Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system

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The distribution of compliance and outflow resistance between cerebral and spinal compartments was measured in anesthetized, ventilated cats by analysis of the cerebrospinal fluid (CSF) pressure response to changes in CSF volume. Cerebral and spinal compartments were isolated by inflating a balloon positioned epidurally at the level of C-6. The change of CSF volume per unit change in pressure (compliance) and change of CSF volume per unit of time (absorption) were evaluated by inserting pressure data from the experimental responses into a series of equations developed from a mathematical model. It was found that 68% of total compliance is contributed by the cerebral compartment while the remaining 32% is contained within the spinal axis. The cerebral compartment accounted for 84% of total CSF absorption. The mechanism for spinal absorption appears to be similar in that no differences were obvious on the basis of pressure dynamics.

KEY WORDS • compliance • pressure-volume index • cerebrospinal fluid absorption • intracranial pressure

Our understanding of intracranial pressure (ICP) dynamics has led us to believe that compliance, as defined by the volume pressure curve, and the resistance to fluid absorption are the major parameters that control the rate of change and resting level of the ICP. This report describes the methods used in dealing with the nonlinear compliance of the cerebrospinal fluid (CSF) space and its relation to pressure, with emphasis on special techniques for rapid determination of both compliance and absorption resistance. These methods are then used to evaluate the relative distribution of compliance and absorption resistance between cranial and spinal compartments of the cat.

Analytical Method

Compliance

Compliance of a distensible or elastic chamber is defined as the ratio of change of volume (ΔV) to the corresponding change in pressure (ΔP). The ratio ΔV/ΔP or compliance coefficient is equivalent to the slope of the volume versus the pressure curve obtained by injecting known amounts of fluid into the CSF space and recording the rise in CSF pressure. Compliance then is a measure of the volume distensibility of the CSF compartment. This is important because according to the Munro-Kellie hypothesis, when a change in volume of any intracranial component — brain, blood, or CSF occurs, the magnitude
of the induced CSF pressure required to return the compartments to their original dimensions is given by the compliance coefficient.

Many inanimate containers have ideal elastic properties. Such properties include a coefficient of compliance which does not vary with time or is constant for all degrees of expansion of the container. In such an ideal container, pressure varies linearly with volume and the slope of the volume-pressure curve, or compliance, is a constant. Pressure and volume in the CSF compartment are not linearly related. This was first demonstrated in 1953 by Ryder, et al., who described the general form of the curve as "hyperbolic." For equal volume increments the AV/AP ratio, or compliance, decreases as pressure increases.

Our studies have confirmed this nonlinear relationship between pressure and volume, a property which unfortunately makes the quantitation of compliance more difficult. We have found, however, that by plotting pressure data on a logarithmic axis against volume, the resulting AV-log P curve can be approximated by a straight line (Fig. 1 left). We defined the slope of the linear volume-log pressure plot as the pressure-volume index (PVI). From this transformation, it was found that the compliance (C) of the CSF space expressed in ml/mm Hg, is inversely related to the CSF pressure (P) at which it is evaluated, and that the degree to which it is inversely related is proportional to the PVI. In equation form,

\[ C = \frac{0.4343 \text{ PVI}}{P} \]  

The PVI can be evaluated either by direct calculation of the slope, given by \( \Delta V/\Delta \log_{10}P \), or by graphic means if one determines the amount of volume (ml) necessary to raise the CSF pressure to a level 10 times the opening pressure (Fig. 1 right). Since the compliance of the CSF space is directly proportional to the PVI, at a given pressure the terms "PVI" and "compliance" are interchangeable. A high PVI is associated with a high level of compliance. The index can also be used as a means of quantifying differences between individual compartments or systems. For example:

1. The compliance of systems A and B will be equal at all pressure levels if their pressure-volume indices are equal.
2. At a pressure P, the ratio of compliance of compartments A and B is equal to the ratio of their respective pressure-volume indices.
3. The total PVI of a system of several compartments is equal to the algebraic sum of the pressure-volume indices of each compartment.
4. The increase or decrease of intracranial volume necessary to change resting level from \( P_1 \) to \( P_2 \) is equal to the product of the logarithm of \( P_1/P_2 \) and the pressure-volume index.

**Establishment of Pressure-Volume Curve**

The pressure-volume curve can be obtained by inserting known volumes into the CSF space and measuring the corresponding rise in pressure. The guidelines for the procedure will become more apparent if the mechanisms affecting the pressure-to-volume curve are examined in greater detail. The pressure-volume curve, in addition to providing an index of compliance, can be interpreted as a graphic representation of all possible equilibria and transient changes of CSF pressure. A stable ICP is analogous to a single point, \( Q_1 \) (Fig. 2), which remains stable. Small perturbations in volume superimposed upon that point will cause the point to shift back and forth on the trajectory described by the pressure-volume curve. The
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We have found that volume insertion by constant infusion or stepwise addition is subject to error, and prefer to obtain the pressure-volume characteristic by a series of rapid injections. After each injection, sufficient time is allowed for the system to return to the initial pressure level. By this technique, we are at least assured that the mechanisms acting to return the pressure to its predisturbance level have remained intact. The peak pressures (Fig. 3) are then plotted on semilogarithmic scale against the magnitude of the corresponding volume increments. This produces a curve such as that illustrated in Fig. 1 right. The PVI is then computed by using Equation 2 or by graphically extending the line to determine the amount of volume necessary to produce an increased pressure ratio of 10. For the adult cat, the maximum rate of injection does not exceed 0.1 ml/sec.

**Determination of Compliance from a Single Injection**

It has been shown that under normal circumstances the compliance of the CSF system maintains a fixed exponential relationship to pressure for extended periods. The pressure-volume curve, then, may be regarded as a fundamental property of the system. This principle is used in the evaluation of compliance from a single volume injection. The mathematical explanation is that since the log pressure-versus-volume plot is a straight line, with the initial pressure given, only one additional point is required to establish the slope or PVI.

Following a suitable control period, a volume $\Delta V$ is injected into the CSF space, raising the pressure from an initial level of $P_0$ to a peak pressure of $P_p$ (Fig. 4). The PVI (ml) is then calculated by use of the relationship

$$PVI = \frac{\Delta V}{\log_{10} \frac{P_p}{P_0}}. \quad (2)$$

Following the computation of the PVI, compliance can be evaluated by Equation 1.

**Outflow Resistance**

From an analysis of CSF dynamics, the CSF pressure ($P_{cat}$) was considered equal to
the sum of the venous exit pressure \( P_{asp} \) and the product of formation \( (I_f) \) and outflow resistance \( (R_o) \) expressed in mm Hg/ml/min. In equation form,

\[
P_{cfr} = P_{asp} + (I_f \times R_o).
\]  

Solving for \( R_o \),

\[
R_o = \frac{P_{cfr} - P_{asp}}{I_f}.
\]

Resistance \( R_o \) is then equal to an effective perfusion pressure \( (P_{cfr} - P_{asp}) \) divided by the rate of outflow. We have reported that if the rate of outflow (ml/min) is artificially increased in stepwise fashion the ICP will increase exponentially and eventually stabilize at new equilibrium levels. If the equilibrium levels are plotted against inflow, the slope of the curve is equal to the outflow resistance \( R_o \) expressed in mm Hg/ml/min. This is the same principle upon which the Katzman infusion test is based. The accurate assessment of the outflow resistance hinges on the assumption that the venous exit pressure remains constant as the ICP is increased.

Data obtained in the present study show that the transient change of sagittal sinus pressure is less than 4 mm Hg; the pressure returns to the original steady-state level after injection (0.1 ml/sec). It has not been completely resolved that the absolute magnitude of sagittal sinus pressure (SSP) equals the true venous exit pressure. Fortunately, the method presented here requires only that the venous exit pressure, whatever its magnitude, must not change significantly during a tran-
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sient increase in CSF pressure. The determination of compliance and outflow resistance from a single bolus injection is based upon our studies of a mathematical model of the CSF system which has yielded a general equation relating the intracranial pressure to compliance and outflow resistance for any form of volume addition, whether it be by injection, infusion, or withdrawal. From this analysis, it has been established that the outflow resistance can be computed by the following equation:

$$R_o = \frac{t_2 \cdot P_o}{PVI \cdot \log_{10} \left[ \frac{P_2 - P_o}{P_p - P_2} \right]}$$

(5)

where $P_o$ = initial pressure prior to volume injection (mm Hg), $P_p$ = peak pressure induced by volume injection (mm Hg), $P_2$ = the instantaneous pressure at an elapsed time ($t_2$) on the recovery slope, and $t_2$ = the elapsed time from the instant of volume injection to the point at which $P_2$ is determined.

The technique for calculation of the outflow resistance from response data is a two-step process. First, the PVI is computed from the initial rise in pressure in response to a volume addition ($AV$) by use of Equation 2. The outflow resistance $R_o$ can then be computed by substituting the PVI and the values of initial ($P_o$), peak ($P_p$), and recovery ($P_2$) pressures into Equation 5. The graphic definition of these pressures is illustrated in Fig. 4.

The value of $R$ obtained by analysis of the response to bolus injection when cerebral and spinal compartments are in free communication is a quantitative measure of the total resistance to CSF absorption of both compartments acting in parallel fashion.

Summary of Analytical Methods

Compliance, by definition, is equal to the ratio of volume change to pressure change and is given by the first derivative or slope of the volume-pressure curve. Since pressure varies exponentially with volume, compliance is not uniform throughout the pressure range. An expression for compliance was developed by plotting pressure on a logarithmic scale versus volume and approximating the transformation by a straight line. The slope of this line was defined as the pressure-volume index (PVI). Compliance is directly proportional to the PVI and inversely proportional to pressure. The change of volume per unit change of pressure (compliance) and change of volume per unit time (absorption) are intimately related and govern the dynamics of the ICP. When a change in pressure is evoked, values of the initial pressure rise and subsequent recovery yield data which are used to compute both the compliance and the outflow resistance.

Experimental Methods

A series of 12 adult cats, weighing from 1.5 to 4.0 kg, was anesthetized with intravenous pentobarbital (50 mg/kg) and placed in a stereotaxic holder in the sphinx position. A midline incision was made in the posterior fossa and pressure in the cisterna magna was measured by a 21-gauge scalp vein needle inserted through the foramen magnum and held
in position by the stereotaxic angular probe. In six animals, a laminectomy was performed at L-7 and a polyethylene catheter was inserted in the lumbar subarachnoid space and positioned at the level of C-6. Reversible high cervical block was produced by inflation of the balloon to a volume of approximately 0.3 ml. The blocked condition was confirmed by insertion of volume into the cisterna magna, with no observable pressure rise in the spinal recording. All pressure catheters were connected to Statham gauge transducers* for strip chart recording. All pressure transducers were positioned halfway between the sternum and tip of the dorsal spine. A valve system was inserted between the pressure line and each gauge for connection to either a syringe, for volume injection, or a calibrating manometer. The system sensitivity was adjusted so that CSF pressures could be measured over a range of 0 to 100 mm Hg with an accuracy of ± 0.5 mm Hg.

The initial control sequence consisted of five or more injections, ranging from 0.1 to 0.5 ml, which were inserted into the cisterna magna prior to balloon inflation. The compliance data from this segment represented the total CSF compliance. A block was then introduced by infusion of saline into the balloon to a volume of approximately 0.3 ml at a rate which did not exceed 0.2 ml/min. In several cases, the infusion rate was held to 0.04 ml/min to prevent transient increases in blood pressure which usually occurred in the process of balloon inflation. During the blocked condition, known volumes of fluid were injected sequentially into the cisterna magna and lumbar catheters. The balloon was then deflated, and when pressure equilibrium was re-established between the cranial and spinal axes, the control sequence of volume injections was repeated. An average of three control-block sequences were conducted in each experimental animal.

*Transducers made by Statham Laboratories, Hato Rey, Puerto Rico 00919.
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**TABLE 1**

**Summary of animal data**

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Initial Pressure (P₀) (mm Hg)</th>
<th>Pressure-Volume Index (PVI) (ml)</th>
<th>Total Compliance at P₀ (ml/mm Hg)</th>
<th>Mean Arterial Pressure (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>16.5</td>
<td>1.0778</td>
<td>.028</td>
<td>156</td>
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<td>2</td>
<td>16.0</td>
<td>0.8611</td>
<td>.023</td>
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<tr>
<td>3</td>
<td>16.0</td>
<td>0.8970</td>
<td>.024</td>
<td>187</td>
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<td>4</td>
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<td>.026</td>
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<td>.0266</td>
<td>120</td>
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<td>6</td>
<td>16.5</td>
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<td>mean</td>
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<td>.0257</td>
<td>151.8</td>
</tr>
<tr>
<td>SD</td>
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<td>0.1272</td>
<td>.0018</td>
<td>—</td>
</tr>
<tr>
<td>SE</td>
<td>—</td>
<td>0.0519</td>
<td>.0007</td>
<td>—</td>
</tr>
</tbody>
</table>

**TABLE 2**

**Distribution of pressure volume index (PVI) of cranial and spinal compartments**

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Control, Total PVI (ml)</th>
<th>Block PVI (ml)</th>
<th>Distribution (%)</th>
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</thead>
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<td>Spinal</td>
<td>Total</td>
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<tr>
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<td>.5543</td>
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<td>3</td>
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<td>.8933</td>
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<tr>
<td>6</td>
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<td>.1798</td>
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<tr>
<td>mean PVI</td>
<td>.9048</td>
<td>.6523</td>
<td>.3064</td>
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<td>SD</td>
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<td>.0497</td>
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<tr>
<td>SE</td>
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<td>.0529</td>
<td>.0141</td>
</tr>
</tbody>
</table>

**Results**

**Compliance Measurement at Opening Pressure**

During initial control periods, injections of saline into the cisterna magna or lumbar catheters produced similar pressure responses in both compartments with respect to peak magnitude, pulsatile variation and time course of recovery to equilibrium (Fig. 5). In six experiments PVI, computed from values of initial and peak pressure (Equation 2), ranged from 0.705 ml to 1.08 ml (Table 1) with a mean of 0.9 (SD = 0.13). It would require then an average of 0.9 ml to raise the CSF pressure from its initial resting pressure to 10 times its initial level. Compliance for all animals at initial resting level computed from Equation 1 were almost identical (mean = 0.0257 ml/mm Hg, SD = 0.0007). Figure 6 shows the variation of compliance at raised CSF pressure according to Equation 1. At the mean opening pressure of 10 mm Hg, average compliance is equal to $40 \times 10^{-3}$ and is reduced by 50% for a steady state pressure increase of 10 mm Hg.

**Distribution of Compliance Between Cerebral and Spinal Compartments**

With the introduction of a block the pressure waveforms in response to sequential cerebral and spinal volume addition were not identical. For equal volume additions, the lumbar pressure response was characterized by a higher initial peak, longer recovery and a greater respiratory fluctuation than that of the cisterna magna pressure (Fig. 7). The PVI values obtained from the analysis of the pressure responses from cerebral and spinal compartments are presented in Table 2. The total PVI measured prior to block reflects the contribution of both cranial and spinal PVI's. During the blocked condition both cranial
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Distribution of Outflow Resistance

Outflow resistances were determined by extraction of the initial, peak, and recovery data from the pressure responses to volume addition according to the methods described in this report. In general, the greater the recovery time to equilibrium, the greater the outflow resistance. Total resistance (R_T) measured prior to block reflects the combined absorptive properties of cerebral and spinal compartments in communication. The initial control (R_C), cerebral (R_C), and spinal (R_S) outflow resistances measured during block are presented in Table 3.

Total CSF resistance averaged 52.7, SD = 14.5 mm Hg/ml/min. The distribution between cranial and spinal axes is depicted in Fig. 9 in terms of percentage absorption (reciprocal of outflow resistance). The values of absorption obtained from the pressure trajectories were subject to greater variation among animals than the compliance function, with spinal absorption averaging 16% of total absorption for this series. We were concerned that in some cases the individual differences between total absorption during control and block segments exceeded our estimates of experimental error. Realizing that these values were averaged over repeated control-block intervals, we decided to examine the experimental time course by averaging across control block segments for all animals (Fig. 10). Although the percentage distribution was not affected, the total outflow resistance decreased by 25% over time. This change was attributed to the repeated mechanical stimulation of the system.

Discussion

The pressure-volume curve is a fundamental property of the CSF system. By definition, it refers to the immediate change of CSF pressure induced by changes in CSF volume, and describes the total compliance of the cerebral and spinal compartments. Graphically it represents the trajectory that intracranial pressure must follow in response to uncompensated rapid changes in intracranial blood, brain, and CSF volume. The response of "steady-state" pressure to other forms of volume disturbance such as an expanding extra- or intracerebral mass also involves CSF absorption processes and therefore is
not a true measure of compliance of the CSF system.

If the CSF pressure-volume curve was a straight line, an increment of volume would produce the same increase in pressure regardless of the initial resting pressure. Since the pressure-volume curve is exponential, the magnitude of pressure produced by addition of fluid varies as a function of the initial resting pressure. At low levels of pressure, the curve is less steep, the compliance is maximum, and relatively large increases of volume can be tolerated with small increases in the ICP. At high initial pressure, the compliance is reduced and small volume additions will result in large increases in pressure. This accounts for the increase in magnitude of the pulsatile component of ICP as resting levels are increased.

Based on the results of these studies, the total CSF compliance can be subdivided into cerebral and spinal components. Approximately two-thirds of total compliance or available compensatory reserve was found to be contained within the cranial compartment. The mechanism providing the compliance must be associated with resiliency of the vascular elements since the meninges, in close proximity to the skull, cannot expand.

Lofgren, et al., and Lofgren and Zwetnow studied compliance distribution in dogs and reported a 50% contribution by the spinal axis above 20 mm Hg ICP. Lim, et al., in studies of dogs with aqueductal stenosis, reported that 52% of total compliance was attributed to the combination of infratentorial and spinal compartments. The results of our study are in closer agreement with the distribution found by Lim, et al. Combining their values with the data obtained in this investigation would result in an approximate compliance distribution of 48% supratentorial, 20% infratentorial, and 32% spinal.

Distribution of compliance in man can be derived from Gilland's pressure studies of patients with spinal block and the results of Katzman and Hussey's infusion tests in normal patients. Gilland found the pressure-volume relationship of the isolated spinal compartment to be exponential, with a corresponding spinal PVI of 8 ml. Our computations of compliance derived from data obtained by Katzman show that the total PVI in man is approximately 25 ml, suggesting a
two to one distribution of compliance between cerebral and spinal compartments.

It is our concept that in the closed skull the compliance is provided by the compressibility of the low-pressure venous or capacitance segment of the vascular bed. The magnitude of compliance must then be governed by those factors that determine the "collapsibility" of the cerebral vasculature. Compliance, as we define it, refers to CSF volume change per unit change in CSF pressure. With reference to arteries and veins, compliance is defined as change in vessel volume ($\Delta V$) per unit change in intravascular pressure ($\Delta P$) per unit vessel length. These two forms of compliance, in our opinion, are directly related, with a high CSF compliance associated with a high vessel compliance. Vessel compliance is a function of internal pressure, radius, and wall tension. For compliance to exist, vessel volume must be reduced in response to the increase of volume of the surrounding fluid environment. In our analytical studies we have related the intravascular pressure to flow and have ex-
Analyzed the effects of these parameters in response to compression. In an elastic tube, these parameters are all interdependent and in most cases insufficient data are given to calculate the exact behavior of the vessel. We can, however, derive certain fundamental properties from the studies of physical models. The combination of internal pressure and wall tension of thick-walled vessels, such as arteries, is high compared to the physiological range of external fluid (CSF) pressure. Arteries then are relatively "stiff" and their contribution to the bulk compliance is minimal.

For thin-walled vessels, a reduction in radius produces a rise in intravascular pressure which in turn is transmitted to the surrounding fluid environment. This rise of intravascular pressure due to compression will not occur if flow through the vessel decreases in proportion to its reduced volume. In the absence of an induced pressure gradient ($\Delta P = 0$), compliance ($\Delta V/\Delta P$) would be infinitely high. For vessels maintaining constant flow, the internal vessel pressure in response to compression is inversely proportional to the square of vessel volume. Given this relationship, if intravascular pressure is plotted against decreasing vessel volume an exponential curve similar in shape to the CSF pressure-volume curve is obtained. On this basis it can be postulated that the exponential increase in intravascular pressure caused by the rapid addition of fluid is transmitted to the extravascular space, resulting in the exponential variation of CSF pressure to volume. Secondly, at abnormally high input volumes, CSF pressure does not increase indefinitely, but gradually reaches a plateau. This point of divergence, according to the concept expressed above, is the point at which flow is reduced and blood volume more easily displaced. The system under this condition of reduced flow is "soft," resulting in an increase of compliance when the physiological limits of ICP are exceeded.

The resistance to outflow expressed in mm Hg/ml/min is a measure of the impedance to CSF drainage. Conductance is the reciprocal of resistance and is more commonly referred to as "absorption," expressed in units of ml/min/mm Hg. Data from this investigation indicate that most absorption (84%) takes place within the cerebral compartment.

The mechanism for absorption in the spinal compartment appears to be similar in that we cannot determine obvious differences on the basis of the pressure dynamics.

The relatively low value of spinal absorption suggests that loss of communication between cerebral and spinal compartments should have a negligible effect on the steady-state level of the ICP. From our studies of compliance, approximately 30% of potential compensatory reserve would be lost, making the cerebral compartment more susceptible to increases of pressure due to fluctuations in volume. We conclude that determination of both the pressure-volume index and outflow resistance is important for a more thorough evaluation of detrimental shifts in the volume compensatory mechanisms of the neural tube. It is hoped that the techniques for quantitative determination of the available brain storage and degree of fluid compensation will be applicable in patients undergoing continuous ICP monitoring.

References


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