Experimental feline hydrocephalus

The role of biomechanical changes in ventricular enlargement in cats

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In a craniectomy-durectomy model of kaolin-induced feline hydrocephalus, the pressure-volume index (PVI) technique of bolus manipulations of cerebrospinal fluid (CSF) was used to study the biomechanical changes associated with hydrocephalus. Steady-state intracranial pressure (ICP), PVI, and the resistance to the absorption of CSF were determined acutely and 3 to 5 weeks later in hydrocephalic cats and time-matched control cats. Steady-state ICP was 11.0 ± 2.1 mm Hg (± standard deviation) in the hydrocephalic cats, compared to 10.8 ± 2.2 mm Hg in the chronic control group (p > 0.1). The ICP in both the chronic hydrocephalic and chronic control groups was significantly higher (p < 0.001) than after acute durectomy (mean ICP 8.5 ± 1.2 mm Hg). Immediately after dural opening, the mean PVI was 3.6 ± 0.2 ml (± standard error of the mean); over time, it decreased to 1.3 ± 0.1 ml in the chronic control group (p < 0.001), but remained elevated in the hydrocephalic group at 3.5 ± 0.4 ml (p < 0.001). Resistance to CSF absorption was 9.1 ± 1.4 mm Hg/ml/min immediately after dural opening and increased to 28.8 ± 4.5 mm Hg/ml/min (p < 0.001) in the hydrocephalic cats; it increased even further in the chronic measurements in control cats, to 82.3 ± 9.2 mm Hg/ml/min (p < 0.001). Ventricular size was moderate to severely enlarged in all hydrocephalic cats, and normal in the control group.

These results indicate that the biomechanical profile of the altered brain container model of kaolin-induced feline hydrocephalus resembles that described in hydrocephalic infants. As shown in the control subjects, an absorptive defect alone is not sufficient to cause progressive ventricular enlargement. Increased volume-buffering capacity coupled with a moderate increase of CSF absorption resistance facilitates volume storage in the ventricles.

KEY WORDS • hydrocephalus • cerebrospinal fluid dynamics • intracranial pressure • pressure-volume index • craniectomy • durectomy

Previous studies of infantile hydrocephalus from this laboratory have documented enhanced neural axis volume-buffering capacity and increased resistance to the absorption of cerebrospinal fluid (CSF). It was inferred that this combination of impaired absorption of CSF and facilitation of volume storage may work synergistically and lead to the accumulation of CSF within the ventricles. Although these alterations in neural axis biomechanics were consistently documented in a well defined group of hydrocephalic infants, these studies were performed after the hydrocephalic process had become established. In order to investigate this process earlier in its course, we chose to apply these investigative techniques to a laboratory model of hydrocephalus which simulates the hydrocephalic infant.

Laboratory studies of the hydrocephalic process have shown that ventricular size increases progressively after the container of the brain is altered. Most studies have shown that the intact feline hydrocephalic model using kaolin to incite an inflammatory response produces moderate enlargement of the ventricles which stabilizes over time. This compensation of the hydrocephalic process has been explained by the development of accessory pathways of absorption, utilizing the central canal of the spinal cord. After altering the confines of the brain by removing the calvaria and opening the dura, Hochwald, et al., demonstrated that apparently stabilized kaolin-hydrocephalic cats would undergo extreme ventricular enlargement. This model was likened to hydrocephalic infants with open calvarial sutures, who also have greater ventricular
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enlargement than their older counterparts with rigid skulls.

This laboratory has demonstrated that acute alterations in the container of the normal feline brain lead to dramatic changes in volume-buffering capacity, coupled with a reduction in the resistance to the absorption of CSF. In these studies, the propensity for volume storage that was created by removing the calvaria and opening the dura was offset by the reduced CSF absorption resistance. The reciprocal changes in these parameters led to preservation of a hydrodynamic steady state without storage of CSF in the ventricles.

With this model of alteration of the container of the feline brain, the present studies were carried out in order to: 1) assess the effects of craniectomy and durectomy on the neural axis volume-buffering capacity and CSF absorption resistance in the chronic preparation; 2) determine whether an absorptive defect was necessary to initiate the hydrocephalic process; and 3) determine the role of altered volume-buffering capacity on progressive ventricular enlargement.

Materials and Methods

Adult mongrel cats, each weighing 3 to 5 kg, were anesthetized with intraperitoneal pentobarbital (30 mg/kg) followed by endotracheal intubation. Indwelling arterial and venous catheters were inserted for measurement of systemic arterial blood pressure and administration of drugs. The animals were paralyzed with gallamine (4 mg/kg), mechanically ventilated using a conventional Starling respirator with a 2:1 mixture of nitrous oxide and oxygen, and secured in the sphinx position in a stereotaxic frame. Arterial blood gases were monitored periodically. The respirator was adjusted to maintain PaCO$_2$ between 28 and 35 torr and PaO$_2$ greater than 90 torr. Rectal temperature was monitored continuously and was maintained within the physiological range.

Bilateral craniectomies were performed; the calvaria was removed between the coronal and lambdoid sutures, with the exposure extending medially to within 5 mm of the sagittal suture and laterally to the floors of the middle fossa. Under magnification, a cruciate opening was made in the dura. A No. 19 scalp vein needle, coupled via saline-filled tubing to a conventional strain-gauge transducer, was inserted into the cisterna magna. Microscope.

Mock CSF was infused slowly to distend the CSF spaces. Ventricular fluid pressure was monitored by means of a No. 25 needle placed stereotaxically in the lateral ventricle and connected by saline-filled tubing to a strain-gauge transducer. Ventricular fluid pressure to bolus injections of fluid in chronic control (upper) and hydrocephalic (lower) animals. Po represents the initial intracranial pressure (ICP) prior to fluid injection. Following bolus injection (ΔV), Pp is the immediate peak ICP and P$_t$ is the ICP 1 minute after injection. Pressure-volume index (PVI) and cerebrospinal fluid absorption resistance (Ro) are calculated from these measurements. These injection sequences show that PVI increases in hydrocephalic animals as compared to chronic control subjects, even though ICP is similar.

The animals were divided into two study groups: chronic control cats and hydrocephalic animals. The cats selected for the hydrocephalus group were placed in the head-down position; 1 ml of CSF was withdrawn from the cisterna magna and replaced with an equal volume of kaolin suspension (250 mg/ml). In the chronic control group, the animals had bilateral craniectomy and dural opening, but kaolin was not instilled. Both groups of animals were allowed to recover from the acute procedure and were supported as required.

Three to 5 weeks later the animals were reanaesthetized, intubated, and placed in the stereotaxic frame. The cisterna magna was recannulated as described above. Ventricular fluid pressure was monitored by means of a No. 25 needle placed stereotaxically in the lateral ventricle and connected by saline-filled tubing to a strain-gauge transducer. Bolus manipulation of CSF was performed through the ventricular catheter as well as via the cisterna magna site. Determinations of PVI and CSF absorption resistance were repeated and compared to values for each parameter determined during the initial experiment (Fig. 1).
After completion of these procedures, the animals were sacrificed with intravenous KCl and the brains were removed. After fixation in formalin, the brains were sectioned in the coronal plane. Ventricular size was assessed visually and categorized as normal, mildly hydrocephalic, moderately hydrocephalic, or severely hydrocephalic. In addition, these visual estimates were compared with two indices of ventricular size. Using the coronal section through the foramen of Monro, the minimum breadth at the floor of the lateral ventricle was measured \(a\), and divided by the maximum span of the lateral ventricle \(b\), to obtain the \(a/b\) ratio. An additional estimate of ventricular size was obtained by measuring the minimum width of the lateral ventricles at the floor of the ventricle on a coronal section taken through the body of the ventricle. This measurement has been shown by Bull to correlate best with ventricular volume. Visual scores were correlated with both measurements.

Results

Sixteen cats in the hydrocephalic group and 10 control animals survived the acute and chronic phases of these experiments. In all hydrocephalic cats, the scalp overlying the sites of craniectomy was full and, in many animals, bulging. This usually occurred in the 1st week after the instillation of kaolin and persisted unchanged throughout the observation period. Initially the scalp over the craniectomy area in the control group of animals was soft and did not bulge. However, over 2 to 3 weeks the scalp became more rigid but never distended. When the brains were removed in both groups of animals, dense adhesions were found between the temporalis muscle and the residual dura. The temporalis muscle had also become quite fibrotic, accounting for the “rigidity” of the scalp observed in the control group.

Intracranial Pressure

The mean ICP immediately following durectomy in the animals destined to be hydrocephalic was 8.5 ± 1.2 mm Hg (± standard deviation). This was not statistically different from the control animals whose mean ICP was 8.1 ± 1.7 mm Hg. When both groups were studied in the chronic stage of these experiments, the ICP measured in the hydrocephalic cats was 11.0 ± 2.1 mm Hg, which did not differ statistically from the mean ICP of 10.8 ± 2.2 mm Hg measured in the chronic control group (p > 0.1). However, the ICP's measured in both the chronic control and the chronic hydrocephalic animal groups were statistically different from the pressures measured in the acute phase (p < 0.001) (Fig. 2).

Pressure-Volume Index

As shown in Fig. 3, the PVI measured in hydrocephalic cats (mean ± standard error of the mean (SEM) 3.5 ± 0.4 ml) was not statistically different from the values obtained immediately after opening the cranium and dura (mean 3.6 ± 0.2 ml). However, the PVI values determined in hydrocephalic cats differed considerably from values obtained in the time-matched control group (mean PVI 1.3 ± 0.1 ml) (p < 0.001). There was no correlation between ventricular size and PVI.

Resistance to the Outflow of CSF

The resistance to the absorption of CSF immediately
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after durotomy was 9.1 ± 1.4 mm Hg/ml/min (±SEM), and, with the establishment of hydrocephalus, increased to 28.8 ± 4.5 mm Hg/ml/min (p < 0.001). In the time-matched chronic control animals without hydrocephalus it increased to 82.3 ± 9.2 mm Hg/ml/min (p < 0.001). The differences in CSF absorption resistance determined in both groups of chronic preparations were statistically significant (p < 0.001) (Fig. 3).

Ventricular Size

There was excellent correlation of ventricular size determined by visual inspection with linear measurements. In ventricles graded as normal by visual inspection, the a/b ratio was below 0.29 and the minimum ventricular width never exceeded 1.0 mm. All of the control animals were judged to have normal-sized ventricles by all criteria. Moderate ventricular enlargement was observed in 50% of the hydrocephalic group. This designation corresponded to a mean a/b ratio greater than 0.45 and a measurement of ventricular width greater than 2.5 mm. The remaining 50% of the hydrocephalic cats had marked ventricular enlargement; the a/b ratio exceeded 0.60, and minimum ventricular span was 5.5 mm or greater.

Discussion

The laboratory model of feline kaolin-induced hydrocephalus with alteration of the brain container to augment ventricular size was first used by Hochwald, et al., to simulate infantile hydrocephalus. This model was chosen for these laboratory experiments in order to determine whether the biomechanical abnormalities demonstrated in clinical studies of infants with hydrocephalus could be reproduced in the laboratory setting. By selecting a model that simulates not only the morphology of the clinical disease but also has other descriptors in common, we hoped to validate its relevance as a laboratory model of this particular form of clinical hydrocephalus. In the first experiments in this series, we found that acutely altering the container of the feline brain enhances volume-buffering capacity. However, this change was offset by a diminution in the CSF absorption resistance component, which negated this apparent propensity for volume storage. The intent of the current studies was to establish the course of these parameters in chronic experiments and also to determine how these parameters were affected by the instillation of an agent that incited hydrocephalus.

As demonstrated by the experiments in the chronic control group, significant changes of both CSF absorption resistance and pressure-volume index (PVI) occur over time when compared to the acute alteration of the container. The PVI decreases over time in the chronic group compared to immediately after craniectomy and durotomy, and approaches the values determined acutely in animals undergoing craniectomy alone. While other factors could have accounted for this decrease of volume-buffering capacity over time, the adhesion of the temporalis muscle to the open dura and the contraction of this muscle may have effectively simulated a reconstituted dura. Rather than representing any change in neural axis dynamics, this diminution in PVI may merely indicate the partial restoration of the brain's container over time. Gross inspection revealed no signs of meningitis or cerebral edema to implicate more complicated explanations for the reduction of PVI between the acute and chronic phases of these experiments.

The resistance to absorption of CSF in the chronic control animals exceeded that determined in the acute craniectomy model and was slightly below the range of normal for the intact cat as determined in this laboratory. It is unclear from these studies whether the increase of resistance to CSF absorption in the chronic control group was caused by arachnoid reaction to the blood introduced during the initial procedure. Regardless of the mechanism, increased CSF absorption resistance (R₀) was accompanied by a small but statistically significant increase of CSF pressure. Assuming a relatively fixed rate of CSF formation (Iᵢ), the additional 1.5 mm Hg contributed by the (Iᵢ × R₀) product in the chronic control animals can account for the rise in CSF pressure found in these animals when compared to the acute experiments. This would indicate that the elevated CSF pressure results from the elevation of CSF absorption resistance and represents a reestablishment of steady-state CSF pressure from CSF hydrodynamic factors.

Despite the increased CSF absorption resistance and elevated CSF pressure, the ventricles remained normal in size. Although earlier investigations led some to postulate that an absorptive defect was the cause of hydrocephalus, other investigators have argued that a relative impairment of CSF absorption should not lead to ventricular dilatation. Studies in various clinical settings have also failed to demonstrate that an elevation of CSF absorption resistance alone will lead to ventricular enlargement. Sklar, et al., and Johnston have shown elevated CSF absorption resistance in patients with pseudotumor cerebri and small ventricles. The data from the chronic control group in the present studies lend further support to the notion that a modest absorptive defect is not sufficient to cause ventricular dilatation. Our own studies and the inferences of others show that the CSF absorption resistance parameter should lead to a rise of ICP along a pressure-volume curve determined by the compliance factors with a resetting of steady-state ICP at a hydrodynamic equilibrium between the formation and absorption of CSF. These chronic control preparations support this analysis. When compared to the chronic control group, the changes in the PVI demonstrated in the hydrocephalic cats indicate that enhanced volume-buffering...
capacity accompanies enlargement of the ventricles (Fig. 4). Although others have reported that increased compliance parallels increasing ventricular size, these and other studies from this laboratory have shown that the PVI does not merely reflect ventricular size. As a consequence of the increased PVI that has been demonstrated in hydrocephalic animals, the capacity to store volume increases without elevation of CSF pressure. The changes that enhance volume-buffering capacity are not apparent from the present studies. In non-pathological settings, the mechanism that buffers a bolus injection of fluid is generally attributed to compression of collapsible veins with little participation from the brain parenchyma. As shown in studies described earlier, the integrity of the container of the neural axis probably prevents the brain tissue from buffering additional volume. After altering the container, the CSF pressure response to bolus injections is, in part, buffered by the biomechanical response of the brain. As shown in this report, bolus testing continues to show alteration of the biomechanical properties of the brain with hydrocephalus despite stabilization of the container. Changes in the white matter of brain tissue, including compression of fiber tracts and loss of myelin, have been described in hydrocephalus. We infer from our studies that the biomechanical properties of brain parenchyma are altered as these structural changes occur.

Other investigators have reported tests of compliance in hydrocephalic subjects. Lim, et al., measured compliance (dV/dP) in dogs with and without manipulation; but their studies were in the acute stage, which would not include the progressive changes characteristic of chronic infantile or chronic kaolin hydrocephalus. Drapkin and Sahar reported significantly reduced ICP over time associated with the altered container model of kaolin-induced hydrocephalus described by Hochwald, et al. They found increased ventricular distensibility over time in hydrocephalic cats, results that are similar to those of the present studies.

In hydrocephalic cats we found a threefold increase in the CSF absorption resistance parameter when compared to acute control animals after durectomy. This is consistent with our clinical observations in hydrocephalic infants. However, these values are considerably below the results obtained in the chronic control group. While it might appear illogical to interpret these studies as showing impaired absorption when even higher CSF absorption resistance values were found in time-matched control experiments, these findings are consistent with the observations of others. Several investigators have reported enhancement of the absorptive reserve in experimental animals rendered hydrocephalic with kaolin. Others have noted that the central canal of the spinal cord dilates with feline hydrocephalus, and have suggested that this may be a pathway for accessory absorption.

The biomechanical profile revealed in these studies is similar to that described using similar techniques in well established infantile hydrocephalus. While it is unclear in the present series of animal experiments that the ventricular enlargement would continue to progress, other reports describing this model provide reasonable assurances that ventricular enlargement does continue. Both by gross inspection and biomechanical profile these studies show that the craniectomy-durectomy model of kaolin-induced feline hydrocephalus resembles the hydrocephalic infant. From these studies it is apparent that an absorptive defect is not sufficient to cause progressive ventricular enlargement. While changes in the biomechanical property of the brain facilitate ventricular expansion, it is not clear that this alteration alone will lead to hydrocephalus.

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References
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