Cerebrospinal fluid volume measurements in hydrocephalic rats

Laboratory investigation

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Object. Experimental data about the evolution of intracranial volume and pressure in cases of hydrocephalus are limited due to the lack of available monitoring techniques. In this study, the authors validate intracranial CSF volume measurements within the lateral ventricle, while simultaneously using impedance sensors and pressure transducers in hydrocephalic animals.

Methods. A volume sensor was fabricated and connected to a catheter that was used as a shunt to withdraw CSF. In vitro bench-top calibration experiments were created to provide data for the animal experiments and to validate the sensors. To validate the measurement technique in a physiological system, hydrocephalus was induced in weanling rats by kaolin injection into the cisterna magna. At 28 days after induction, the sensor was implanted into the lateral ventricles. After sealing the skull using dental cement, an acute CSF drainage/infusion protocol consisting of 4 sequential phases was performed with a pump. Implant location was confirmed via radiography using intraventricular iohexol contrast administration.

Results. Controlled CSF shunting in vivo with hydrocephalic rats resulted in precise and accurate sensor measurements (r = 0.98). Shunting resulted in a 17.3% maximum measurement error between measured volume and actual volume as assessed by a Bland-Altman plot. A secondary outcome confirmed that both ventricular volume and intracranial pressure decreased during CSF shunting and increased during infusion. Ventricular enlargement consistent with successful hydrocephalus induction was confirmed using imaging, as well as postmortem. These results indicate that volume monitoring is feasible for clinical cases of hydrocephalus.

Conclusions. This work marks a departure from traditional shunting systems currently used to treat hydrocephalus. The overall clinical application is to provide alternative monitoring and treatment options for patients. Future work includes development and testing of a chronic (long-term) volume monitoring system.

Key Words • hydrocephalus • juvenile rat • impedance sensor • cerebrospinal fluid volume • ventriculoperitoneal shunt

The dynamics of ventricular enlargement remain elusive to researchers of hydrocephalus, a disease in which CSF accumulates in the ventricular system. In normal pressure hydrocephalus, the observable CSF flow pathway remains open, yet the ventricles enlarge despite normal intracranial pressure. Continuous monitoring of the disease is difficult for patients with normal pressure hydrocephalus. There remains a lack of research related to the continuous evaluation of intraventricular volume. Thus, the importance of validating a novel volume sensor is crucial to better understanding the pathophysiology of hydrocephalus.

We have recently proposed a method, based on the impedance technique, to measure intraventricular volume change.1,23,24 The measurement principle is based on differences in electrical conductivity (or its inverse impedance) between CSF and brain tissue. If a potential voltage field is generated by 2 excitatory electrodes in the CSF-filled ventricles, the potential decrease at any 2 locations can be measured with additional measurement electrodes typically placed between the 2 excitatory electrodes. The measured potential decrease depends on the electrical properties of the fluid, but is also influenced strongly by surrounding brain tissue, whose conductance is substantially lower than that of CSF. Specifically, the voltage decrease is small when the volume near the sensor is filled with CSF and high when a larger fraction of the space is occupied by poor electrically conducting brain tissue. Accordingly, the voltage measurement is proportional to the size of the fluid-filled volume. Conductance measurements to estimate neuron electrical activity—without exploiting the impedance differences used in volume measurement—have been applied to measure property changes in the lung,23,24 thoracic imaging,25 blood stroke volume,26,27 breast imaging to detect cancer,28 tissue characterization,29,30 and intracranial blood flow.31,32,33 We have demonstrated the feasibility in bench-top models; an animal device implantation study is now shown in this paper to validate the technique.

In the weanling rat hydrocephalic model, sterile ka-
alin clay is injected into the cisterna magna. This method of inducing hydrocephalus has been shown experimentally to block the reabsorption of CSF, which causes extreme ventricular enlargement.26 Hydrocephalic rats also approximate the type of ventricular expansion observed in human infants.25 Much research has also been conducted with this animal model in relating structural and behavioral changes as the disease progresses.14,27 Histological measurements show a reduction in ventricular size after shunt treatment in hydrocephalic weaning rats.19 In a recent study, acute intracranial pressure measurements were obtained in an infusion protocol with hydrocephalic rats.28

Three-dimensional models of the ventricles in hydrocephalic rats show a 3000% increase in CSF volume compared with baseline in normal rats with a ventricular volume of 10 μl (Fig. 1). At 14 days after induction of hydrocephalus, 300 μl of CSF accumulates in the ventricular system. At 21 days, the ventricles contain up to 340 μl of CSF. According to the computer-aided sensor design, a 600-μm-outerriameter sensor with a length of 5 mm is sufficient to fit inside the enlarged ventricles of a hydrocephalic rat after 28 days of induction. We chose the lateral ventricles to implant our sensor, because the surface area of that region is larger than any other part. These ventricles also expand the most during hydrocephalus; therefore, we presumed it to be the most compliant region of the brain suitable for tracking acute CSF volume change.

In this paper, we validate ventricular volume and intracranial pressure measurements in an animal model of hydrocephalus as a first step toward understanding dynamic properties of brain tissue in hydrocephalus. The paper is organized as follows: volume sensor and hardware setup are described first, followed by in vitro calibration with bench-top models. The induction of hydrocephalus and the in vivo experiment are described next. Volume measurements were confirmed independently by imaging the sensor implant system. The results section provides dynamic volume and pressure data with measurement error.

Methods

Sensor Fabrication

The outer diameter of most commercially available volume sensors is approximately 1 mm. The size constraints posed by the hydrocephalic rat model prohibit the use of these commercially available volume sensors. To overcome this limitation, we fabricated miniature sensors sized for the ventricles in hydrocephalic rats. To define the proper size of the sensors, the corresponding ventricular size in hydrocephalic rats was calculated from a stack of MR images that were obtained to create a 3D representation (raw MRI data courtesy of M. R. Del Bigio; Fig. 1). The volume sensors were designed using the computer-aided design module in Mimbics reconstruction software (Materialise) to determine suitable electrode distance and catheter dimensions.

To fabricate our sensor, holes were drilled in a 1-Fr silicone tube using a dicing saw at the Nanotechnology Core Facility at the University of Illinois at Chicago. Wires were passed through these holes to platinum/iridium cylinders (Johnson-Matthey Medical) to create ring electrodes (Fig. 2B). The total outer diameter of our device was less than 600 μm. Line pressure was measured with a Transpac disposable pressure sensor (ICU Medical). Real-time measurements were collected on a computer using LabVIEW (National Instruments Corporation). The data were sampled at a rate of 10,000 samples/second, with a low-pass eighth-order Butterworth filter applied.

In Vitro Testing (Brain Phantom)

Volume sensors were tested in brain phantoms and silicone balloon models prior to animal testing for calibration. The brain phantom consisted of 0.02% NaCl/0.6% agarose gel to exactly match a brain tissue:CSF electrical conductivity ratio2 of 12.1. The volumes in the brain phantom cavities ranged from 15 to 150 μl, which were chosen to cover the ventricular volume range in normal to hydrocephalic rats. Measurements were obtained by repeatedly placing the sensor in 4 cavities of the gel. A second in vitro test was performed using a compliant balloon model. The silicone balloon model (DSB detachable silicone balloon, Boston Scientific) was developed to assess the dynamic tracking capabilities of the sensor. The sensor was placed in a silicone balloon whose fluid content could be easily manipulated by adding artificial CSF through a syringe pump (Fig. 3A). The known relationship between voltage and volume was used to calculate relative CSF volume change in the animal model. Relative volume change was calculated due to unknown properties of CSF in the animal model. The exact geometrical shape of the ventricles, as well as CSF conductivity values, was unknown. The constraints of using the bench model for calibration of the sensor are described in the discussion section below.

In Vivo Testing (Hydrocephalic Rat)

Animal experiments were approved by the Animal Care and Use Committee at the University of Illinois at Chicago. An acute experiment was designed that consisted of sequential shunting and infusing CSF from the ventricles of a hydrocephalic rat. The objective was to measure dynamic volume changes. Animals were weighed prior to induction of hydrocephalus and regularly throughout the experimental end point. Fifteen 3-week-old Sprague-Dawley rats were injected with 20 μl of 25% w/v sterile kaolin suspension into the cisterna magna using a 26-gauge needle. The animals were allowed to recover from anesthesia and were closely monitored after injection. Weights of kaolin-injected animals were compared with the weights of control animals; kaolin-injected animals exhibiting qualitatively retarded weight gain, a dome-shaped head, and gait instability were considered hydrocephalic,21 and hydrocephalus was quantitatively verified postmortem.

Four weeks following the induction of hydrocephalus in the rats, we implanted the sensor and obtained measurements during controlled CSF drainage (shunting) and infusion using a pump (Fig. 2). In each hydrocephalic