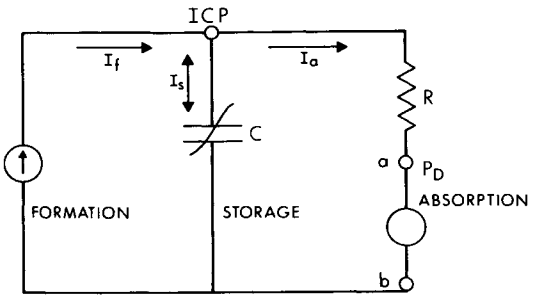


FIG. 1. The CSF system was depicted by an equivalent electrical circuit that distributed the CSF parameters among three fundamental mechanisms: formation, represented by a constant current generator; storage, represented by a nonlinear capacitance (C); and absorption represented by resistance element (R). The venous outflow site (dural sinus) was represented by a constant pressure source P_d. The system equations were derived from this configuration.

Definition of Equation Symbols

I_f	=	rate of CSF production (ml/min)
I_s	=	component of CSF production that is stored (ml/min)
I_a	=	component of CSF production that is absorbed (ml/min)
P	=	intracranial pressure, CSF pressure (mm H_2O)
P_d	=	intradural sinus pressure (mm H_2O)
C	=	intracranial compliance, change in CSF volume per unit change in CSF pressure (ml/mm H_2O)
PVI	=	pressure-volume index (ml)
K	=	mathematical constant (1/.04343 PVI) (ml)
R	=	resistance to CSF absorption (mm H_2O/ml/min)

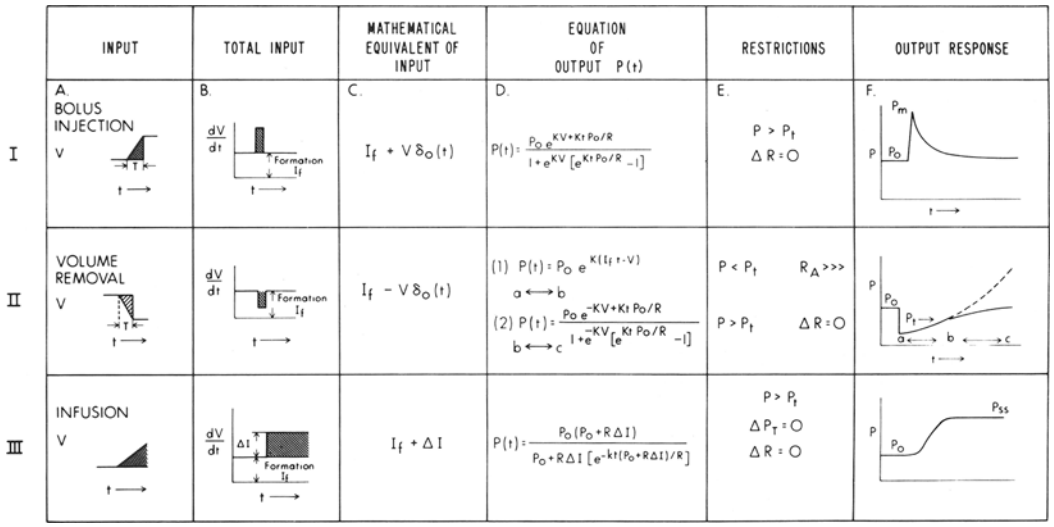


FIG. 2. Summary of input-output relationships of the CSF system. Each type of volume change (A) was added to CSF formation to define the total volume input (B). The mathematical equivalent of the total volume input (C) applied to the general equation produces a specific solution (D). When the physiological conditions (E) are met, the specific solution predicts the response of CSF pressure (F).

We now have expressions for the stored volume flow (I_s) (Equation 6), and the amount absorbed I_a (Equation 2) in terms of pressure. Substituting these terms in Equation 1 we obtained the following differential equation describing the hydrodynamics of the proposed model:

$$dP/dt - P^2 K/R - P K (I_f + P_d/R) = 0. \quad (7)$$

Our objective was to solve this equation for the time course of intracranial pressure P(t) in terms of other parameters. This could not be done using ordinary methods because of the nonlinearity introduced by the exponential pressure-volume relationship.

By a special technique, a solution was found for P(t) using a transformation of the dependent variable (P). (See Appendix Equations A1 through A3). Equation 8 represents the general solution of the time course of intracranial pressure since it predicts both the transient response and shifts in resting level that would occur for any volume input described by the term $I(\tau)$:

$$P(t) = \Psi(t) / \{1/P_o + (K/R)_o \int^t \Psi(\tau) d\tau\}, \quad (8)$$

where $\Psi(t) = e^{K_o \int^t I(\tau)\, d\tau}$ The term $\Psi(t)$ is used to simplify the mathematical form of the general equation.

To check the accuracy of this theoretical equation and examine the hydrodynamics of the model in greater detail, we derived the theoretical response of ICP to three specific terms of input: a bolus injection, a continuous infusion, and bolus withdrawal of CSF volume (Fig. 2). For each case, the volume change was described in mathematical terms in order to define the volume input function $I(\tau)$ (I-C, II-C, III-C). The volume term $I(\tau)$ was then substituted in Equation 8 to yield a specific solution for the time course of pressure P(t) (I-D, II-D, III-D).

As an example, the bolus injection was described as an amount of fluid volume (V) inserted into the CSF space within an interval T (Type I, Fig. 2 A). The total volume input to the model consisted of this short pulse of flow, expressed mathematically as $V\delta_o(t)$, added to a constant rate of formation (I_f). The theoretical time course of the ICP in response to a bolus injection is given by the equation shown in I-D (Fig. 2), and sketched in I-F. Before the volume input (V), the pressure is at equilibrium (P_o). At the peak of the injection interval, the pressure rises to a maximum value P_m, which is equivalent to the

value of P(t) immediately after the injection, as computed in the equation shown in I-D (Fig. 2). Following the initial rise, the pressure decays toward the pre-stimulus level P_o at a rate determined by the compliance and resistance to outflow parameters. The instantaneous values of P(t) during this recovery phase is given by Equation I-D (Fig. 2), and is based upon the assumptions that formation (I_f) and resistance (R) remain stable and independent during the injection sequence. A similar reasoning and mathematical procedure was applied to the development of specific solutions and response curves for the bolus withdrawal (Type II, Fig. 2) and continuous infusion (III-D, Fig. 2).

The response to bolus injection or continuous infusion can be described by a single equation. This is not the case for bolus withdrawal. When volume is removed from the CSF space, there is an additional nonlinearity that must be taken into consideration in the analysis of the pressure response. In the formulation of the model, it was assumed that when the ICP fell below a threshold pressure (P_t), the resistance to the absorption (R) increased and that absorption of fluid would only occur in the presence of a positive gradient between CSF and the dural venous sinus pressure. Incorporation of these restrictions in the model (II-E, Fig. 2) results in two equations for the response to volume removal (II-D, Fig. 2). Below threshold, if no absorption occurs, the pressure follows an exponential rise toward the initial pressure (region a–b) as the newly formed fluid enters the CSF space. This initial rate of rise is dependent only on the compliance and rate of formation. The exponential rise of pressure continues until threshold P_t is reached. When the ICP exceeds the threshold level, absorption takes place (regions b–c) and the ICP gradually returns to equilibrium following the trajectory given by the second equation of II-D (Fig. 2).

A continuous infusion of fluid was considered as a step disturbance of input volume flow (ml/min) added to the existing formation rate of CSF (Type III, Fig. 2). The time course of ICP given by the equation in III-D (Fig. 2) increases at a rapid rate initially, but gradually stabilizes at a new steady-state value (P_{ss}). The rate of rise is governed by the combination of compliance and resistance to absorption.

Theoretical Considerations of the Steady State

From the conditions imposed upon the model at equilibrium, the ICP is governed by the pressure of the dural sinus (P_d) and the product of formation rate (I_f) and absorption resistance (R):

$$P = P_d + I_f R \qquad (9)$$

Note that the compliance parameter does not appear in the steady-state equation. Theoretically, the intracranial compliance affects only the transient behavior and not the equilibrium level of CSF pressure.

Under this condition, if venous pressure and absorption resistance were held constant, a linear increase in formation rate produces a linear or straight-line increase of ICP. Secondly, the slope of this line equals the absorption resistance. This process is pictured graphically in Fig. 3 A. At zero formation, the CSF pressure (P) equals dural sinus pressure (P_d). At normal formation rate, P increases to normal opening levels (P_o). If the formation rate were suddenly increased to a new level and held constant, the CSF pressure would increase and finally approach a steady-state value (P1). Higher steady-state pressures would also follow a straight line as formation was further increased (for example, P2, P3, P4). The instantaneous course of pressure during the transient phase is given by the equation in III-D (Fig. 2). The new steady-state pressure at equilibrium is given by Equation 9, which is of the same form as proposed by Pappenheimer, *et al.*[18]

Experimental Methods

One main objective was to test the validity of the theoretical model. First the equations describing the predicted response of pressure to known changes of CSF volume (Fig. 2) were programmed onto a digital computer. Next, techniques were developed for measuring and quantifying the intracranial compliance and outflow resistance of the adult cat. These biological parameters were substituted into the computer equations. Finally, the accuracy of the model was determined by changing the animal's CSF volume, and comparing the experimental pressure response recorded on strip chart with the computer-predicted time course of pressure.

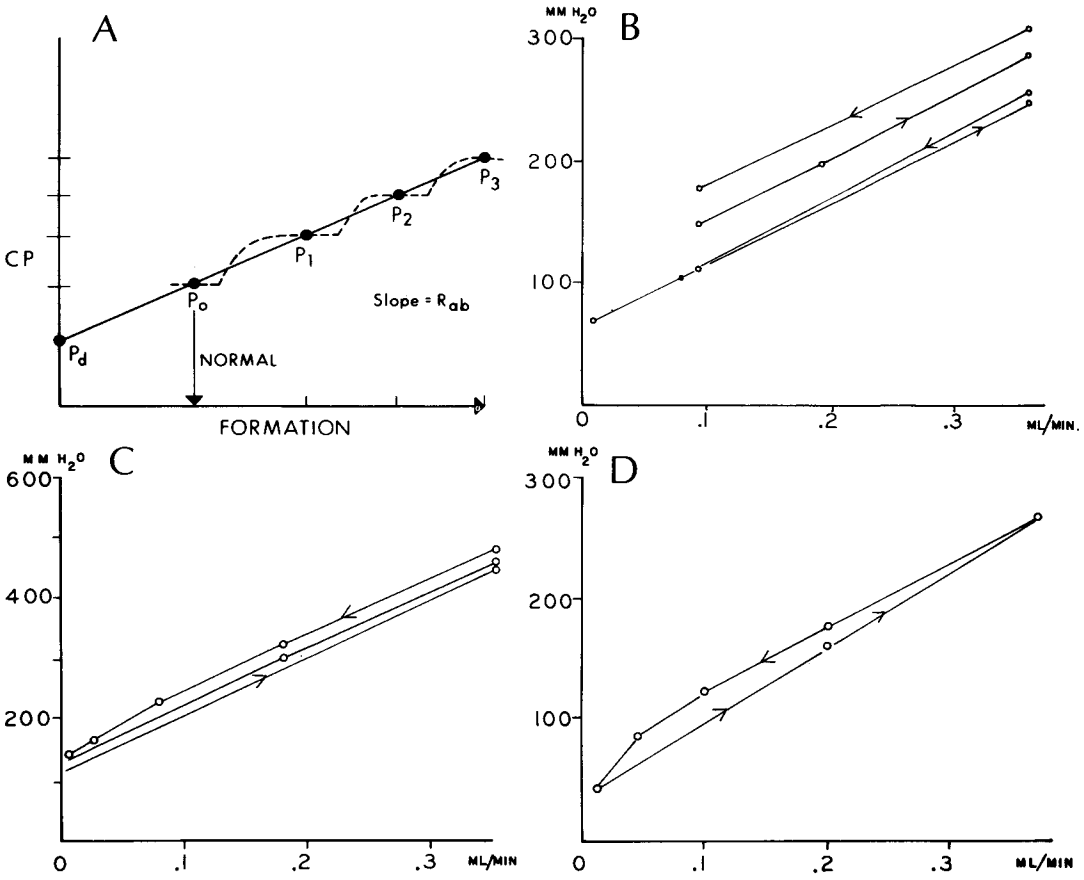


FIG. 3. Graphical description of analytical model relationship of ICP and formation. A: An increase in formation would result in proportional increase in resting level (P1, P2, P3). The slope equals absorption resistance. A graded infusion of fluid into the CSF system simulates this process. When this is performed in the adult cat, responses shown in B, C, and D are obtained. *Arrows* show direction of change. Resistance to absorption was calculated from the slopes of these curves.

Adult cats (6) weighing 2 to 5.0 kg were anesthetized with intravenous pentobarbital (50 mg/kg) and placed in a stereotaxic holder in sphinx position. A midline incision was made in the posterior fossa, and pressure in the cisterna magna was measured by a No. 21 scalp vein needle inserted through the foramen magnum and held in position by a stereotaxic angular probe. Catheters were inserted in the femoral artery for recording of systemic blood pressure and in the femoral vein for administration of fluid and drugs. The pressure-sensing catheters were filled with saline and connected to low-volume displacement strain gauge transducers (Statham P23de).* The gauges were positioned and fixed at one-half the distance between the sternum and tips of the dorsal spine. This datum was considered as heart level in the prone animal. A valve system was inserted between the CSF pressure line and the gauge for connection to either a Harvard infusion pump,† a syringe for volume injection, or a calibrating manometer. The pressure system was calibrated before each experiment and allowed to stabilize for a 30-minute period. The system sensitivity was such that CSF pressure could be measured over a range of zero to 100 mm H_2O with an accuracy of ± 2 mm H_2O.

The pressure-volume curve for each animal was obtained by injecting known quantities of

*Transducers made by Statham Laboratories, Hato Rey, Puerto Rico.

†Infusion pump made by Harvard Apparatus, 150 Dover Rd., Millis, Massachusetts.

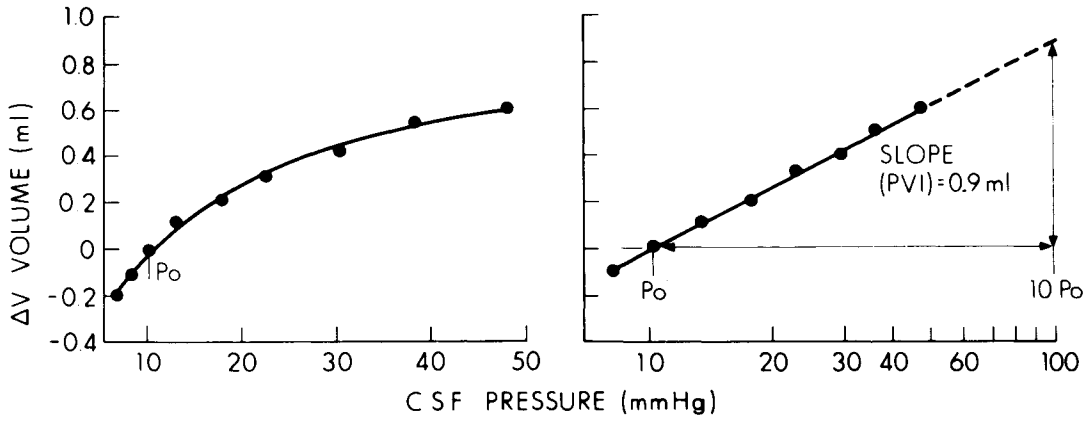


FIG. 4. The CSF volume-pressure curve plotted on a linear axis *(left)* was found to be exponential. The compliance given by the slope $\Delta V/\Delta P$ is not constant but decreases as pressure increases. The same data plotted on semilogarithmic axis can be approximated by a straight line *(right)*. The slope of the straight-line segment is equal to the pressure-volume index (PVI), and can be defined as the amount of volume necessary to raise pressure by a factor of 10.

saline (0.1 to 0.5 ml) into the cisterna magna or ventricles and recording the time course of pressure. The resistance parameters were computed from data points on the recovery curve. During the injection, the valve system was adjusted so that the transducer would not be exposed to the injection pressure. This protected the transducers and reduced the electrical artifact. When the injection was completed, the transducer valve was repositioned and the in-line pressure recorded. The maximum rate of injection did not exceed 0.1 ml/sec. Following the rapid rise in pressure, the ICP was permitted to return to the initial control level before the next injection sequence.

The ICP response to a sudden increase in formation was obtained by infusing fluid into the cisterna magna at a constant rate using a Harvard pump. First, a valve system was adjusted so that the pump input line was diverted to atmosphere. This allowed the pump and connecting lines to equilibrate for each flow setting. At a selected time the valve was quickly repositioned for connection to the cisterna magna and the in-line pressure was recorded. The range of input flow rates was 0 to 354 μl/min. Similar procedures were used for removal of known volumes, with the exception that the rates of withdrawals were lower to prevent tissue from being drawn into the catheter and blocking the pressure recording (0.05 ml/sec).

All experimental pressure versus time data were manually reduced from the strip chart recordings. Visual readings of each chart were made at 10-second intervals in the region close to the input stimuli and where pressure was changing rapidly. Recordings beyond the first 2 minutes were spaced at 30-second intervals. Fortunately, beyond this point, analysis procedures were relatively automated. The model equations were programmed onto a digital computer (PDP-12) and segmented into several subroutines. Each subroutine computed the theoretical response of CSF pressure for each type of input disturbance and thus duplicated the experimental protocol used in the laboratory.

Experimental Results

The CSF pressure increased exponentially as volume increments of 0.1 ml to 0.6 ml were added to the CSF space (Fig. 4 *left*) and a linear approximation of the exponential P-ΔV curve was made by plotting the same data on a logarithmic pressure scale against volume (Fig. 4 *right*). The slope of this linear segment was used for calculation of the PVI and the constant parameter, K ($K = 1/0.4343$ PVI) (see Appendix). The exponential relationship of pressure and volume was found in all animals and similar plots of log P vs ΔV (Fig. 5 *left*) yielded values of PVI ranging from 0.48 to 1.09 ml ($PVI_{AV} = 0.76$

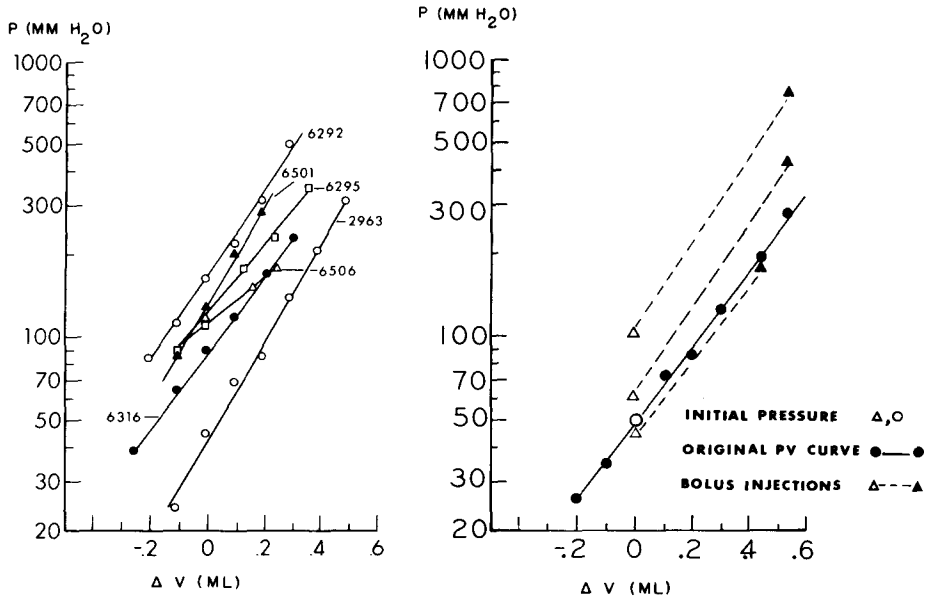


FIG 5. *Left:* The exponential CSF pressure–volume relationships found in the adult cat were plotted on a semilogarithmic pressure axis and approximated by linear segments. The slopes of these lines were used to calculate the pressure-volume index (PVI). Group average PVI = 0.726; SD = 0.212. *Right:* Bolus injections at increased equilibrium pressure levels result in pressure-volume data which closely parallel the original curve measured at normal resting pressure, demonstrating that in a normal system the slope of the pressure-volume curve is stable and independent of shifts in ICP.

ml, SD = 0.212). Following each injection, the time required to return to equilibrium after the initial rise in pressure varied among animals and as a function of the amount of volume injected. Equilibrium was established in approximately 6 minutes, and an average experimental time of 30 minutes was required to obtain the data points of the pressure-volume curve. In a few animals, resting pressure increased and stabilized at a higher equilibrium level in the course of obtaining the pressure-volume curve. When volume increments were superimposed upon the new equilibrium level, the slopes of the pressure-volume changes closely paralleled those obtained at normal levels (Fig. 5 *right*). This supports the principle that in a normal system the pressure-volume curve remains stable and is independent of shifts in resting intracranial pressure. As a result of this stability, a single injection could be used to measure the PVI.

Theoretically, for constant sinus pressure (P_d), the ratio of change in steady-state level (ΔP_{ss}) to change in infusion (ΔI) equals the effective resistance to absorption. This value is represented by the slope of the steady-state pressure versus inflow curve. These curves were obtained by routing the pump inflow to the cisterna magna and recording the rise in line pressure. When inflow rates were adjusted to the animal's approximate rate of formation (0.020 ml/min), the rise in CSF pressure did not exceed 20 mm H_2O. Flow rates were increased, and it was observed that CSF pressure stabilized at levels of infusion greater than 15 times normal formation. Blood pressure and respiration remained constant. The plot of steady-state pressure versus inflow was linear within a pressure range of 0 to 600 mm H_2O (Fig. 3 C). Differences in magnitude of pressure change were observed in some animals for changes in flow rate and seemed to vary in proportion to the duration of the control period at higher pressure levels. The arrows of Fig. 3 show the direction of the infusion sequence. In most cases, pressures on the descending cycle were slightly higher than on the ascending cycle (Fig. 3 C, D) demonstrating a mild hysteresis effect. When the infusion was sustained for long periods (> 30 min), the resting level gradually increased to a new equilibrium point. However,

when the infusion level was decreased, the proportional change in steady-state level equaled that of the ascending cycle (Fig. 3 A). The hysteresis and shifts in equilibrium level were attributed to changes in the venous exit pressure.

The magnitude of the average absorption resistance was calculated from the slopes of these curves and was found to vary over a range of 400 to 1000 mm H_2O/ml/min (R_{av} = 609, SE = 91). This linear change of steady-state ICP in response to a simulated increase in formation supports Equation 9 and the concept (Fig. 3 A) that absorption resistance is independent of pressure over a wide range of ICP.

The validity of the dynamic aspects of the theoretical model was tested by comparing the transient portion of the animal's pressure response to changes in volume with those predicted by computer (Fig. 6). When fluid was removed, pressure decreased and then slowly returned toward equilibrium. We postulated that negligible absorption takes place below a critical threshold pressure (P_t) (Fig. 2, II-F). Under these conditions, all newly formed fluid is retained by the CSF space and the slow increase of ICP reflects this filling process. It was on this basis that we derived the appropriate equations for estimation of the CSF formation rate. The computed rates of formation (average I_f = 0.016 ml/min, SE = 0.001) were comparable to values reported by other investigators using more complex techniques (0.015 ml/min,[4] and 0.022 ml/min[5]).

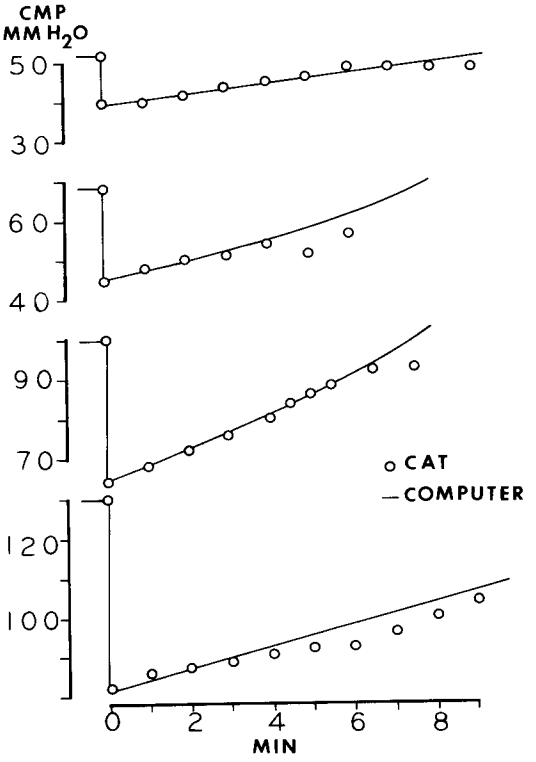


FIG. 6. Comparison of theoretical (computer) and experimental (cat) pressure responses to removal of CSF volume. The equation relating the time course of pressure (Fig. 2 II-D), although exponential in form, describes an almost linear path in the region below opening pressure. This is due to the high compliance and absorption resistance at these pressure levels.

The agreement between the theoretical and experimental time course of pressure in response to an infusion of saline into the CSF system was close in all experimental trials. An example of the infusion response is shown in Fig. 7 *upper*. The predicted computer trajectory for an infusion of 0.354 ml/min rose sharply from an initial resting level of 100 mm H_2O, and stabilized at an increased pressure level of 500 mm H_2O in approximately 3 minutes. The animal responded in a similar manner, with the exception of a slight overshoot in pressure caused by a brief period of hyperventilation. The fluctuation of pressure did not occur at lower rates of infusion. The correspondence of pressure dynamics in both ascending and descending trials indicates that compliance and absorption mechanisms act uniformly, independent of the direction or magnitude of volume change. Furthermore, the compliance values used by the computer were derived from the PVI's obtained from the pressure-volume curve 1 hour before the start of the infusion tests. The close agreement of theoretical and experimental curves obtained after this time lapse indicate that the PVI in a normal system is stable and non-time varying.

A close correspondence between predicted and experimental pressure response was also obtained for the bolus injection. A maximum of 0.8 ml was injected into the cisterna magna (Fig. 7 *lower*). Pressure increased from 100 to 950 mm H_2O, and recovered completely within an 8-minute period.

It was considered that the amount of volume inserted into the CSF system in the

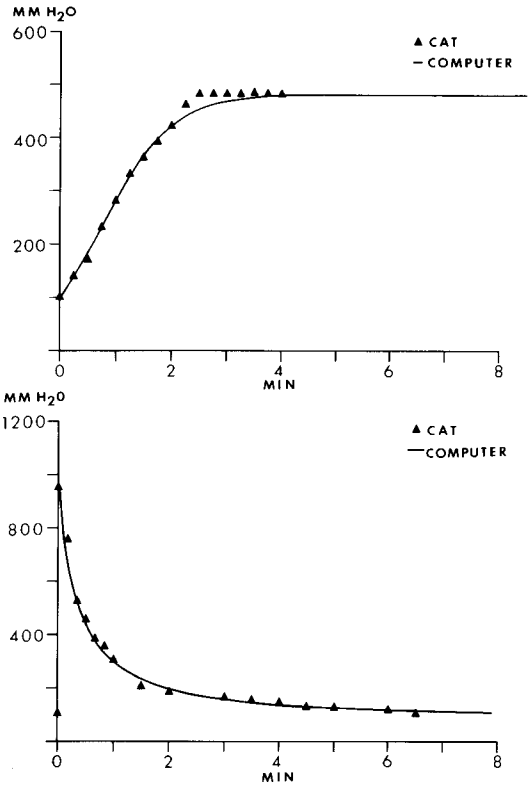


FIG. 7. Comparison of theoretical (computer) and experimental (cat) pressure responses to infusion of fluid into cisterna magna (0.354 mm/min) (*upper*), and bolus injection of 0.8 ml (*lower*).

process of obtaining the pressure-volume (Fig. 4) or steady-state-ICP (Fig. 3) curves for defining compliance and resistance could be excessive if these techniques were applied to man. To reduce the physiological stress, we examined the possibility of using a single bolus injection response for evaluation of both resistance and compliance. First, it was necessary to study the equation defining the recovery process (Fig. 2, II-D) and use the computer to determine the sensitivity of the ICP return curve to variations in these parameters. These studies showed that compliance altered both the peak induced pressure and the initial rate of return. The pressure trajectory beyond 1 minute was less sensitive to changes in compliance. Resistance seemed to have the opposite effect. The initial portion of the return curve was relatively insensitive to small variations in resistance and the maximum pressure variations due to resistance change occurred 1 to 2 minutes following the injection. Based on these results, the pressure at t = 1 minute for each animal response to bolus injection was selected as the optimum point for calculation of absorption resistance. Compliance was extracted from values of initial and peak induced pressure. Resistance calculations based on the bolus injection method (R_{av} = 602, SEM = 69 mm H_2O/ml/min) were in close agreement with resistance values derived from the infusion studies (R_{av} = 609, SEM = 91 mm H_2O/ml/min).

We concluded from these results that both resistance and compliance parameters could be derived from the pressure response to a single bolus injection, which is a more acceptable technique for studies of patients with ICP monitoring where the frequency of injection and amount of volume input may be critical.

Discussion

The nonlinear behavior of the CSF system is attributed to the exponential curve relating pressure to volume, that is, the curve that pressure must follow when the normal volume equilibrium of the CSF compartment is disturbed. The slope of the curve or compliance decreases as CSF volume is increased and, as a result of the hydrodynamics of the system, is not uniform throughout the range of pressure. This is reflected by the complexity of the theoretical equation predicting the ICP response to changes in volume. If the intracranial compliance is assumed constant, the structure of the nonlinear equation derived in this study mathematically reduces to the linear approximation proposed by Guinane,[7] Benabid, *et al.*,[2] and Ommaya, *et al.*[17] Agarwal,[1] and Hofferberth, *et al.*,[8] used both mechanical and electrical models in the analysis of the CSF system, but did not extend these studies to the development of a general ICP equation.

To the best of our knowledge, this is the only study in which the nonlinear compliance function observed in animals[10-12] and man[3,6,16,19,21] is included in the development of the system equation.

The close agreement between theoretical and experimental results show that for a defined volume input, four parameters are necessary to adequately describe the static and dynamic response of CSF pressure: 1) the rate of CSF production; 2) the variable com-

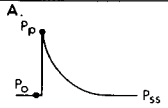
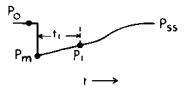
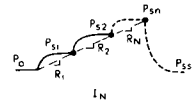
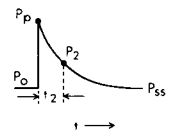
	RECORD OUTPUT	KNOWN INPUT	EXTRACT PARAMETERS	COMPUTE	UNITS	RESTRICTION
	A.	B.	C.	D.	E.	F.
I		ΔV (ML)	P_o, P_P	$PVI = \frac{\Delta V}{\log_{10} P_p/P_o}$ $C = \frac{.4343\ PVI}{P}$	ML ML/MMHg	$P > P_o$ $\frac{\Delta V}{\Delta T} \gg I_F$ $P_{ss} \simeq P_o$
II		$-\Delta V$ (ML)	P_o, P_m, P_1, t_1	$PVI = \frac{\Delta V}{\log_{10} P_o/P_m}$ $I_{FORM} = \frac{PVI}{t_1}(\log \frac{P_1}{P_m})$	ML ML/MIN	$R \gg$ FOR $P < P_D$ $P_{ss} \simeq P_o$
III		$I_N = \frac{\Delta V_N}{\Delta t}$ (ML/MIN)	P_o, $P_{s1} \cdots P_{sn}$	$R_1 = \frac{P_{s1} - P_o}{\Delta I_1}$ $R_n = \frac{P_{SN} - P_{S(N-1)}}{I_N - I_{(N-1)}}$ $R_{AV} = \frac{\Sigma R_N}{n}$	MMHg/ML/MIN	$\Delta P_D = o$ $P_{ss} \simeq P_o$
IV		ΔV (ML)	P_o, P_P, P_2, t_2	$PVI = \frac{\Delta V}{\log_{10} P_p/P_o}$ $R = \frac{t_2 P_o}{(PVI)\log\left[\frac{P_2}{P_P} \cdot \frac{P_P - P_o}{P_2 - P_o}\right]}$	ML MMHg/ML/MIN	$\Delta P_D = o$ $P_{ss} \simeq P_o$

FIG. 8. A summary of the methods developed for extracting CSF parameters from the static and dynamic responses of intracranial pressure. The recorded pressure output (A) in response to known volume input (B) is evaluated to obtain specific pressure points (C). These pressure values are substituted in equations (D) to compute the CSF parameters subject to the conditions listed in (F).

pliance given by the exponential relationship of CSF pressure to volume; 3) the outflow resistance; and 4) the intradural sinus pressure. With knowledge of these parameters, the pressure response (output) to a known volume change (input) can be predicted (Fig. 2). By reversing the process, methods for extracting the values of the parameters solely on the basis of pressure changes can be derived (Fig. 8).

For example, the pressure-response record for a bolus injection of volume ΔV ml is shown in Fig. 8 (I-A). By extracting the initial pressure (P_o) and the peak pressure (P_p) and inserting these values into the equation of I-D, both the pressure-volume index (PVI) and compliance (C) can be computed. For the calculation to be valid (I-F), this difference between initial and peak pressure must be significant ($P > P_o$), the rate of injection must be greater than the rate of production ($\Delta V/\Delta t \gg I_f$), and the resting pressure before and after injection should be approximately equal ($P_{ss} = P_o$). The production rate of CSF (I_f) can be calculated from the pressure response to a volume withdrawal (Fig. 8 II-A), by extracting three parameters: the initial pressure (P_o), the pressure immediately following withdrawal (P_m), and a point (P_1) on the return curve displaced t_1 minutes from P_m. These data yield both PVI and production rate (Equations of II-D) with the restriction (II-F), that negligible absorption takes place below dural sinus level ($R \gg$ for $P \ll P_d$), and that the pressure eventually recovers to the initial resting level.

The calculation of resistance to CSF absorption (R) by the infusion and bolus injection techniques are described in sections III and IV of Fig. 8. The assumption in both cases is that the dural sinus pressure (P_d) remains constant during the injection interval ($\Delta P_d = 0$). We prefer the bolus injection method. Three data points are extracted from the pressure response: the initial (P_d), peak (P_p), and recovery (P_2) pressure evaluated t_2 minutes after injection. The PVI is computed by the first equation of IV-D and inserted in

the second equation for calculation of outflow resistance. All pressures refer to the diastolic level of the pulsatile ICP wave.

Data from these studies show that pressure equilibrium is governed by the reference level established by the venous vasculature and the resistance to absorption of fluid. For a fixed rate of production, these two factors control the resulting steady-state-pressure level while compliance provides the reactive force necessary to compensate for transient disturbances of volume. If volume is increased above the normal resting level, the concomitant rise in pressure increases absorption; as fluid exits from the system, pressure falls and gradually returns to the predisturbance level. With reduction of volume, pressure decreases and no fluid is absorbed. This is followed by a gradual increase of pressure as the system refills with newly formed CSF to the original steady-state volume. These biomechanical events derived from this analysis support the concept of a "dynamic equilibrium" described by Ryder, *et al.*[19]

How is this dynamic equilibrium altered in cases of raised ICP? According to the model, a sustained elevation of pressure can develop with an increase in CSF formation, an increase in outflow resistance, or an increase in the venous pressure at the site of fluid absorption. Our computer studies show that the contribution of product of outflow resistance and formation rate ($I_f \times R_o$) of the ICP is approximately 10%. The remainder is attributed to the magnitude of dural sinus P_d. With this distribution, the outflow resistance would have to increase markedly in order to effect a significant rise in the ICP. In contrast, elevations of sagittal sinus pressure by venous sinus obstruction would be transmitted directly to the CSF system, resulting in an increase of resting ICP level. Since the increase in P_d equals the change in ICP, the gradient across the arachnoid villi is not altered, CSF absorption remains constant, and the equilibrium shift to a higher ICP level is sustained. This concept is supported by the work of Johnston, *et al.*,[9] who demonstrated normal CSF resistance in the presence of raised ICP induced by venous obstruction.

A second possibility for loss of dynamic equilibrium is suggested by the structure of the general equation (Equation 8). The formulation implies that under normal conditions, compliance effects only the transient response of pressure, and not the steady-state level of ICP. However, if the outflow resistance and compliance parameters become mutually dependent, such that an increase in stiffness is accompanied by a concomitant increase in resistance, the general equation becomes unstable. This coupling of elastic and resistive elements would result in the loss of dynamic equilibrium and a relentless increase of CSF pressure. In the closed skull of fixed intracranial volume, this condition is realized when the normal buffering capacity is depleted, such as by an expanding process where eventual obstruction of outflow pathways by compressed tissue increases (R), thus effecting the egress of fluid.

The systems analysis approach to ICP-volume relationships can be applied to clinical settings, providing parameters useful in characterizing ICP and assessing changes induced by therapy. By bolus injection and withdrawal of small amounts of CSF, a PVI can be calculated in patients that characterizes the steepness of their pressure-volume curve. The slope indicates the intracranial volume buffering capacity with higher slopes identifying patients in jeopardy of marked ICP elevations with small volume increments whether there be CSF blood, tissue water (edema), or discrete mass. The ICP decrement after bolus injection depends on the outflow of resistance (R) of the system, with a higher R found in conditions such as subarachnoid hemorrhage, which are often accompanied by impaired absorption of CSF. Knowledge of high R identifies patients whose elevated ICP may effectively be handled by CSF diversion procedures.[20] In patients with elevated ICP, removal of CSF at a rate equal to formation negates the contribution of the CSF impedance (R) to the level of ICP and the equilibrium in pressure resulting from such a maneuver provides an estimate of venous outflow pressure. By this technique the percentage rise in ICP due to impaired absorption and/or increased threshold pressure at the sites of absorption can be determined.[15]

It is hoped that these dynamic tests will provide additional information for isolating the factors leading to sustained elevation of the intracranial fluid pressure and help identify clinical descriptors that will be useful as therapeutic and prognostic guides, particularly with head injury.

APPENDIX

Solution of the General Equation

The approach to the general solution of the nonlinear equation (Equation 8) was to transform the dependent variable (P) and convert to a linear differential equation. First, let the dependent variable (P) be represented by the term $1/x$. Differentiating $1/x$ and substituting $(-dx/x^2\ dt)$ for the variable dP/dt of Equation 7 in the text results in the expression:

$$dx/x^2\ dt - K/x^2\ R + K\ I(t)/x = 0. \quad (A1)$$

Next, let the parameters K/R and K of Equation A1 be represented by the terms U and B, respectively. Substituting U and B in Equation A1 and multiplying both sides of the equation by x^2 yields a linear equation (A2) that can be solved by the integrating factor technique:[13]

$$dx + B\ I(t)\ dt = U\ dt. \quad (A2)$$

The integrating factor (IF) is defined as follows:

$$IF = e^{{}_{t_o}\int^{t} B\ I(\tau)\ d\tau}. \quad (A3)$$

Multiplying each term of Equation A2 by the IF, integrating both sides, and replacing P for $1/x$ yields the solution of the nonlinear equation (Equation 8).

Definition of Compliance

A means for quantifying the compliance was developed by plotting the exponential pressure-volume curve on a logarithmic pressure axis against volume. The slope of the straight line approximation was defined by us as the pressure-volume index,[14] or PVI. Expressed mathematically, the slope is given by $\Delta V/\Delta P$:

$$PVI = V\text{-}V_0/(\log P - \text{Log } P_0), \quad (A4)$$

for $P > P_0$.

Differentiating Equation A4 to remove the log function, and solving for the compliance coefficient (C) physically defined as dV/dP, we obtain

$$C = (\text{Log e})\ PVI/P = 0.4343\ PVI/P. \quad (A5)$$

To simplify the text notation, the constant terms of Equation A5 were combined into a single parameter K which was defined as 1/0.4343 PVI.

The intracranial compliance (C) decreases as pressure (P) increases according to Equation A5. The absolute level of compliance at a given intracranial pressure P is determined by the pressure-volume index (PVI), which in practical terms is the amount of fluid (ml) that, if injected into the CSF space, would increase pressure by an even factor of 10.

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