Brain tissue pressure: physiological observations in anesthetized cats

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This study of direct tissue pressure measurement from brain parenchyma in 25 anesthetized cats focuses on steady-state observations and responses to some common physiological manipulations. Tissue pressure recording by a needle system can be done accurately without significant alterations of the blood-brain barrier, brain water content, regional cerebral blood flow, and cerebrovascular reactivity to changes in PaCO₂ and cerebral perfusion pressure. Methodological details, including in vitro and in vivo validation, are described.

KEY WORDS • intracranial pressure • brain tissue pressure • cisternal pressure • ventricular fluid pressure • cerebral edema

Intracranial pressure-volume relationships have been studied for two centuries. Monro²⁶ and Kellie¹⁵ first formulated the concept that pressure and volume within the intact skull are interdependent. In 1848, Burrows³ showed that a volume increase of one compartment must be accompanied by a decrease in the others in order to maintain pressure constant. Since those early observations, the relevance of pressure-volume relationships to experimental and clinical problems has been demonstrated by many investigators.⁵,¹⁶,²¹,²⁵,⁴³

Measurement of intracranial pressure (ICP) was not developed until 1896 when Quincke³⁰ analyzed cerebrospinal fluid (CSF) pressure dynamics during lumbar puncture in man. Later, ICP was measured reliably from the ventricles and from the subdural, subarachnoid, and epidural spaces.¹²,¹⁷,¹⁹,²⁷,³³,⁴¹

Because it fluctuates with arterial pulsation and pulmonary ventilation, ICP does not reflect compartmental pressures within blood, CSF, and brain parenchyma. Nor does ICP identify focal pressure changes and tissue pressure gradients within the cranial vault. In fact, Cushing⁶ postulated that focal pressure changes might develop within the intact skull without any apparent overall effect on ICP. Those pressure gradients he suspected to exist within the intact skull have now been shown: between the supra- and infratentorial fossae when transtentorial herniation occurs, and between the intracranial cavity and the spinal subarachnoid space after tonsillar herniation develops.¹⁴,¹⁸,⁴²

Other pressure gradients exist normally within the cranial vault. The hydrostatic pressure of blood, for instance, varies normally within the intact skull depending upon the size of the vessel, the resistance of the vascular bed, and other factors. Similarly, CSF pressure varies from the ventricles to the cisterns to the lumbar theca, depending upon posture and other variables.³⁷ Parenchyma pressure or tissue pressure (TP) may or may not differ from ICP as measured from the ventricles or subdural space, and it may be relatively independent of blood and CSF pressure.¹³,²²,²³,²⁵,³⁶

Attempts to measure brain TP directly have not been uniformly successful. Wick catheters, catheter tips, and catheter transducers have all been used to sense parenchymal pressure. Usually substantial recording artifact, excessive tissue injury, and poor reproducibility have hampered interpretation of the recorded data.¹,²,⁴,⁷,¹¹,¹²,²⁷,³¹,⁴⁰ We have modified the technique for measuring brain TP that was originally proposed by Marmarou, et al.,²³ and we have tested its reliability during some common physiological manipulations. The measurement method and results from studies in intact animals are described here.

Materials and Methods

Animal Preparation

Twenty-nine mongrel cats (weighing 2 to 4 kg) were anesthetized with intraperitoneal sodium pentobarbital (30 mg/kg). Each animal was tracheostomized, paralyzed with gallamine triethiodide (4 mg/kg intravenously), and mechanically ventilated. Cannulas (PE-90)
were placed in a femoral artery and vein to measure systemic arterial pressure (SAP), to sample arterial blood gases and hematocrit, and to administer fluids or drugs as necessary. Body temperature was monitored and maintained at 37 °C to 38 °C using a heating pad. Each animal was placed prone in the sphinx position with the head fixed in a Kopf stereotaxic frame. End-tidal carbon dioxide (ETCO₂) was monitored continuously from expired air by an infrared CO₂ gas analyzer, and SAP and ETCO₂ were displayed on an electrostatic recorder. Arterial blood was sampled intermittently; PaCO₂ and PaO₂ were maintained within physiological limits by ventilator adjustment.

Ventricular Fluid Pressure

Ventricular fluid pressure (VFP) was measured with a No. 23 needle (Popper) inserted stereotaxically through a burr hole into the right lateral ventricle at the coordinates A12, L4.5, H+8 in 25 cats. The needle was connected to a P23ID Statham transducer by polyethylene tubing (PE-50). The signal was amplified by a Gould pressure processor and recorded on an electrostatic recorder. The system was zeroed at the level of the interaural line.

Tissue Pressure

Tissue pressure was measured from the tips of No. 23 needles (0.635 mm outer diameter, 0.343 mm inner diameter) in 25 cats. The needles were attached to pressure transducers by semirigid PE-50 tubing through four-way stopcocks. The stopcocks were in turn attached to 1-cc tuberculin syringes held in a Harvard infusion pump (Model 945). Each system was filled with saline, free of all air bubbles and leaks that might create high compliance or artifactual pressure. Pressures were measured continuously by the electrostatic recorder. Two TP needle systems were used in each experiment.

In Vitro Validation of Needle System for TP. The total compliance (compliance = volume change/pressure change) of each system, including the needle, connecting tubing and stopcocks, was measured by infusing saline through the system at a known rate against an occluded needle. Compliance was considered satisfactory if it was less than 0.2 × 10⁻⁵ ml/mm Hg. The baseline drift of each system at atmospheric pressure, evaluated over 8 hours, was less than 0.1 mm Hg/hr. Movement of the connecting tubing and changes in room temperature that caused baseline fluctuations were eliminated by insulation and immobilization of the tubing.

We tested our system sensitivity to pure hydrostatic pressure, without the influence of matrix pressure, by the methods of Scholander, et al., and of Snashall, et al. The level of each needle was placed in close contact with filter paper moistened by isotonic saline. The system was zeroed at the level of the contact point between the needle and the paper. The filter paper was dipped in a Petri dish that lay below the level of the needle. The wet filter paper simulated a hollow tube and the measured transducer pressure equaled atmospheric pressure minus the distance (cm H₂O) between the level of saline in the Petri dish and the level of the needle tip. Different weights applied to the needle did not change recorded pressure from the filter paper. After equilibration, this distance for our system was calculated to have less than a 3% margin of error.

In Vivo Validation by Subcutaneous Measurement of TP. Interstitial fluid pressure in the subcutaneous tissue of various species is consistently negative when recorded by various methods. We inserted needles into the subcutaneous space of the upper hindleg of four cats to validate our in vivo method. After stabilization, the average pressure was -2.6 ± 0.85 mm Hg; a value in agreement with that obtained by other investigators. Infusion of 0.1 μl of saline through the recording needle did not cause any change in the recorded pressure. Subcutaneous tissue pressure began to rise only after 0.4 μl was infused.

In Vivo Brain TP. A No. 23 TP needle was inserted stereotaxically through a burr hole into the caudate nucleus at the coordinates A16, L5, H+4. The system had been previously zeroed at the level of the interaural line. Saline was injected through the needle by the infusion pump during insertion to prevent air bubble formation at the tip of the needle. The infusion, at a rate of 0.01 μl/sec, was stopped when the needle reached its predetermined position. No more than 0.1 μl was infused during insertion. The burr hole was then sealed with dental acrylic cement to prevent loss of CSF.

A pulsatile pressure synchronous with ventilation was observed immediately after insertion. This initial pressure, which was positive and higher than VFP, fell soon thereafter, reaching a steady state after 40 to 60 minutes (Fig. 1). The time for equilibration was probably related to delayed dispersion of local pressure caused by penetration through the brain tissue. Measurements taken prior to reaching steady state were discarded. Pulsatile waveforms were usually maintained for 60 to 90 minutes, after which ventilatory waves began to attenuate and pressure to fall. An infusion of 0.1 to 0.2 μl of saline over 10 to 20 seconds usually restored the waveform. Although pressure returned to steady state within 3 to 5 minutes after the infusion, measurements were not taken until at least 15 minutes later. When 0.2 μl

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* Statham P23ID transducer manufactured by Statham Instruments, Inc., 2230 Statham Boulevard, Oxnard, California.
† Pressure processor, Model 13-4615-52, manufactured by Gould, Inc., Measurement Systems Division, 2230 Statham Boulevard, Oxnard, California; Electrostatic recorder, Model ES 1000, manufactured by Gould Instruments, 3631 Perkins Avenue, Cleveland, Ohio.
‡ Infusion pump, Model 945, manufactured by Harvard Apparatus Co., Inc., 150 Dover Road, Millis, Massachusetts.
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was infused during the steady-state period, pressure rose by 1 to 3 mm Hg, but returned to the preinfusion value within 5 minutes. A system was considered inadequate if it did not allow steady-state pressure to be maintained for a period of at least 60 minutes. No more than 0.2 µl/hr was infused in any one experiment per needle.

Blood Flow

Regional cerebral blood flow (rCBF) was measured by the hydrogen clearance method in 25 cats. A 250-µ diameter Teflon-coated platinum-iridium Medwire electrode, with the tip exposed 0.5 to 0.7 mm, was placed stereotaxically 1 mm posterior to the TP probe. The electrode was polarized at +600 mV to a silver/silver chloride reference electrode placed in the temporal muscle. Hydrogen gas (7% to 10%) was administered for about 2 minutes through the inspired air and then discontinued abruptly. The desaturation curves were analyzed by the initial-slope method and rCBF was expressed as ml/100 gm⁻¹.

Blood-Brain Barrier

All 29 animals received 8 ml of Evans blue dye (2% in 0.9% saline) as an indicator of blood-brain barrier permeability 30 minutes before sacrifice. Each experiment was terminated with an intravenous overdose of barbiturate.

Brain Water

Four animals, without TP or rCBF probes, received Evans blue dye 30 minutes before sacrifice, and were killed 8 hours after induction of anesthesia. Findings in these four animals established brain water control values for this set of experiments.

After sacrifice, the whole brain was removed rapidly and chilled at 9°C for 15 minutes. Coronal sections (2 mm thick) were then cut at the level of the TP probes and placed immediately in kerosene. Samples were taken by a 1-mm curette from the area of brain surrounding each TP probe and placed immediately in a bromobenzene-kerosene column for specific gravity determination. The column was used only if a linear (r > 0.996) specific gravity gradient was present. The specific gravity of each sample was measured 2 minutes after immersion. Water content was calculated using the equation proposed by Marmarou, et al.²⁰,²⁴

Physiological Observations

Steady-state TP, rCBF, and VFP were measured hourly over a 4-hour period in seven cats. No physiological manipulations were performed. After sacrifice the brains were examined for the presence of Evans blue dye extravasation. Water content was measured in the areas surrounding the TP needles.

Cerebrovascular reactivity to changes in PaCO₂ and to changes in cerebral perfusion pressure (CPP) were evaluated after a steady state had been established for 1 hour in 11 cats. Ten percent CO₂ was added to the inspired air; rCBF was measured when PaCO₂ elevation was stable in six animals. Regional CBF was measured before and after the hypercarbia period.

Cerebral perfusion pressure was increased by the intravenous infusion of Aramine (metaraminol, 50 mg in 500 cc saline, as an intravenous drip) in five cats; CPP was lowered by exsanguination in three animals and by increasing ICP with 37°C mock CSF infused by a needle cannula into the cisterna magna in two. Again, rCBF was determined before, during, and after CPP alteration to establish the degree of change from baseline.

The relationship between TP and VFP and between TP in the right and left caudate nuclei was evaluated in four animals. The VFP was increased or decreased in a gradual manner by infusing mock CSF at various rates into the cisterna magna. A catheter was placed in the right atrium to monitor central venous pressure (CVP) continuously in three other cats. The CVP was raised by increasing intra-abdominal pressure with a blood pressure cuff placed around the abdomen of the animal. Finally, the relationship of TP to VFP was evaluated during hypercarbia established by inhalation of 10% CO₂, and during arterial hypertension caused by the intravenous infusion of Aramine.

Results

Waveforms from a TP needle placed in the caudate nucleus and from a ventricular fluid needle are shown in Fig. 2. Both ventilatory and arterial pulse components were apparent in both. The amplitude of TP waveforms was consistently less than that observed for VFP, but mean TP and VFP were usually the same. During steady state, TP often oscillated 1 mm Hg above or below VFP.

Hourly measurements of VFP, TP, and rCBF were made for 4 hours. Time zero was defined as 2 hours after implantation of the last TP probe in order to allow...
FIG. 2. Comparison of ventricular fluid pressure (VFP) and tissue pressure (TP) waveforms; with systemic arterial pressure (SAP) and end-tidal CO2 (ET-CO2) levels shown below. Means of VFP and TP are similar, whereas the amplitudes of the respiratory and arterial pulse pressure artifacts are smaller in the TP wave.

FIG. 3. Right (R) and left (L) tissue pressure (TP), ventricular fluid pressure (VFP), and caudate regional cerebral blood flow (rCBF) during 4 hours of steady state in anesthetized cats. The upward trend for VFP and TP is not significant (p > 0.05).

FIG. 4. Left: Reactivity of regional cerebral blood flow (rCBF) to change in PCO2. Twelve response curves in six animals are shown. Right: Values of rCBF are shown at different cerebral perfusion pressures (CPP).

enough time to reach steady state. The SAP remained stable over the 4-hour period at a mean arterial blood pressure of 90 to 130 mm Hg, as did PaCO2 (32 ± 1.5 mm Hg), pH (7.35 ± 0.02), and PaO2 (> 100 mm Hg). The total period of anesthesia at sacrifice was 8 ± 1 hours.

During the 4-hour observation period, VFP and TP in all animals was 5 to 12.5 mm Hg and 4.4 to 13.5 mm Hg, respectively. There was no significant difference between right and left caudate TP's and none between TP and VFP at any time, a finding in accord with earlier observations. Although a trend of slightly increasing pressure was apparent, no significant change in VFP or TP developed over the 4-hour observation period (Fig. 3). Mean rCBF was 30.0 ± 10.5 ml/100 gm⁻¹ min⁻¹ at 1 hour and it did not change during the following 3 hours.

The specific gravity of tissue from the right and left caudate nuclei, sampled after sacrifice, was 1.0460 ± 0.0022 and 1.0454 ± 0.0030 mm Hg, respectively. Water content estimated from these values (78.70 ± 0.22 and 78.58% ± 0.32%) was not statistically different from the water content (78.64% ± 0.14%) of the caudate nucleus in the four animals used as controls.

Evans blue dye extravasation was seen occasionally on the cortical surface of the brain at the placement sites of the needles. Heat or trauma due to drilling was probably responsible for this local alteration in the blood-brain barrier. Evans blue dye rarely extravasated along the needle tract. Blue staining was seen occasionally at the tip of the needle in the caudate nucleus, when it appeared the animal was excluded from the study. Other reasons for exclusion were the presence of a hematoma at the tip of a probe, a subarachnoid hemorrhage due to injury of a cortical vessel during implantation of a needle, and malfunction of the TP system. As previously noted, a TP system was considered to malfunction if it failed to maintain steady state without the infusion of fluid for at least 60 minutes. Functioning systems were able to sense pressure for approximately 60 to 90 minutes before the waveforms dampened.

Reactivity of the vascular bed to changes in PaCO2 and CPP in areas where TP was measured is shown in Fig. 4. The mean CO2 reactivity of CBF when PaCO2 was between 30 and 70 mm Hg was 3.63 ± 1.39 ml/100 gm⁻¹ min⁻¹/mm Hg CO2. Regional CBF was constant when CPP ranged from 60 to 130 mm Hg. When
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CO₂ was administered, the rise in VFP was followed by a parallel rise in TP (Fig. 5). Tissue pressure followed the variations in VFP whether CVP was increased by abdominal compression (Fig. 6), or VFP was raised by cisternal infusion of mock CSF (Fig. 7). The correlation between TP and VFP was highly significant. No pressure gradients between right and left TP's were evident at any point during these physiological manipulations.

A sudden rise in ICP often caused attenuation of the TP recording, a phenomenon also observed when pressure recordings were made by other investigators with wick catheters. Presumably, tissue obstructed the needle tip when the pressure change was substantial and relatively rapid. The needle system was highly sensitive both to small variations in pressure and to large pressure changes that developed slowly.

Discussion

Some conclusions may be drawn from the studies described here. First, brain tissue pressure is positive during steady state in anesthetized cats, and it approximates VFP. Second, TP and VFP remain relatively constant during 4 hours of undisturbed anesthesia. Third, TP and VFP respond similarly to hypercarbia, abdominal compression, arterial hypotension, CSF drainage, and cisternal infusion of mock CSF. Fourth, tissue damage by needle penetration is minimal during most experiments, as shown by little or no Evans blue staining adjacent to the recording needle tip, no change in brain water at the recording site, and no alteration in rCBF 1 mm from the recording site.

Waveforms corresponding to arterial pulsation and pulmonary ventilation were recorded from brain parenchyma consistently when each recording system demonstrated low compliance. The compliance of each needle system was tested in vitro before insertion into brain tissue and only systems with high sensitivity were used. In general, the amplitude of waveforms from brain tissue was less than that derived from ventricular fluid.

Measurements of tissue pressure obtained from the needle system or wick catheter have certain similarities (Table 1). Experiments with filter paper, first described by Snashall, et al., in 1971, showed that wicks and needles have equal sensitivity for measuring hydrostatic pressure. Both systems measure pressure through a column of fluid which establishes a connection between the tissue and the transducer. Both techniques assume that interstitial fluid communicates with the fluid in the recording system, allowing a small but finite exchange in fluid in and out of the recording site.
device, and both depend upon volume displacement of fluid for recording sensitivity. While both methods enable the measurement of tissue pressure, the needle system described here appears to be less harmful to brain tissue and to have less recording artifact. In contrast to needles, wick fibers probably attenuate the response to high-frequency pulsations, including systolic and diastolic arterial pressures.

Errors in measurement might be attributed to leaks or evaporation of fluid from each system. For example, a leak could account for the loss of the steady state in some of our animal studies. In fact, the loss of fluid from a single needle system, tested in vitro, amounted to an estimated 0.1 μl/hr, a quantity of fluid required to reestablish a lost steady state in vivo. A minute amount of fluid might conceivably be lost from the needle tip by diffusion in vivo, adding further artifacts. Actually, water content of the area around the TP needles was not altered from control values, indicating that the needle method did not change hydration of the tissue and diffusion artifact was insignificant.

This study of brain tissue pressure has focused on physiological observations in intact, anesthetized animals. An accurate recording method for assessing TP has been developed, which allows the direct assessment of parenchymal pressure and hydrostatic pressure gradients. The study shows that TP from brain can be recorded effectively by a needle system without altering the blood-brain barrier, brain water content, rCBF, and cerebrovascular reactivity to changes in PaCO₂ and CPP. Direct TP measurement of this kind provides a useful means of studying various brain parenchymal problems, including ischemia and the process of edema formation.

### Table 1

Measurements of tissue pressure in different series.

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Method &amp; Animal</th>
<th>Tissue Pressure (mm Hg)</th>
<th>CSF Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brock et al., 1972</td>
<td>wick, cats</td>
<td>5.52 ± 2.60</td>
<td>6.14 ± 2.45</td>
</tr>
<tr>
<td>Brodersen et al., 1972</td>
<td>split catheter tip or modified wick, cats</td>
<td>-3 to -12</td>
<td>6-13 (CMP)</td>
</tr>
<tr>
<td>Cervós-Navarro et al., 1980</td>
<td>Wick, dogs</td>
<td>0-0.5</td>
<td></td>
</tr>
<tr>
<td>Furuse et al., 1975</td>
<td>wick, cats</td>
<td>7.2 ± 0.8, 7.4 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Halsey et al., 1975</td>
<td>catheter transducer, cats</td>
<td>2-9</td>
<td></td>
</tr>
<tr>
<td>Marmarou et al., 1976</td>
<td>wick, cats</td>
<td>12.36 ± 6.86, 10.70 ± 7.43</td>
<td></td>
</tr>
<tr>
<td>Reulen &amp; Kreysch, 1973</td>
<td>wick, cats</td>
<td>1.81 ± 0.62, 5.17 ± 0.83</td>
<td></td>
</tr>
<tr>
<td>Tulleken et al., 1975</td>
<td>wick, baboons &amp; macaques</td>
<td>2.2 ± 2.8</td>
<td></td>
</tr>
</tbody>
</table>

*CSF = cerebrospinal fluid; CMP = cisterna magna pressure; VFP = ventricular fluid pressure. Two mean values indicate values in different regions of the brain.

### Acknowledgment

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