Dynamic Response of the Intracranial System in the Conscious Dog to Papaverine Hydrochloride

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SUMMARY The influence of papaverine on the intracranial system of the dog was studied by measuring the pressure-depth-time response for the intact intracranial system, i.e., for the subarachnoid and subpial compartments. This was accomplished by a measurement system which provided an accurate pressure-depth determination and a uniform rate of transducer insertion. Distinct regions of the intracranial system (subarachnoid, transitional, and subpial) were identified from inflections in the pressure response curve. The test parameter, brain relative stiffness (BRS), was obtained by determining the slope of the pressure response values within the subpial region. This parameter is a measure of the "stiffness" or elasticity of brain tissue within the test configuration. A bolus injection of papaverine (1 mg per kilogram, i.v.) caused an increase in the transitional region, a compensatory reduction in the subarachnoid space, and an increase in BRS. It is postulated that at normotensive arterial blood pressure, cerebrovascular expansion caused by papaverine resulted in increased brain tissue elasticity, i.e., an increase in the pressure-depth response for the subpial region. Possible implications for this increase are discussed. Experiments should be conducted in which local blood flow studies are coupled with measurements of brain elastic response.

Introduction

THE EFFICACY of cerebral vasodilators, particularly papaverine hydrochloride, in occlusive cerebrovascular disease remains controversial.1 It has been stated that in the presence of cerebral ischemia, cerebral vasodilating drugs are either ineffective or cause dilation of vessels in normal brain areas while shunting blood from the ischemic area.2,3

It is well documented that papaverine is the most potent pharmacological cerebral vasodilator.4 Because it relaxes the smooth muscles of arteries and arterioles, papaverine-induced vasodilatation is accompanied by arterial hypotension. When hypotension is prevented, papaverine consistently increases cerebral blood flow and volume.4,4 When cerebrovascular volume increases, a new intracranial dynamic equilibrium with fluid redistribution (CSF and blood) must occur because of the relatively fixed volume capacity of the cranium. However, the mechanical response of the in vivo brain to variations in cerebral hemodynamics is unknown; it cannot always be predicted either from the CSF pressure level or from the behavior of the CSF compliance (ΔV/ΔP).7

As do most biological tissues, brain exhibits viscoelastic response properties8-10; that is, the brain's response to a force or load cannot be predicted as an elastic (solid) or a purely viscous (e.g., CSF) material, since the brain exhibits response behavior similar to both. This viscoelastic behavior, however, can be quantitated in terms of relaxation, creep, delayed recovery, and elastic response.9,11

Because the brain is enclosed by the pial membrane and enveloped by a dense vascular network, its mechanical response properties in vivo and in situ are influenced by the status of cerebral hemodynamics at the time of measurements.

In previous works we have shown that by measuring the pressure-depth-time response for the intact intracranial system (i.e., for the subarachnoid and subpial compartments), it is possible to identify distinct regions that have particular pressure-displacement characteristics.12 The pressure-depth-time response for the subpial region is most significant because it resembles an elastic response; it represents brain resistance to deformation on compression.13 The slope of subpial pressure-depth response is a measure of the elasticity or the "relative stiffness" (BRS) of the in vivo brain in its hydrostatic environment (CSF).14

In preliminary experiments we found that BRS closely reflected changes in intracranial vascular volume.14 This prompted us to investigate the influence of papaverine on the pressure-depth-time response of the normal intracranial system and on brain stiffness while maintaining the integrity of the intact dura. The experiments were performed in chronically prepared dogs that were sedated but not anesthetized, so that observed changes could be attributed solely to papaverine. To detect qualitative changes in cerebral blood flow and volume we monitored brain electrical impedance at 1 kHz. Brain electrical impedance at low frequency is essentially a measure of the volume and ionic strength of brain extracellular space.15 When an alternating current of low frequency and constant low density is injected into brain tissue, it passes through only brain extracellular space (ECS), since the high cell membrane resistivity impedes the flow of current intracellularly.16,17 But, because blood is a good conductor, it causes a low resistance shunt in the nervous tissue, exerting an overall effect on brain impedance.18 The net effect of vasodilatation and increased blood flow is to cause a small (<5%) gradual fall in impedance (increased conductivity).

Methods

Nine dogs (10 to 15 kg) were prepared for chronic measurement of brain electrical impedance and dynamic intracranial pressure measurements, epidurally. The implantation procedure was performed under general anesthesia, sterile conditions, and in two stages. In the first stage a small burr hole (1.2 cm OD) was trephined over the left parietal area, 1.5 cm lateral to the midline. The dura was pierced with a sharpened four-pointed probe, and a four-electrode probe, previously sterilized in glutaraldehyde solution (Cidex), was embedded 1 to 1.5 mm into the dog brain cortex. After ensuring hemostasis, the impedance probe was secured in place by means of a Teflon collar that was...
fastened to the burr hole with stainless steel screws and acrylic cement. Additional cement was poured between impedance probe and collar to seal the skull opening. The scalp tissues were then sutured in layers around the collar, and the animal was thereafter placed on broad spectrum antibiotic therapy for three days.

Impedance and capacitance were measured daily, until the capacitance represented less than 5% of the total brain impedance. The impedance response was then tested with an intravenous infusion of 50% dextrose in water. In the animal with a positive impedance response (15% to 20% rise) a stainless steel threaded collar was implanted over a burr hole (1.6 cm OD) trephined on the hemisphere opposite that of the impedance probe (second stage of implant). Extreme care was taken to control bleeding and prevent perforation of the dura. Acrylic cement and stainless steel screws were again used to fasten the collar in place. Scalp tissues were sutured in layers around the collar, which was then sealed with a threaded cap. A femoral artery was also chronically cannulated for recording pressure and for determining blood gas tensions and pH.

**Impedance Instrumentation**

A four-electrode method was used to measure brain electrical impedance. With this method the effects of electrode polarization and electrode-tissue impedance were negligible, allowing accurate measurement of tissue impedance changes. The phenomenon of electrode leakage current and capacitive effects as shown by Ranck, however, must be accounted for. To minimize electrode leakage current, a high-impedance operational amplifier circuit was used to sense the voltage changes at the voltage measuring electrodes. To assure a minimal capacitive element in the impedance measurements a radial electrode configuration (Augat transistor socket) was combined with a measurement frequency of 1 kHz. This allowed accurate resolution of the resistive component of the total impedance measurement. In addition, current density was maintained at 6 × 10^-12 Amp/m², which is well within the safe limits recommended in order to avoid cortical stimulation.

Isolation of the in-phase and out-of-phase frequency components was achieved through a JB-6 lock-in amplifier, which was calibrated by intermittent substitution of a decade resistor and capacitor boxes for the electrode-tissue system.

**Intracranial Pressure-Displacement Transducer**

This instrumentation has been described in earlier works. Basically, it consists of a diaphragm-type pressure transducer mounted at the base of a small piston, and secured in place by a rigid coplanar ring. The transducer piston is coupled to a finely threaded cylinder, both being enclosed in a stainless steel barrel. As the cylinder is rotated, the piston, and thus the pressure gauge, can be inserted or withdrawn. To provide simultaneous measurement of the insertion depth (displacement) a multiturn rotational potentiometer was geared to the cylinder and yielded a continuous accurate measure of the piston (pressure sensor) relative to an initial or reference position (fig. 1).

The pressure transducer was calibrated in a hydrostatic chamber maintained at 37°C; the potentiometer was calibrated separately. The pressure measurements were accurate to within ±1 mm Hg, while depth measurements (displacement) were accurate to within ±0.05 mm.

Because of the time-dependent nature of the response properties, transducer insertion and withdrawal needed to be carefully controlled. This was accomplished by means of a motor-driven system that provided uniform displacement over a range of 0.015 to 0.050 mm per second and could be programmed to stop and withdraw at a preset pressure level. This semiautomatic system was connected to the transducer by means of a flexible shaft. Pressure and displacement signals were recorded simultaneously on an oscillographic recorder, an X-Y recorder, and a magnetic tape. For the analysis, the data were retrieved in the form of pressure versus time and displacement versus time diagrams.

**Test Procedure**

Approximately 45 minutes before taking intracranial pressure measurements, continuous recording of brain electrical impedance was begun; the animal was sedated lightly (Innovar-Vet, 0.1 ml per kilogram, i.v.), and an intravenous infusion of 0.45% NaCl in 5% dextrose in water was started through a cephalic vein. The dog was then placed in a recumbent lateral position, and the indwelling arterial (femoral) catheter was exteriorized and connected to a pressure transducer and to the oscillographic recorder. Arterial blood was drawn for measurement of blood gas tensions, pH and base deficit through a microelectrode system maintained at 37°C. Any base deficit was corrected with intravenous administration of NaHCO₃ (base deficit × kilograms body weight × 0.3).

Two milliliters of 2% Xylocaine were instilled into the collar, over the dura in order to block nociceptive stimuli from the transducer compressing the dura. Next, the sterilized transducer was firmly threaded to the implanted collar, and the transducer cylinder was manually rotated until the pressure sensor made initial dural contact. This depth was recorded as the zero reference point for the remainder of the experiment. The transducer was then connected to the precalibrated motor-driven system and the recording system was made ready to go. When the automatic signal was turned on, the transducer compressed the dura at a uniform constant rate to a depth corresponding to a preset pressure (approximately 30 mm Hg), followed by immediate withdrawal at the same rate.

Six minutes after the “control” pressure test papaverine hydrochloride was given in a bolus intravenous injection of 1 mg per kilogram. The pressure test was repeated at four minutes and again at 15 minutes after papaverine, thus allowing a resting interval of 10 minutes between tests. In one dog (#B326) where additional sedation was not required, the pressure test was repeated again at 40 minutes. Arterial blood pressure was maintained near control value with phenylephrine infusion given through a microdrip system.
Table 1  Intracranial Pressure/Depth Measurements at the Vault, Before (T\text{v}'\text{v}) and After (T\text{v}'\text{v}'\text{v}) Papaverine

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>T\text{v}'\text{v}'</td>
<td>0.46</td>
<td>0.93</td>
<td>0.79</td>
<td>0.79</td>
<td>0.26</td>
<td>0.66</td>
<td>0.66</td>
<td>0.53</td>
<td>0.53</td>
</tr>
<tr>
<td>T\text{v}'</td>
<td>0.40</td>
<td>0.79</td>
<td>0.66</td>
<td>0.09</td>
<td>0.20</td>
<td>0.79</td>
<td>0.79</td>
<td>0.69</td>
<td>0.26</td>
</tr>
<tr>
<td>T\text{v}</td>
<td>0.13</td>
<td>0.70</td>
<td>0.53</td>
<td>0.72</td>
<td>0.33</td>
<td>0.53</td>
<td>0.72</td>
<td>0.69</td>
<td>0.53</td>
</tr>
<tr>
<td>P\text{c} (mm Hg)</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>P\text{p} (mm Hg)</td>
<td>5.8</td>
<td>1.6</td>
<td>0.5</td>
<td>2.3</td>
<td>1.0</td>
<td>0.5</td>
<td>1.0</td>
<td>0.5</td>
<td>2.3</td>
</tr>
</tbody>
</table>

The observed changes were statistically evaluated by a two-factor repeated measure analysis of variance (p < 0.05). Each dog was measured at three distinct times (T\text{v}', T\text{v}''\text{v}'\text{v}'\text{v}'\text{v}) to establish the levels of factor A (time), while the dogs themselves became factor B with nine levels. One measurement of each random variable was made at the times T\text{v}', T\text{v}''\text{v}'\text{v}'\text{v}'\text{v}'\text{v}'. A Scheffe test (<0.05) was used for "post-hoc" comparison of group means. 

Results

Animal Physiological Status

Throughout the experiments arterial blood pH and gas tensions remained within normal limits (pH\text{a} = 7.397 ± 0.006; P\text{aco} = 35.8 ± 0.82 mm Hg; P\text{ao} = 99.4 ± 5.6 mm Hg; \text{HCO}_3 = 22.05 ± 0.5 mEq/L). Mean arterial blood pressure was maintained near control value with phenylephrine microdrip infusion (MABP = 95.5 ± 10.4 mm Hg to 101.0 ± 9.9 mm Hg). When the papaverine study was completed, each dog was fully alert and exhibited normal behavior, and was walked to its cage.

Pressure Test

Figure 2 illustrates the results of a pressure test (dog #Y296, control). From this test insertion, depth and corresponding pressure response for each region of the intracranial system at the cranial vault were identified as in our

![Pressure-displacement transducer](http://stroke.ahajournals.org/)

Figure 1. Pressure-displacement transducer.
The displacement trace (broken line in fig. 2) shows that as the transducer advances from the zero position (initial dural contact) at uniform insertion rate, definite inflections in the pressure response can be recognized; these, in turn, can be related to changes in the system representing distinct regions of the intracranial system at the cranial vault. Accordingly, in figure 2, point \( bc \) designates the transducer firm contact with the dura, and the pressure response is that of subarachnoid CSF at the cranial vault. At \( dp \) the transducer leaves the subarachnoid compartment and makes initial contact with the subpial region. Point \( ds \) represents substantial contact with brain surface, beyond which the brain is compressed. Position \( dm \) is the maximal insertion depth to a predetermined pressure level (29 to 32 mm Hg). It follows then that the difference \( dp-bc \) corresponds to the subarachnoid compartment depth at the transducer site; that \( ds-dp \) is a transitional region between subarachnoid and subpial regions; and that \( dm-ds \) identifies the subpial area of brain compression. As the transducer is withdrawn at the same rate as on insertion, identical inflections (\( bc, dp, ds \)) can be detected in reverse order. However, the pressure is less because the compression-induced pressure during insertion is continually relaxing.

A resting interval of about 10 minutes appears to be sufficient for the intracranial system to recover 90% of the delayed recoverable deformation (0.4 to 0.6 mm) induced by the pressure test.

### Intracranial Compartments and Influence of Papaverine

Table 1 presents the values for the individual points of the pressure test and their corresponding pressures. Because of the time dependency history in dealing with viscoelastic materials such as brain, transducer insertion-withdrawal rate had to be uniform. Throughout each papaverine experiment, insertion rate did not vary significantly \((p < 0.05)\) for any single dog. There was some slight rate variation among all nine dogs, which was due to difference in calibration of the motor control drive for that dog on that day (table 1).

After papaverine administration, initial contact with the dura \((bc)\) and the transitional region \((dp)\) occurred earlier \((p < 0.05)\) than in the control, and the corresponding pressures decreased \((p < 0.05)\). The influence of papaverine on the subpial region individual point \((ds \text{ and } dm)\) was less manifest (table 1). When we looked at the differences between individual points as indicative of the depth measurements for the respective subregions, definite influences associated with papaverine could be recognized for the transitional \((ds-dp)\) and for the subpial \((dm-ds)\) regions but not for the subarachnoid space \((dp-bc)\). Transitional region \((ds-dp)\) increased while subpial area of brain compression \((dm-ds)\) decreased. These changes were significant \((p < 0.05)\) at 4 and 15 minutes, but not between 4 and 15 minutes (table 1), whereas points \( ds \) and \( dm \) both moved in opposite directions in the tight subpial region. Therefore, the difference \( dm-ds \) became significant \((p < 0.05)\) (table 2).

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**Table 1.** Values for the individual points of the pressure test and their corresponding pressures.

<table>
<thead>
<tr>
<th>Position</th>
<th>( T_V ) (mm)</th>
<th>( T_P ) (mm Hg)</th>
<th>( T_M ) (mm)</th>
<th>( T_V )</th>
<th>( T_P )</th>
<th>( T_M )</th>
<th>Rate (mm/min)</th>
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<tr>
<td>( bc )</td>
<td>1.26</td>
<td>1.19</td>
<td>1.21</td>
<td>1.21</td>
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<tr>
<td>( dp )</td>
<td>3.24</td>
<td>3.27</td>
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<td>3.27</td>
<td>3.27</td>
<td>3.27</td>
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<tr>
<td>( ds )</td>
<td>3.37</td>
<td>3.34</td>
<td>3.34</td>
<td>3.34</td>
<td>3.34</td>
<td>3.34</td>
<td>3.34</td>
</tr>
<tr>
<td>( dm )</td>
<td>1.92</td>
<td>2.08</td>
<td>2.08</td>
<td>2.08</td>
<td>2.08</td>
<td>2.08</td>
<td>2.08</td>
</tr>
<tr>
<td>( dm )</td>
<td>1.85</td>
<td>1.79</td>
<td>1.79</td>
<td>1.79</td>
<td>1.79</td>
<td>1.79</td>
<td>1.79</td>
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<tr>
<td>( dm )</td>
<td>2.21</td>
<td>2.18</td>
<td>2.18</td>
<td>2.18</td>
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<td>( dm )</td>
<td>1.78</td>
<td>1.98</td>
<td>1.98</td>
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<td>( dm )</td>
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<td>( dm )</td>
<td>4.58</td>
<td>2.71</td>
<td>2.56</td>
<td>2.56</td>
<td>2.56</td>
<td>2.56</td>
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</table>

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**Figure 2.** Example of pressure-depth-time response (Dog J296, control). As the transducer is inserted from the zero position at a constant uniform rate (displacement = broken line), the rate of pressure increase changes, indicating a difference in the material structure. The resultant inflections in the pressure curve can be related to distinct intracranial subregions at the vault. \( bc = \) coplanarity with the dura, \( dp = \) transition region, \( ds = \) substantial brain contact, \( dm = \) maximal insertion in the subpial region to a preset pressure (30 mm Hg). Top tracing is the mean arterial pressure (MAP); next tracing is brain cortical impedance in ohms (scale on left ordinate).
Reciprocal Compensatory Changes

If we assume that δs-δp difference (transitional region) reflects both subpial vascular structure and initial brain contact, then with papaverine-induced cerebral vasodilatation, δs-δp should increase at the expense of CSF (δp-δc) and subpial (δm-δs) spaces, respectively. To verify this hypothesis the "Δ" test statistic was used. As an illustrative example, Δ (δp-δc) T4-T0 represents the change in the CSF compartment (δp-δc) between the times T0 and T4, e.g., for dog #2155 (δp-δc) T4-T0 = 0.026 - 0.33 (table 3). The "Δ" for the three intracranial subregions were determined between control (T0) and four minutes, and between 4 and 15 minutes. Both analysis of variance (p < 0.05) and a "post-hoc" Scheffe test (p < 0.05) were used to determine statistically significant changes in the group means.

With the increase in the transitional region (δs-δp) a significant (p < 0.05) compensatory decrease could be demonstrated for the CSF (δp-δc) space, at four minutes, but not for the subpial region (table 3). All changes between T4 and T15 were not significant, implying that with papaverine-induced cerebral vasodilatation the major compensatory changes occurred in the first four minutes.

Brain Elasticity and Influence of Papaverine

Consider the pressure response in figure 2 as the transducer advances from δs (substantial brain contact) to δm (maximum insertion) position. Recall that δs defines that insertion depth beyond which further insertion results in brain tissue compression. A relatively small displacement in this region yields a significant pressure rise, and the pressure rises at an increased rate even though insertion rate is unchanged. This change in pressure (δp) associated with a

![Figure 3](https://example.com/figure3.png)
DYNAMIC RESPONSE OF THE INTRACRANIAL SYSTEM TO PAPAVERINE/Schettini et al. 623

Table 3

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Δ(Δp-Δd)</th>
<th>Δ(Δp-Δs)</th>
<th>Δ(Δm-Δs)</th>
<th>Δ(Δp-Δd)</th>
<th>Δ(Δm-Δs)</th>
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<tr>
<td>2155</td>
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<td>-0.13</td>
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<tr>
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<td>0.07</td>
<td>-0.13</td>
<td>1.24</td>
<td>-0.13</td>
</tr>
<tr>
<td>Y296</td>
<td>0.0</td>
<td>0.2</td>
<td>-0.16</td>
<td>-0.13</td>
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<td>2156</td>
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</tr>
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<td>233</td>
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<td>-0.08</td>
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<tr>
<td>Y22</td>
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<tr>
<td>B2140</td>
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<td>-0.07</td>
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</tr>
<tr>
<td>X</td>
<td>-0.18</td>
<td>+0.23</td>
<td>-0.12</td>
<td>0.12</td>
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</tr>
<tr>
<td>SD</td>
<td>0.25</td>
<td>0.19</td>
<td>0.085</td>
<td>0.06</td>
<td></td>
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<tr>
<td>SE</td>
<td>*0.12</td>
<td>0.06</td>
<td>0.02</td>
<td>0.15</td>
<td></td>
</tr>
</tbody>
</table>

*Significant difference from Δ(Δp-Δd)TV-TV p < 0.05.
Depth measurements are from table 2.

The stiffness of a viscoelastic material is the ratio of stress/strain as a function of time. With the intracranial system the term relative is used to indicate that the parameter (pressure/displacement) reflects both the kinematic test configuration as well as tissue response.

**This is equivalent to neglecting bulk compressibility of brain tissue, and appears to be a reasonable assumption.**
Discussion

In all dogs BRS increased significantly ($p < 0.05$) after papaverine, while arterial blood pressure was maintained within normal limits with phenylephrine infusion. Phenylephrine influence on brain stiffness appears unlikely, because of the Smith et al.\textsuperscript{29} finding that this vasopressor does not change cerebrovascular tone. Further, Haggendal\textsuperscript{24} demonstrated that with or without vasopressor, papaverine hydrochloride caused both a marked increase in cerebral blood flow and a fall in cerebrovascular resistance. There also was no reason to suspect that either hypoxia or metabolic or respiratory acidosis played a role in our results because arterial $P_{O_2}$, $P_{CO_2}$ and $pH$ were unchanged.

Validity of BRS Measurements

It may be questioned that the mechanical measurements contributed to the increased stiffness. This is possible, but did not occur in our measurements. Analogous to all viscoelastic materials, brain tissue exhibits rate dependence, relaxation, and delayed recovery behavior.\textsuperscript{11-13} These properties may introduce three major sources of error in calculating brain stiffness: rate effect, relaxation behavior, and delayed recovery.

1. Rate Effect. An apparently increased stiffness can be produced by a higher insertion rate than in previous tests. The reverse is also true. For each individual dog of our studies insertion and withdrawal rate did not change significantly ($p < 0.05$).

2. Relaxation Behavior. As the transducer is inserted into the subpial region through the intact dura and compresses brain tissue, the pressure continually relaxes.\textsuperscript{10} The superimposed relaxation may result in a low pressure-depth response for the subpial region. This did not appear to be the case in our experiments. Control values for BRS were within the range of those reported for the monkey brain elastic modulus.\textsuperscript{29} But even so, as long as insertion rate is held constant throughout each experiment, loading rate and possibly superimposed relaxation introduce a fixed constant which should not alter actual changes induced by the experiment. Whether or not this holds true, however, for all experimental conditions (e.g., brain edema) is uncertain.

3. Delayed Recovery. On transducer insertion the pressure may rise monotonically so that changes in the pressure slope as indicative of distinct intracranial sub-regions (i.e., CSF, transition, subpial) cannot be detected readily. Thus, the slope of subpial pressure-depth response cannot be accurately determined. This may occur when the deformation (delayed recovery) from a previous test has not recovered; the pressure test then is carried out entirely in the subpial region.\textsuperscript{14} In our studies the delayed deformation was recovered during the resting interval between pressure tests. It was recognized by monitoring simultaneously pressure and displacement throughout each experiment.

The method of determining brain tissue elasticity from the pressure test proved adequate for this investigation, but impractical for wider application. Our primary interest in the present experiments was to study intracranial dynamic response to changes in cerebrovascular volume by means of one single mechanical test with the least amount of disturbance to the system. Earlier studies showed that ventricular CSF and sagittal sinus pressures were minimally affected during this test.\textsuperscript{25} Of course, a more direct method of determining brain elasticity (reciprocal of brain tissue compliance) is to measure the short-time (instantaneous) elastic response, after the subpial region has been identified from the pressure test.\textsuperscript{26}

Intracranial Dynamic Response to Papaverine

In our dogs papaverine caused a biphasic response. First, at four minutes, brain stiffness increased while brain electrical impedance gradually declined; then, ten minutes later, brain stiffness further increased but at a decreased rate, while brain impedance gradually rose. The initial response may be interpreted as reflecting increased intracranial blood flow and volume; indirect evidence for this is provided by the pressure test. The first change concerns the transition region ($\delta s-\delta p$), i.e., transition from the local pressure of the CSF compartment (cranial vault) to the pressure associated with the surface of the brain. In previous studies, it was shown that the difference $\delta s-\delta p$ varied among animals and in the same animal from day to day. These variations were attributed to both the influence of the anatomical characteristics of the subarachnoid space and the pial vascular structures at the surface of the brain.\textsuperscript{15} In the present study the distance $\delta s-\delta p$ increased significantly ($p < 0.05$) after papaverine, and was associated with reciprocal compensatory reduction in the subarachnoid space ($p < 0.05$). This is consistent with O'Connell's view that systolic expansion of the cerebrum and its arteries tends to obliterate the supratentorial subarachnoid space.\textsuperscript{28}

The other change concerns the subpial compartment depth ($\delta m-\delta s$). This is the subpial area of brain compression, which under normal conditions remains relatively stable.\textsuperscript{19} With papaverine, $\delta m-\delta s$ decreased ($p < 0.05$). These changes in the pressure test suggest that papaverine caused an expansion of the pial vasculature, which led to both a reduction of the cranial subarachnoid space and some compression of subpial brain tissue. This interpretation of our data would reconcile with the observations made by Roos and Betz,\textsuperscript{29} who found that after papaverine, cortical blood flow and brain volume both increased. Because their test configuration did not permit them to characterize brain tissue mechanical properties, their increased brain volume was most likely due to the expanded pial vasculature (i.e., transition region of our pressure test).

The secondary effect of papaverine, a further rise in BRS, can be attributed either to increasing cerebrovascular volume, albeit at a decreased rate, or to a tissue response that is opposing the expansion of cerebral blood vessels because of sustained vasodilatation. Since the major volumetric changes occurred in the first four minutes and the subarachnoid space ($\delta p-\delta c$) returned to normal at 15 minutes, any further increase in flow and volume may be discounted. This would agree with Betz and Heuser's\textsuperscript{28} observations. They found that a bolus injection of papaverine (0.8 mg per kilogram, i.v.) in the cat raised cortical blood flow in the first four minutes, and then flow normalized in the next ten minutes.\textsuperscript{29} It appears, however, that papaverine's vasodilating effect may last up to one hour.\textsuperscript{39} In our study the increased BRS was associated with some tissue compaction (decreased $\delta m-\delta s$), suggesting that brain tissue was still compressed by the dilated vessels. Moreover, in dog $\#B326$
BRS returned near the original value at 40 minutes after papaverine, indicating that by that time papaverine drug action on brain vessels had ceased.

Brain electrical impedance response is consistent with the previously discussed vascular changes. In our studies, impedance initially exhibited a small gradual fall. Small decreases in impedance (<5%) are considered to be due to cortical stimulation (electrical, mechanical, etc.) or to be vascular in origin. The former occur rapidly, and the latter are slow as in our dogs.

With the secondary effect of papaverine, the increased BRS was associated with a gradual impedance rise. A rise in impedance is commonly interpreted in terms of reduction in volume of ECS and loss of water and ions from brain ECS. There is no reason to consider a change in neuronal permeability with water and ion shifts intracellularly, because the impedance changes were small and gradual, and the animals were not anesthetized. Thus, we may assume that the impedance rise was due to reduction in brain ECS as a result of expansion in the capacitance vessels.

Implications of Increased Brain Tissue Elasticity

The physiological significance of increased brain tissue elasticity (BRS) in response to variations in cerebral hemodynamics is unknown. If we make a physical analysis of mechanical forces acting at the capillary-tissue interface certain implications concerning tissue perfusion and hydration become apparent.

An increased brain tissue elasticity associated with some tissue compression (decreased δm-δs) means that the modulus of elasticity of brain tissue has increased. Consequently, brain tissue compressional force has increased. With a short-lasting vasodilating response, as with papaverine single dose injection, the increased compressional force (extraluminar pressure) is just sufficient to balance the increased hydrostatic force (intraluminar pressure) of the resistance and capacitance vessels. However, when the compressional force (e.g., elastic modulus) increases out of proportion to the hydrostatic force, and/or autoregulation of CBF is defective, intracerebral vessels may collapse. A cycle of local edema and further increase in compressional force ensues. This in turn may lead to focal arrest of the circulation and ischemic changes. Accordingly, an increase in arterial blood pressure (for example, in the presence of swollen congested brain) causes a further rise in tissue elastic response and more brain ischemia.

This hypothesis of tissue elastic response has already been proposed by Symon and Dorsch to explain intracranial pressure gradients between the two hemispheres and loss in autoregulation of blood flow in the hemisphere comprised by a supratentorial mass. This hypothesis needs to be verified further by experiments in which local blood flow studies are coupled with measurements of brain elastic response. The latter is easier to measure and reflects the elastic modulus of brain tissue in vivo, in situ, more directly than does brain relative stiffness.

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