Pressure gradients in the brain in an experimental model of hydrocephalus

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Object. The goal of this investigation was to establish whether pressure gradients exist between the ventricles, brain tissue, and subarachnoid space when acute or chronic hydrocephalus develops. Such gradients are hypothesized by many models of hydrocephalus, but considerable controversy continues about their existence.

Methods. A stereotactic frame was used for surgery in dogs to implant pressure sensors within the right lateral ventricle, the frontal lobe, and forward in the subarachnoid space. The dogs were allowed to recover for 10 to 14 days postoperatively. Then, 800 mg of sterile kaolin in water was injected into the cisterna magna region by using a percutaneous approach. Both real-time and long-term intracranial pressures were measured.

Of the six dogs, one experienced an intracranial hemorrhage, one dog displayed status epilepticus after a second injection of kaolin and was killed, one experienced acute hydrocephalus, and three experienced mild chronic hydrocephalus. No consistent pressure differences were found in any dog between the ventricle, brain, and subarachnoid space before kaolin administration or afterward when hydrocephalus developed. In addition, no pulse pressure gradients occurred between the brain and the ventricle or subarachnoid space.

Conclusions. Precise monitoring of pressure before and during the development of hydrocephalus did not detect pressure gradients between the ventricle, brain, and subarachnoid space. This was true for long-term measurements over weeks and for real-time measurements that allowed accurate assessment of pulse pressures. Theories predicting pressure gradients greater than the resolution of these sensors (0.5 mm Hg) across brain tissue have to be reevaluated in light of these findings.

Key Words • hydrocephalus • intracranial pressure • kaolin • transmural pressure • long-term intracranial pressure monitor • dog

The cause of ventricular enlargement in cases of hydrocephalus remains controversial despite decades of debates, experiments, and theories. At the core of the problem is the lack of convincing evidence of a pressure gradient in brain tissue that would produce movement or compression of brain tissue. Without a pressure difference between the ventricles and the brain tissue or subarachnoid space there is no physical reason why brain tissue should move or be compressed. The hypothesis posed by Nakra and associates, that fluid is pressed out of the brain tissue extracellular space explicitly posits such radial pressures, but any other theory must rest on similar forces to enlarge the ventricles. The only alternative would be some mysterious loss of tissue caused by the hydrocephalic process. A number of reasons for the lack of strong experimental evidence for a pressure gradient can be suggested. In patients, it is technically difficult to obtain accurate measurements because of the inaccuracy of invasive ICP measurements and positional changes of the head over time. Furthermore, it has not been possible to perform long-term continuous measurements as hydrocephalus develops. The careful work by the Göteborg Group found no transmantle pressure gradient in cases of either communicating or noncommunicating hydrocephalus; however, that study was criticized because no measurements were made during the active process of ventricular expansion. Another possibility is that the pulsatile nature of CSF flow has not been considered. As Eggnor and colleagues recently emphasized, the pulsatile forces of CSF flow could be an important driving force in the creation of ventricular enlargement. If so, transient imbalances between pulse pressure waves in the ventricle, brain, and subarachnoid space could provide the force necessary to displace or compress tissue without requiring the mean pressures within these spaces to be different.

To resolve these issues, we have used a new way of measuring pressures intracranially with the aid of the InSite monitor system (Medtronic Neurological, Minneapolis, MN). As described in a previous paper, both long-term and real-time pressures can be accurately obtained in dogs with this device. In a recent Phase I/II study, the InSite system was shown to work in patients with hydrocephalus. To have control over the timing of the development of hydrocephalus and to allow appropriate simultaneous long-term and real-time measurements in the ventricles, brain tissue, and subarachnoid space, we chose to use the well-studied

Abbreviations used in this paper: CSF = cerebrospinal fluid; ICP = intracranial pressure.
kaolin dog model of hydrocephalus. In a series of preliminary experiments (J S Kroin and R D Penn, unpublished data) we established that a ventriculally placed InSite device could accurately monitor pressure in the presence of kaolin-induced acute and chronic hydrocephalus. We now report the use of three monitors in single dogs for simultaneous pressure recordings in the ventricle, brain, and subarachnoid space before, during, and after both acute and chronic hydrocephalus.

Materials and Methods

All animal experiments were performed at the Medtronic Research Facility under a protocol approved by the Institutional Animal Care and Use Committee. Six mongrel dogs were used in this study. Three InSite devices were implanted in each dog (surgery performed by M.C.L. and R.D.P.). Each dog was intubated and placed in a stereotactic frame. Anesthesia was maintained with 1.5% isoflurane in oxygen. A midline scalp incision was made and muscles were retracted to expose the frontal, parietal, and temporal regions of the left lateral ventricle. A small (~3-mm) burr hole was drilled to expose the frontal, parietal, and temporal regions of the left lateral ventricle. A small (~3-mm) burr hole was drilled and a ventricular catheter was placed to locate the ventricle by stereotactic frame (David Kopf Instruments, Tujunga, CA) was used to identify the region of the left lateral ventricle. A small (~3-mm) burr hole was drilled and a ventricular catheter was placed to locate the ventricle by stereotactic frame. A small (~3-mm) burr hole was drilled and a ventricular catheter was placed to locate the ventricle by stereotactic frame. The stereotactic frame contained a microprocessor, memory, battery, and radiofrequency telemetry link; an external pressure reference, which recorded barometric pressure once a minute; and a custom personal computer-based program. The absolute pressure sensor has a total range of 500 mm Hg, however, the range was reduced to approximately 100 mm Hg to yield maximal pressure resolution for the purposes of this experiment. After barometric correction this absolute pressure range equated to a gauge pressure of approximately 0 to +50 mm Hg with a resolution of approximately 0.35 mm Hg. The actual range of the gauge pressure, which can be resolved by the sensor, was dependent on the barometric pressure. The InSite system can be operated in one of two modes. The first mode provides continuously telemetered real-time pressure data. The pressure data are band passed from the direct current to 40 Hz and sampled at 250 Hz. The high data-sampling rate provides clear measurements of pulse pressure waveform. When simultaneous real-time measurements were recorded from the three devices, the dogs were either placed in a sling or allowed to rest quietly on the floor to maintain the head in a horizontal position. The vertical heights of the sensors, relative to each other, were therefore approximately equal for these measurements over multiple recording sessions. The second mode provided long-term storage of mean pressures. Every 2 seconds the device sampled the pressure waveform for 500 msec and entered the lowest pressure measurement into a histogram. After 37 data samples had been collected in the histogram, the median of the histogram was calculated and placed in permanent storage. In this manner, the device was able to record mean pressure sampled once every 74 seconds over 7 days. Long-term pressure data were downloaded and data acquisition reinitiated every 7 days. The pulse pressure waveform was sampled frequently in the days before kaolin delivery and after kaolin had been injected and produced hydrocephalus.

Statistical Analysis

Because all of the data collection devices had been implanted, the animals were allowed to walk around, sleep, or assume any position they pleased. This led to variability in the long-term mean pressures. To uncover underlying trends in the mean pressures more fully, long-term mean pressure data were low pass filtered using a 121-point (1.5-hour) median filter. To improve the legibility of scatter plot figures, the long-term trend data were down-sampled to 45 minutes per sample. Linear regression models for the relationship between the ventricular, parenchymal, and subarachnoid pressures were fitted using the least square method. Pressure variations due to posture changes in the pulse pressure recordings were not severe because the dogs’ heads were held still during each recording session. The pulse pressure waveforms were low pass filtered at 30 Hz by using a first order Butterworth filter to reduce the effects of quantization noise. Postprocessing was done using Matlab (The Mathworks, Natick, MA).

Results

In all six dogs InSite systems were successfully placed in the lateral ventricle, brain, and subarachnoid spaces for long-term and real-time recordings (Fig. 1). In one dog a