The pressure-volume function of brain elasticity

Physiological considerations and clinical applications

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The intracranial pressure-volume function as determined by brain elasticity is reported in normal dogs. Rapid subarachnoid infusions clearly define an exponential relationship between pressure and volume. An aliquot technique to measure elastance (dP/dV) at multiple intracranial pressures demonstrates a linear relationship between elastance and pressure. This follows mathematically from the exponential nature of the basic pressure-volume function.

The clinical significance of brain elastance measurements is discussed. It is emphasized that the effects of pressure on CSF dynamics are superimposed on the pressure-volume function of brain elasticity and probably account for the process of spatial compensation for an expanding mass lesion. It is not apparent that elastance measurements can serve as indicators of impending decompensation, since the pressure-volume function of brain elasticity provides no direct information about CSF dynamics. Accordingly, the clinical usefulness of elastance measurements is seriously questioned.

KEY WORDS • intracranial pressure • cerebrospinal fluid • pressure-volume function • brain elasticity

THE significance of the intracranial pressure-volume relationship has been a topic of extensive clinical and laboratory investigation. The elasticity of brain, meninges, and blood vessels determines the immediate pressure response to a rapid alteration of intracranial volume.4,14,26,27 It has been suggested that quantitative consideration of the pressure-volume relationship has important clinical and therapeutic applications.21,24,28

This paper reviews the relationship of intracranial pressure as a function of volume. The pressure-volume function is studied in dogs with two experimental techniques; pressure measurements are made as intracranial volume is changed by 1) rapid subarachnoid infusions, and 2) aliquot volume additions and withdrawals. The significance of the exponential pressure-volume function is discussed.

Materials and Methods

Mongrel dogs of either sex weighing 8 to 14 kg were used in the study. The dogs were
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given intravenous sodium pentobarbital (Nembutal), 30 mg/kg, for anesthesia and pancuronium bromide (Pavulon), 0.2 mg/kg, for muscle relaxation. Additional pancuronium bromide, 0.2 mg/kg, was given as needed every 30 to 45 minutes. The animals were intubated, ventilated on a Harvard animal respirator,* and positioned prone in a stereotaxic frame. Body temperature, pO2, pCO2, and pH were maintained in normal ranges. Arterial blood pressure was monitored continuously.

A No. 18 needle with multiple end openings was introduced stereotaxically through a parietal burr hole into the trigone of each lateral ventricle. The sites of dural penetration were sealed with fast setting glue (Aron Alpha). Through one needle, ventricular pressure was measured with a Statham pressure transducer and a Sanborn polygraph.† The atlanto-occipital membrane was exposed and a No. 18 Silastic catheter was positioned in the cisterna magna through a small opening in the dura and arachnoid. A watertight seal was insured with the application of glue. The cisterna magna pressure was monitored with a Statham transducer.

Measurements of the intracranial pressure response to rapid subarachnoid infusions provided the means of relating volume and pressure in the first group of animals. A syringe pump‡ was used to infuse mock cerebrospinal fluid (CSF)§ into the cisterna magna at a constant rapid rate (3.87 cc/min), and the intracranial pressure (ICP) response was recorded. Pressure versus volume graphs were plotted.

In the second group of animals, small aliquots (0.2 to 0.5 cc) of mock CSF were rapidly introduced by gravity into a ventricle or cisterna magna from a 2.00-cc pipette graduated in 0.02 cc markings. In these animals, pressure was monitored from the contralateral ventricle and cisterna magna simultaneously. In several animals, aliquots were introduced into the cisterna magna while pressures were recorded from both lateral ventricles. The pressure responses to rapid reductions of ventricular volume (0.2 to 0.5 cc) were also studied by lowering the pipette below the head. Volume alterations were made in rapid sequence with no attempt to wait for ICP to drift toward baseline. Baseline pressures ranged from 0 to 65 mm Hg. It was attempted to randomize both the order of pressures studied and the aliquot size.

Results

Rapid infusions at a constant rate by means of the syringe pump provided data relating total infused volume with ICP. Fifteen constant-rate infusions were made into the subarachnoid space of nine dogs. The animals were studied from resting pressure through pressures of 40 mm Hg. The results consistently demonstrated a semi-logarithmic relationship between pressure and volume, provided the error resulting from overlooking the intracranial volume changes due to concurrent changes in CSF formation and absorption was minimized. During an infusion, the rate of change of intracranial volume (dV/dt) was determined by the pump rate R and the rates of CSF formation (F) and absorption (A) as follows:

\[
\frac{dV}{dt} = R - (A - F). \tag{1}
\]

It follows that the change in intracranial volume is closely approximated by the pump rate when the infusion rate is large compared to (A - F). Figure 1 A illustrates a typical ICP versus time curve during constant infusion at 3.87 cc/min. Figure 1 B shows ICP plotted against infused volume for this same animal. A linear relationship between the natural logarithm of the pressure value and infused volume increments is demonstrated in Fig. 1 C. In this animal, CSF absorption and formation were subsequently determined at multiple ICP's with a closed recirculatory spinal perfusion technique.§ The CSF dynamics are plotted as functions of pressure in Fig. 2 left. The pressure-volume relationships were then recalculated at each pressure to adjust for

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*Harvard animal respirator manufactured by Harvard Apparatus Co., Inc., 150 Dover Road, Millis, Massachusetts.
†Statham pressure transducer manufactured by Statham Instruments Co., 2230 Statham Boulevard, Oxnard, California. Sanborn polygraph manufactured by Hewlett-Packard Co., Medical Electronics Division, 175 Wyman Street, Waltham, Massachusetts.
‡Harvard Apparatus syringe pump made by Harvard Apparatus Co., Inc., 150 Dover Road, Millis, Massachusetts.
§Elliott’s “B” Solution obtained from Travenol Laboratories, Inc., 6301 Lincoln Avenue, Morton Grove, Illinois.
Fig. 1. A: Curve showing ICP versus time during rapid infusion at 3.87 cc/min. B: Curve showing ICP versus infused volume for the same animal. C: Semi-logarithmic graph of curve shown in B. Natural logarithm of pressure vs volume infused.

Fig. 2. Left: Rates of CSF formation (circles) and absorption (squares) at multiple intracranial pressures determined by recirculatory perfusion technique. Shaded area estimates net volume adjustment that can be attributed to CSF dynamics at a particular pressure. Right: Pressure-volume curve measured in same animal as shown on left. Curve adjusted for volume changes due to concurrent CSF formation and absorption. Closed circles represent raw data; open circles, adjusted data.
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these values of A and F according to Equation 1. The resulting curves were not significantly different (Fig. 2 right). It is therefore evident that in dogs, a rapid infusion rate of 3.87 cc/min effectively minimizes the error resulting from volume changes due to concurrent CSF formation and absorption. This conclusion is consistent with the observations of Cohadon, et al., who recorded pressure-volume curves in dogs with numerous rates of infusion. They concluded that pressure-volume measurements from rapid infusions reflect primarily the properties of brain elasticity, and are not altered by CSF dynamics.

Fifteen rapid subarachnoid infusions were done at a constant rate. Infusions were terminated at 40 mm Hg to avoid disturbances of cerebral blood flow autoregulation. To facilitate graphic interpretation of the data (Fig. 3), infusion volumes were arbitrarily adjusted to be equal at a pressure of 8 mm Hg, a value close to the mean resting pressure in this series. For each animal the relationship between infused volume and the natural logarithm of pressure was analyzed with the least squares method to determine a linear line of regression; the statistics are summarized in Table 1. The results show that each infusion could be accurately described as a direct proportion between volume and the natural logarithm of pressure, with an extremely high coefficient of correlation (none under 0.93). In this series the mean slope was 0.930 ± 0.242 (SD).

In a second series of six animals, aliquots of mock CSF were introduced into the ventricles and the resulting pressure responses were recorded. These data were expressed as $\Delta P/\Delta V$ and were compared to initial pressures as well as initial pressure plus one-half of the pressure response. Linear lines of regression were calculated with the least squares method. The data are presented graphically in Fig. 4, and the statistics are summarized in Table 2. High coefficients of correlation confirm a linear relationship between these parameters. The statistics suggest that $\Delta P/\Delta V$ may be more closely related to the initial pressure plus one-half of the pressure response. In addition, analysis of all the data points considered together confirms this linear relationship with a slope of 0.955, and a coefficient of correlation of 0.891.

In summary, from the first series of infusion experiments, there is a linear relationship between the natural logarithm of the pressure value and a change in intracranial fluid volume:

$$\ln P = b (\Delta V) + a,$$

where a is a constant and b is the slope of the line. Expressed as a first order differential, this relationship can be written as follows:

$$\frac{dP}{P} = b (dV), \text{ or } \frac{dP}{dV} = bP.$$
TABLE 1
Pressure response to constant-rate rapid subarachnoid infusions of mock CSF (Group 1 dogs)*

<table>
<thead>
<tr>
<th>Dog No.†</th>
<th>Slope b</th>
<th>Coefficient of Correlation r</th>
<th>Coefficient of Correlation r₁,₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.25</td>
<td>0.998</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0.818</td>
<td>0.997</td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>0.832</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>Cb</td>
<td>0.825</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0.989</td>
<td>0.986</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>1.25</td>
<td>0.974</td>
<td></td>
</tr>
<tr>
<td>Fa</td>
<td>1.08</td>
<td>0.994</td>
<td></td>
</tr>
<tr>
<td>Fb</td>
<td>1.03</td>
<td>0.933</td>
<td></td>
</tr>
<tr>
<td>Fc</td>
<td>1.33</td>
<td>0.992</td>
<td></td>
</tr>
<tr>
<td>Ga</td>
<td>0.790</td>
<td>0.972</td>
<td></td>
</tr>
<tr>
<td>Gb</td>
<td>0.887</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>Gc</td>
<td>1.04</td>
<td>0.985</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>0.740</td>
<td>0.975</td>
<td></td>
</tr>
<tr>
<td>Ia</td>
<td>0.579</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>Ib</td>
<td>0.500</td>
<td>0.993</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.930</td>
<td>± 0.242 (SD)</td>
<td></td>
</tr>
</tbody>
</table>

*Ln P versus infused volume. Slope b calculated from linear lines of regression.
†Multiple infusions in the same animal indicated by lower case letters.

It is noted that this equation describes a linear function determined experimentally by the latter series of experiments. These two equations theoretically share a common slope. Accordingly, experimental values of b calculated from the data of both series are 0.930 and 0.955, respectively. A weighted mean value of b is 0.937.

TABLE 2
Pressure response to intraventricular injection of aliquots of mock CSF (Group 2 dogs)*

<table>
<thead>
<tr>
<th>Dog No.†</th>
<th>Trials</th>
<th>Slope bp†</th>
<th>Coefficient of Correlation r₁,₂</th>
<th>Slope bp₂‡</th>
<th>Coefficient of Correlation r₁,₂</th>
<th>Coefficient of Correlation r₁,₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>1.39</td>
<td>0.934</td>
<td>1.32</td>
<td>0.978</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>1.20</td>
<td>0.868</td>
<td>1.39</td>
<td>0.888</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>0.999</td>
<td>0.957</td>
<td>0.880</td>
<td>0.963</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>0.406</td>
<td>0.602</td>
<td>0.438</td>
<td>0.672</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>1.03</td>
<td>0.964</td>
<td>0.994</td>
<td>0.967</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>1.01</td>
<td>0.690</td>
<td>1.02</td>
<td>0.790</td>
<td></td>
</tr>
<tr>
<td>all data points</td>
<td>80</td>
<td>1.01</td>
<td>0.819</td>
<td>0.955</td>
<td>0.891</td>
<td></td>
</tr>
</tbody>
</table>

*ΔP/ΔV versus pressure. Lines of regression determined with both initial ICP (P₁) and initial ICP + ½ΔP (P₂).
†ΔP/ΔV = bp₁P₁.
‡ΔP/ΔV = bp₂P₂.

Discussion
Although early research suggested a linear relationship between ICP and volume, the current experiments clearly relate pressure as a semi-logarithmic function of intracranial volume changes with a high statistical coefficient of correlation. Reports of data from animals and man in the more recent literature are consistent with these present results. Shulman and Marmarou showed a similar semi-logarithmic relationship between pressure and volume in hydrocephalic children with a protocol analogous to the aliquot method used in the present study. With an aliquot technique, Gilland demonstrated exponential pressure-volume relationships in the spinal subarachnoid space below complete blocks in three patients. On the basis of rapid-rate infusions into the spinal subarachnoid space in dogs, Löfgren, et al., published curves consistent with an exponential pressure-volume function.

It is necessary to define mathematically two terms frequently used in discussions of intracranial pressure-volume relationship. Tissue elastance is defined as dP/dV. The reciprocal of elastance is brain compliance, or dV/dP. The results of the present study, and those of numerous reports in the literature show that tissue elastance (dP/dV) is directly proportional to ICP (Fig. 4). As discussed above (in Results), these experimental observations are consistent with the exponential character of the pressure-volume curve. The present study indicates...
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that the slope of the semi-logarithmic pressure-volume function determined by rapid-rate subarachnoid infusions is the same as the proportionality constant relating brain elastance (dP/dV) to pressure.

Brain compliance (dV/dP) has been said to be relatively constant in animals\(^4,8,3\) and man\(^9\). Constant compliance implies a linear pressure-volume function and is therefore in disagreement with results of the present study. More recent measurements of brain compliance do conform to the exponential nature of the pressure-volume relationship\(^6,7\).

Lim, et al.,\(^13\) measured ventricular compliance in normal and hydrocephalic dogs with aqueductal stenosis. Although their preparation examined only the very narrow range of pressures between 5.5 and 15 mm Hg, it was concluded that compliance (dV/dP) is an exponential function of pressure:

\[
dV/dP = ke^{-0.002P}. \tag{4}
\]

Their data suggested that hydrocephalus had no effect on the exponential character of the curve, but was associated with a significant reduction of the constant \(k\). At a given pressure, the value of ventricular compliance in a hydrocephalic dog was nearly half that of a control.

However, this concept that compliance is an exponential function of pressure contradicts the mathematical model in which pressure is exponentially related to volume. It is recalled that dP/dV is linearly related to pressure (Equations 2 and 3; Fig. 4). It follows that the mathematical function relating the inverse of dP/dV (that is, dV/dP or compliance) to pressure is hyperbolic, not exponential:

\[
dP/dV = bP + a; \tag{5}
\]

\[
\frac{1}{dP/dV} = \frac{1}{bP + a}, \quad \text{or} \quad (dV/dP) (bP + a) = 1. \tag{6}
\]

Accordingly, the published compliance versus pressure data of Lim, et al.,\(^13\) were examined as both exponential and hyperbolic functions. As shown in Fig. 5, these curves are very similar and are nearly identical over the narrow pressure range examined in the original study. It is therefore concluded that the data of Lim, et al., are, in fact, quite consistent with an exponential pressure-volume function. The data of Marmarou, et al.,\(^19\) also indicate the compliance-pressure function to be hyperbolic in nature.

In summary, both compliance and elastance are dependent on pressure. Like brain elastance, no one value of compliance can accurately describe the pressure-volume function.
The mathematical relationship of pressure and volume are thought to be determined by specific physical properties of the brain and its vascular bed. Also important are the effects of pressure on CSF dynamics, since CSF absorption is a sensitive function of pressure. It is assumed that the CSF compartment can dynamically adjust for changes of intracranial volume in the process of spatial compensation for an expanding mass lesion. Langfitt, et al., showed in monkeys that slow expansion of a supratentorial epidural balloon is not associated with a significant pressure increase until a balloon volume of 5.0 cc is reached. The ICP then rises rapidly with each additional increment in balloon volume (Fig. 6 upper). They concluded that spatial compensation through adjustments in the CSF compartment allows for a mass of 5.0 cc with a net effect of displacing an equivalent CSF volume from the head. Failure of the CSF compartment to accommodate for additional mass volume results in decompensation of the system; a large pressure effect is seen with small volume changes.

It seems likely that once the compensatory process fails, the pressure-volume relationship is determined primarily by brain elasticity. This argument is supported by the graphic data of Langfitt, et al., which summarizes the pressure-volume curves of six monkeys during the compensation-decompensation process (Fig. 6 upper). This curve is plotted as a semi-logarithmic function in Fig. 6 lower. Accordingly, a linear relationship is apparent above the critical balloon volume, which causes the compensatory process to fail. Thus, it seems apparent that the contribution of the CSF system to the intracranial pressure-volume relationship is superimposed on the pressure-volume function determined by tissue elasticity.

Miller, et al., have made extensive measurements of the volume-pressure response (VPR) to 1-cc bolus additions and reductions of ventricular volume in patients with a variety of neurosurgical conditions. In essence, their VPR is dP/dV and is entirely analogous to the aliquot measurements of the present study. Their data confirm the linear relationship between dP/dV and pressure, although very low slopes were reported. Linear lines of regression showed slopes of 0.14 and 0.20 mm Hg/cc with coefficients of correlation of 0.45 and 0.41 respectively, in

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Fig. 6. Upper: Pressure response to enlarging extradural supratentorial balloon in monkeys. (Reproduced from Langfitt TW, Weinstein JD, Kassell NF: Vascular factors in head injury: contribution to brain swelling and intracranial hypertension, in Caveness WF, Walker AE (eds): Head Injury: Conference Proceedings. Philadelphia/Toronto: JB Lippincott, 1966, pp 172-194, with permission of the publisher.) The balloon was inflated slowly in 1 cc increments. Lower: Pressure-volume data replotted as a semi-logarithmic graph. Open circles depict interpolated data points. Shaded area represents period of spatial compensation by concurrent adjustments in CSF dynamics. Ln P = 0.60V + 0.11 with a coefficient of correlation of 0.998 (excluding balloon volumes less than 4 cc).

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curve dictated by the elasticity of the brain and its vasculature. The steep part of the curve is physiological and is not synonymous with intracranial decompensation. Moreover, the slope of this exponential curve at any one point (dP/dV) is elastance and is linearly related to pressure. Thus the normal individual will show high elastance (dP/dV) at elevated pressures.

On the other hand, the more crucial consideration is how close a patient is to decompensating in the process of spatial compensation. To answer this question involves testing the rate at which CSF volume can shift in response to a pressure change to restore a stable ICP. The volume changes resulting from CSF dynamics involve fluid shifts occurring over a distinct time period, on the order of minutes. These shifts do not take place instantaneously. This is in contrast to the elasticity pressure-volume function which represents immediate pressure responses to sudden volume alterations.

What then is the clinical significance of the pressure-volume relationship determined by brain elasticity? From the exponential nature of this function, it follows mathematically that the pressure response to a sudden volume change will be greater at an elevated ICP. This is a characteristic of the normal physiology of brain elasticity and is not a feature of disease. Certainly brain elasticity may be altered by disease. It has been suggested that the elastance-pressure function is adversely affected by mass effects and midline shift, but this remains to be proven conclusively. It may be possible to relate alterations in brain elasticity to the changes in ventricular size under pathological circumstances, since ventricular enlargement may be the expression of a change in elasticity. However, it is not apparent at this time that measurement of brain elasticity provides useful clinical information pertinent to the management of the critically ill neurosurgical patient. Such measurements give no indication of the remaining compensatory capacity. Attention to the fundamental mathematical relationships of the pressure-volume function of brain elasticity requires a clear understanding of what this function actually measures.

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