
Idiopathic intracranial hypertension (IIH), or pseudotumor cerebri, is a debilitating neurological disorder characterized by elevated CSF pressure of unknown cause. IIH manifests as severe headaches, and visual impairments. Most typically, IIH prevails in overweight females of childbearing age and its incidence is rising in parallel with the obesity epidemic. The most accepted theory for the cause of IIH is reduced absorption of CSF due to elevated intracranial venous pressure. A comprehensive MRI study, which includes structural and physiological imaging, was applied to characterize morphological and physiological differences between a homogeneous cohort of female IIH patients and an age- and BMI-similar control group to further elucidate the underlying pathophysiology. A novel analysis of MRI measurements of blood and CSF flow to and from the cranial and spinal canal compartments employing lumped parameters modeling of the cranio-spinal biomechanics provided, for the first time, evidence for the involvement of the spinal canal compartment. The CSF space in the spinal canal is less confined by bony structures compared with the cranial CSF, thereby providing most of the craniospinal compliance. This study demonstrates that the contribution of spinal canal compliance in IIH is significantly reduced.


BACKGROUND AND PURPOSE: Impaired CSF homeostasis and altered venous hemodynamics are proposed mechanisms for elevated pressure in IIH. However, the lack of ventricular expansion steered the focus away from CSF homeostasis in IIH. This study aims to measure intracranial CSF volumes and cerebral venous drainage with MR imaging to determine whether increased CSF volume from impaired CSF homeostasis and venous hemodynamics occur in obesity-related IIH. MATERIALS AND METHODS: Two homogeneous cohorts of 11 newly diagnosed pretreatment overweight women with IIH and 11 overweight healthy women were prospectively studied. 3D volumetric MR imaging of the brain was used to quantify CSF and brain tissue volumes, and dynamic phase contrast was used to measure relative cerebral drainage through the internal jugular veins. RESULTS: Findings confirm normal ventricular volume in IIH. However, extraventricular CSF volume is significantly increased in IIH (290 +/- 52 versus 220 +/- 24 mL, P = .001). This is even more significant after normalization with intracranial volume (P = .0007). GM interstitial fluid volume is also increased in IIH (602 +/- 57 versus 557 +/- 31 mL, P = .037). Total arterial inflow is normal, but relative venous drainage through the IJV is significantly reduced in IIH (65 +/- 7% versus 81 +/- 10%, P = .001).

CONCLUSIONS: Increased intracranial CSF volume that accumulates in the extraventricular subarachnoid space provides direct evidence for impaired CSF homeostasis in obesity-associated IIH. The finding of larger GM interstitial fluid volume is consistent with increased overall resistance to cerebral venous drainage, as evident from reduced relative cerebral drainage through the UV. The present study confirms that both impaired CSF homeostasis and venous hemodynamics coexist in obesity-associated IIH.


OBJECT: The outflow resistance (Rout) of the cerebrospinal fluid (CSF) system has generally been accepted by most investigators as independent of intracranial pressure (ICP), but there are also those claiming that it is not. The general belief is that this question has been investigated numerous times in the past, but few studies have actually been specifically aimed at looking at this relationship, and no study has been able to provide scientific evidence to elucidate fully this fundamental and important issue. The objective of this study was to investigate the relationship between ICP and CSF outflow in 30 patients investigated for idiopathic normal-pressure hydrocephalus. METHODS: Lumbar infusion tests with constant pressure levels were performed, and ICP and corresponding flow were measured on 6 pressure levels for each patient. All data were standardized for comparison. RESULTS: In the range of moderate increases from baseline pressure (approximately 5-12 mm Hg, mean baseline pressure 11.7 mm Hg), the assumption of a pressure-independent Rout was confirmed (p = 0.5). However, when the pressure increment from baseline pressure was larger (approximately 15-22 mm Hg), the relationship had a nonlinear tendency (p < 0.05).

CONCLUSIONS: The results of this study support the classic textbook theory of a pressure-independent Rout in the normal ICP range, where the CSF system is commonly operating. However, the theory might have to be questioned in regions where ICP exceeds baseline pressure by too much.

RATIONALE AND OBJECTIVES: Using magnetic resonance imaging (MRI), we investigated cerebral blood and cerebrospinal fluid (CSF) flows in patients with communicating hydrocephalus (CH) and in healthy volunteers to determine the contribution of CSF flow to brain pressure regulation in CH patients. METHODS: Cine phase-contrast MRI data from 16 healthy volunteers and 12 patients with CH characterized by hyperdynamic aqueductal CSF flow were analyzed using in-house image-processing software that automatically measured flow curves. Amplitude and temporal CSF and blood flow parameters were compared in the 2 groups. RESULTS: Jugular peak flow occurred significantly earlier (P < 0.01) in the CH patients than in the healthy volunteers. Cervical CSF oscillations were not significantly different between the 2 groups. CONCLUSION: Venous vessel compression and/or changes in intracranial subarachnoid CSF flow produce an increase in ventricular CSF flush that compensates for vascular brain expansion in patients with CH.


PURPOSE: Despite 100 years of study, the theories of cerebrospinal fluid (CSF) formation and absorption remain controversial. Measuring CSF flow through the aqueduct using magnetic resonance imaging (MRI) provides a unique insight into the physiology of CSF hydrodynamics. The published data in adults tend to refute rather than support the prevailing theories of CSF flow. There are limited data regarding this metric in children. This paper seeks to measure the aqueduct flow in normal and hydrocephalic children to help formulate a more complete theory of CSF flow. METHODS: Twenty-four children with communicating hydrocephalus aged from 4 months to 16 years underwent MRI flow quantification of the aqueduct measuring the net flow. The patients were compared to 19 controls. RESULTS: The controls revealed two different flow patterns: (1) an infantile pattern characterized by flow directed into the ventricular system and (2) a mature pattern with flow directed out of the ventricles, similar to the published findings in adults. In infants with communicating hydrocephalus, the aqueduct flow changed direction but was of similar magnitude compared with the controls (p = 0.001). In the older hydrocephalic children, the flow was elevated 7-fold, but the direction was unchanged compared to the controls (p = 0.002). CONCLUSIONS: There is an abrupt change in the aqueduct CSF flow pattern at the age of 2 years from an infantile pattern to a mature pattern. These findings together with the findings in hydrocephalic children do not support the current theories of CSF hydrodynamics. A new theory of CSF circulation based on capillary absorption is presented.


This article reviews the basic known functions of cerebrospinal fluid (CSF). The traditional concepts of CSF production and absorption are reviewed and recent challenges to these concepts are discussed. MR imaging studies have begun to elucidate the complex interaction between pulsatile CSF movement, bulk CSF flow, and intracranial compliance. An understanding of a variety of disorders, including hydrocephalus and Chiari malformations, continue to evolve as knowledge of CSF physiology is increased.


In an effort to identify critical gaps in the prevailing knowledge of hydrocephalus, the authors formulated 10 key questions. 1) How do we define hydrocephalus? 2) How is cerebrospinal fluid (CSF) absorbed normally and what are the causes of CSF malabsorption in hydrocephalus? 3) Why do the ventricles dilate in communicating hydrocephalus? 4) What happens to the structure and function of the brain when it is compressed and stretched by the expanding ventricles? 5) What is the role of cerebrovenous pressure in hydrocephalus? 6) What causes normal-pressure hydrocephalus? 7) What causes low-pressure hydrocephalus? 8) What is the pathophysiology of slit ventricle syndrome? 9) What is the pathophysiological basis for neurological impairment in hydrocephalus, and to what extent is it reversible? 10) How is the brain of a child with hydrocephalus different from that of a young or elderly adult? Rigorous answers to these questions should lead to more effective and reliable treatments for this disorder.
OBJECTIVE AND IMPORTANCE: Spontaneous intracranial hypotension is an increasingly recognized cause of postural headache. However, appropriate management of obtundation caused by intracranial hypotension is not well defined. CLINICAL PRESENTATION: A 43-year-old man presented with postural headache followed by rapid decline in mental status. Imaging findings were consistent with the diagnosis of spontaneous intracranial hypotension, with bilateral subdural hematomas, pachymeningeal enhancement, and caudal displacement of posterior fossa structures and optic chiasm. INTERVENTION: Despite treatment with lumbar epidural blood patch, worsening stupor necessitated intubation and mechanical ventilation. Contrast-enhanced magnetic resonance imaging and computed tomographic myelography of the spine failed to demonstrate the site of cerebrospinal fluid fistula. The enlarging subdural fluid collections were drained, and a ventriculostomy was performed. Postoperatively, the patient remained semicomatose. To restore intraspinal and intracranial pressures, intrathecal infusion of saline was initiated. After several hours of lumbar saline infusion, lumbar and intracranial pressures normalized, and the patient’s stupor resolved rapidly. Repeat computed tomographic myelography accomplished via C1-C2 puncture demonstrated a large ventrolateral T1-T3 leak, which was treated successfully with a thoracic epidural blood patch. Follow-up magnetic resonance imaging demonstrated resolution of intracranial hypotension, and the patient was discharged in excellent condition. CONCLUSION: Spontaneous intracranial hypotension may cause a decline of mental status and require lumbar intrathecal saline infusion to arrest or reverse impending central (transtentorial) herniation. This case demonstrates the use of simultaneous monitoring of lumbar and intracranial pressures to appropriately titrate the infusion and document resolution of intracranial hypotension. Maneuvers aimed at sealing the cerebrospinal fluid fistula then can be performed in a less emergent fashion after the patient’s mental status has stabilized.


INTRODUCTION: Idiopathic intracranial hypertension (IIH) is a disorder typically affecting young, obese women, producing a syndrome of increased intracranial pressure without identifiable cause. STATE OF THE ART: Despite a large number of hypotheses and publications over the past decade, the etiology of IIH is still unknown. There continues to be no evidence-based consensus or formal guidelines regarding management and treatment of the disease. Treatment studies show that the diagnostic lumbar puncture is a valuable intervention beyond its diagnostic importance, and that weight management is critical. However, many questions remain, regarding the efficacy of acetazolamide, cerebrospinal fluid (CSF) shunting procedures, optic nerve sheath fenestration, and cerebral transverse venous sinus stenting. Identification of subgroups of patients at high-risk for irreversible visual loss, such as black patients,
men, morbidly obese patients, and patients with fulminant IIH, helps determine management approaches and refine follow-up strategies. PERSPECTIVE: Better understanding of the pathophysiology and ongoing clinical trials will hopefully help inform treatment strategies over the next few years.


In this study, we quantified cerebrospinal fluid (CSF) transport from the cranial and spinal subarachnoid spaces separately in sheep and determined the relative proportion of total CSF drainage that occurred from both CSF compartments. Cranial and spinal CSF systems were separated by placement of an extradural ligature over the spinal cord between C(1) and C(2). In one approach, two different radiolabeled human serum albumins (HSA) were introduced into the appropriate CSF compartment by a perfusion system (method 1) or as a bolus injection (method 2). Plasma tracer recoveries in conjunction with a mass balance equation were used to estimate CSF transport. In method 3, catheters connected to reservoirs filled with artificial CSF were introduced into the cranial and spinal CSF compartments. Incremental CSF pressures were established in each CSF system, and the corresponding steady-state flow rates were measured. Total CSF drainage ranged from 0.51 to 0.75 ml. h(-1). cmH(2)O(-1).

Expressed as a percentage of the total CSF transport, the ratios of cranial-to-spinal clearance estimated from methods 1, 2, and 3 were 75:25, 88:12, and 75:25, respectively. Primarily on the basis of the data derived from methods 1 and 3, we conclude that the spinal subarachnoid compartment has an important role in CSF clearance and is responsible for approximately one-fourth of total CSF transport.


BACKGROUND AND PURPOSE: The etiology of idiopathic normal-pressure hydrocephalus (NPH) is unknown. The purpose of this study was to examine the hypothesis that NPH begins in infancy as benign external hydrocephalus due to decreased uptake of CSF by the arachnoid villi. Since this occurs before the sutures fuse, a secondary hypothesis is that the intracranial volumes of patients with NPH should be larger than those of healthy individuals. METHODS: Intracranial volumes of 51 patients with clinically suspected NPH were compared with those of age- and sex-matched control subjects. All patients underwent phase-contrast CSF velocity MR imaging. They had aqueductal CSF stroke volumes of at least 60 microl, which was 50% higher than previously published normal values. Intracranial volumes were measured and compared between groups. RESULTS: The average intracranial volume for men with NPH (n = 22) was 1682 mL compared with 1565 for male control subjects (n = 55). The NPH volume averaged 118 mL (7.5%) larger than the control volume (P = .003). The average intracranial volume for women with NPH (n = 29) was 1493 mL compared with 1405 mL for female control subjects (n = 55). The NPH volume was 88 mL (6.3%) larger than the control volume (P = .002). CONCLUSION: Patients with NPH have intracranial volumes significantly larger than normal, suggesting that the initial insult occurs before the sutures fuse at 1 year of age. The patients somehow remain asymptomatic until their later years, when a second insult must occur, leading to symptomatic NPH.


According to the traditional understanding of cerebrospinal fluid (CSF) physiology, the majority of CSF is produced by the choroid plexus, circulates through the ventricles, the cisterns, and the subarachnoid space to be absorbed into the blood by the arachnoid villi. This review surveys key developments leading to the traditional concept. Challenging this concept are novel insights utilizing molecular and cellular biology as well as neuroimaging, which indicate that CSF physiology may be much more complex than previously believed. The CSF circulation comprises not only a directed flow of CSF, but in addition a pulsatile to and fro movement throughout the entire brain with local fluid exchange between blood, interstitial fluid, and CSF. Astrocytes, aquaporins, and other membrane transporters are key elements in brain water and CSF homeostasis. A continuous bidirectional fluid exchange at the blood brain barrier produces flow rates, which exceed the choroidal CSF production rate by far. The CSF circulation around blood vessels penetrating from the subarachnoid space into the Virchow Robin spaces provides both a drainage pathway for the clearance of waste molecules from the brain and a site for the interaction of the systemic immune system with that of the brain. Important physiological functions, for example the regeneration of the brain during sleep, may depend on CSF circulation.

BACKGROUND AND OBJECTIVES: We investigated whether the injection of 10 mL of normal saline into the subarachnoid space following accidental dural puncture reduced the incidence of postdural puncture headache (PDPH) and the need for epidural blood patch (EBP). METHODS: Twenty-eight patients who experienced accidental dural puncture with an epidural needle had 10 mL of normal saline injected into the subarachnoid space. In 22 patients, the injection was performed immediately through the epidural needle. In 6 patients who had intrathecal catheters placed through the epidural needle, the saline was injected through the catheter before removal. All other patients who experienced wet taps during the same period that the study was in progress but did not receive the saline injection served as a control group, 26 in number. Patients with severe or persistent PDPHs were treated with EBP.

RESULTS: Of those patients who received intrathecal normal saline immediately through the epidural needle, 32% developed a headache compared with 62% of controls. Of these, 1 patient who received saline required EBP compared with nine in the control group (P = .004). Of those patients who had intrathecal catheters placed, there were no headaches in the saline group of 6 compared with 3 in the control group of 5, 1 of whom was treated with EBP (P > .05). CONCLUSIONS: The immediate injection of 10 mL intrathecal normal saline after a wet tap significantly reduced the incidence of PDPH and the need for EBP. When an intrathecal catheter had been placed following a wet tap, injection of 10 mL of normal saline before its removal effectively prevented PDPH.


Cranial magnetic resonance imaging (MRI) findings in spontaneous intracranial hypotension (SIH) are well known, while spinal studies have received less attention. Radiological spinal findings in nine patients with SIH are presented, looking for possible characteristic features. Five of the nine patients had histories of previous minor trauma, one of previous surgery; in three patients possible relevant preceding events were completely absent. All nine patients had cervical, seven thoracic, and four lumbar spine MRI studies; post-contrast studies were obtained in seven cases, MRI myelograms in five. Radioisotope myelocisternography was performed in four patients and myelo-CT in four. Epidural fluid collections were found in seven patients. In six cases the dural sac had collapsed, with a festooned appearance; intense epidural enhancement on post-contrast studies demonstrated marked dilatation of the epidural venous plexus. In three cases an irregular root sleeve suggested a possible point of cerebrospinal fluid (CSF) leakage. Myelo-CT demonstrated the CSF fistula in two cases, radioisotope myelocisternography in three. The pattern of spinal abnormalities is different from that seen in cranial MRI for anatomical reasons: in the spinal canal the dura is not adherent to the bone; therefore, collapse of the dural sac and dilatation of epidural venous plexus occur, rather than subdural hematomas. In most cases the search for the dural tear is difficult. Radioisotope cisternography is probably the most sensitive examination for documenting the leakage of CSF out of the subarachnoid space; myelo-CT may precisely demonstrate the point of the CSF fistula, whereas MRI may only suggest it.


About 70% of the human body consists of salt water. The Nobel Prize 2003 in Chemistry rewards Peter Agre for the discovery of water channels and Roderick MacKinnon for structural and mechanistic studies of ion channels. Their studies have demonstrated how ions and water are transported through cell membranes. This transport is essential for the regulation of size and osmotic pressure in cells and organelles and it plays a major role in salt and water homoeostasis and in the generation of electrical signals in nerve cells. Agre succeeded in isolating a membrane protein which later studies revealed to be a long-postulated water channel, MacKinnon succeeded in determining the spatial structure of a potassium channel.


The present study examines the extent of spinal cerebrospinal fluid (CSF) absorption in healthy individuals in relation to physical activity, CSF production, intracranial pressure (ICP), and spinal CSF movement. Thirty-four healthy individuals aged 21-35 yr were examined by lumbar puncture and radionuclide cisternography with repeated imaging. ICP was registered before and after CSF drainage, and CSF production was calculated. Spinal CSF absorption was calculated as reduction in spinal radionuclide activity. The radionuclide activity in the spinal subarachnoid space was gradually decreased by 20 +/- 13% (mean +/- SD) during 1 h. The reduction was higher in active than in resting
individuals (27 +/- 12% vs. 13 +/- 9%). The mean ICP in 19 of the individuals was 13.6 +/- 3.1 cm H(2)O. B-waves were found in 79% of the individuals, with a mean frequency of 0.6 +/- 0.3 min(-1). The mean CSF production rate was 0.34 +/- 0.13 ml/min. There were no correlations between radionuclide reduction, spinal movement of the radionuclide, and CSF production rate. The spinal radionuclide reduction found in this study indicates a spinal CSF absorption of 0.11-0.23 ml/min, more pronounced in active than in resting individuals.


Two absorptive pathways for contrast media injected into the lumbar subarachnoid space have been postulated: (1) through the intracranial parasagittal arachnoid granulations and (2) direct absorption through the spinal arachnoid villi into the blood. To study the capacity of the spinal absorptive pathway, serial measurements of metrizamide concentrations in blood serum and urine were obtained before and after lumbar intrathecal injection of contrast medium in four patients with arrested intracranial blood circulation ("brain death") and intracranial pressure exceeding systolic blood pressure who had no circulation of cerebrospinal fluid from the spinal subarachnoid space to the parasagittal arachnoid granulations. These measurements indicated a high capacity of the spinal absorptive pathway for metrizamide elimination.


A phase-contrast cine magnetic resonance (MR) imaging technique was used to study normal dynamics of cerebrospinal fluid (CSF) in 10 healthy volunteers and four patients with normal MR images. This pulse sequence yielded 16 quantitative flow-encoded images per cardiac cycle (peripheral gating). Flow encoding depicted craniocaudal flow as high signal intensity and caudo-cranial flow as low signal intensity. Sagittal and axial images of the head, cervical spine, and lumbar spine were obtained, and strategic sites were analyzed for quantitative CSF flow. The onset of CSF systole in the subarachnoid space was synchronous with the onset of systole in the carotid artery. CSF systole and diastole at the foramen of Monro and aqueduct were essentially simultaneous. The systolic and diastolic components were different in the subarachnoid space, where systole occupied approximately 40% and diastole 60% of the cardiac cycle, compared with the ventricular system, where they were equal. This difference results in systole in the intracranial and spinal subarachnoid spaces preceding that in the ventricular system; the same is true for diastole. The fourth ventricle and cisterna magna serve as mixing chambers. The high-velocity flow in the cervical spine and essentially no flow in the distal lumbar sac indicate that a portion of the capacitance necessary in this essentially closed system resides in the distal spinal canal.


IN ADULT MAMMALS, UNDER PHYSIOLOGICAL CONDITIONS, NEUROGENESIS, THE PROCESS OF GENERATING NEW FUNCTIONAL NEURONS FROM PRECURSOR CELLS, OCCURS MAINLY IN TWO BRAIN AREAS: the subgranular zone in the dentate gyrus of the hippocampus, and the subventricular zone (SVZ) lining the walls of the brain lateral ventricles. Taking into account the location of the SVZ and the cytoarchitecture of this periventricular neural progenitor cell niche, namely the fact that the slow dividing primary progenitor cells (type B cells) of the SVZ extend an apical primary cilium toward the brain ventricular space which is filled with cerebrospinal fluid (CSF), it becomes likely that the composition of the CSF can modulate both self-renewal, proliferation and differentiation of SVZ neural stem cells. The major site of CSF synthesis is the choroid plexus (CP); quite surprisingly, however, it is still largely unknown the contribution of molecules specifically secreted by the adult CP as modulators of the SVZ adult neurogenesis. This is even more relevant in light of recent evidence showing the ability of the CP to adapt its transcriptome and secretome to various physiologic and pathologic stimuli. By giving particular emphasizes to growth factors and axonal guidance molecules we will illustrate how CP-born molecules might play an important role in the SVZ niche cell population dynamics.

In a randomized, double-blind cross-over study 10 subjects were exposed to a simulated altitude of 4500 m for 10 h after administration of placebo, acetozolamide (250 mg bid) or theophylline (250 mg bid). T2-weighted magnetic resonances images (MRI) and diffusion weighted MRI were obtained directly after exposure to altitude under hypoxic conditions. Although eight of 10 subjects had moderate to severe acute mountain sickness (AMS), we found no evidence of cerebral oedema, irrespective of the medication taken. Almost all subjects showed a decrease in inner cerebrospinal fluid (iCSF) volumes (placebo - 10.3%, P = 0.02; acetazolamide - 13.2%, P = 0.008, theophylline -12.2%, n.s.). There was no correlation between AMS symptoms and fluid shift. However, we found a significantly positive correlation of large (>10 ml) iCSF volume and more severe AMS after administration of placebo (r = 0.76, P = 0.01). Moderate to severe AMS after high altitude exposure for 10 h is associated with a decreased CSF volume, a consequence of AMS severity or medication without signs of cerebral oedema.


We studied a patient with spontaneous intracranial hypotension whose gadolinium-enhanced MRI revealed an extraordinary degree of dural enhancement and striking displacement of the optic chiasm, flattening of the pons, and downward displacement of the cerebellar tonsils. These changes were reversed when a CSF leak at the site of a T12-L1 arachnoid cyst was closed following an epidural blood patch. Such diffuse meningeal enhancement results from the dural venous dilatation that accompanies a reduced CSF volume, a consequence of the Monro-Kellie rule.


Large-bore lumbar spinal fluid drainage is used frequently as part of the preoperative and intraoperative management of patients undergoing cranial base tumor resection. Such drainage allows displacement of the brain with minimal force, thereby potentially decreasing retraction damage to it. We document 2 patients in whom serious complications resulted from lumbar drainage systems. These patients deteriorated into a coma state following cerebrospinal fluid (CSF) drainage. Reinfusion of synthetic CSF solutions caused a brisk return to normal neurological status. These plus other potential complications associated with lumbar drainage, such as persistent CSF leaks into the back and soft-tissue nerve root injury, warranted abandoning the lumbar cistern drainage route of CSF drainage in favor of drainage directly from the intracranial compartment. Depending on the particular operation performed, drainage of CSF near the cribriform plate, the suprachiasmatic cistern, or from the Sylvian fissure may be effective sites for CSF drainage. Unlike lumbar drainage, intracranial CSF drainage does not have the added risk of promoting cerebral herniation.


**RATIONALE AND OBJECTIVES:** The aim of the study is to elucidate the location and amount of spinal cerebrospinal fluid pulsations and to differentiate and quantify the cardiac and the respiratory influence. **MATERIALS AND METHODS:** An echo planar imaging sequence was applied to 5 different levels of the spinal canal of 7 healthy volunteers. The amount of maximal flow and respiratory signal variation were determined by a time and frequency domain analysis, respectively. **RESULTS:** CSF pulsation was high in the anterior cervical and in the thoracolumbar spine. Respiratory influence rose by 19% at C1 and by 28% at T12. The systolic flow was elevated during late expiration and the diastolic upward movement was pronounced by early expiration. **CONCLUSION:** The pulsation in the lower spine seems to be related to a second motor of CSF movement because there is a rising respiratory influence and a reappearance of pulsation waves. Physiological spinal CSF pulsation contains a relevant respiratory component.


**BACKGROUND:** Ependymal cells form a protective monolayer between the brain parenchyma and cerebrospinal fluid (CSF). They possess motile cilia important for directing the flow of CSF through the ventricular system. While ciliary beat frequency in airway epithelia has been extensively studied, fewer reports have looked at the mechanisms involved in regulating ciliary beat frequency in ependyma. Prior studies have demonstrated that ependymal cells express at least one purinergic receptor (P2X7). An
understanding of the full range of purinergic receptors expressed by ependymal cells, however, is not yet complete. The objective of this study was to identify purinergic receptors which may be involved in regulating ciliary beat frequency in lateral ventricle ependymal cells. METHODS: High-speed video analysis of ciliary movement in the presence and absence of purinergic agents was performed using differential interference contrast microscopy in slices of mouse brain (total number of animals = 67). Receptor identification by this pharmacological approach was corroborated by immunocytochemistry, calcium imaging experiments, and the use of two separate lines of knockout mice. RESULTS: Ciliary beat frequency was enhanced by application of a commonly used P2X7 agonist. Subsequent experiments, however, demonstrated that this enhancement was observed in both P2X7+/+ and P2X7−/− mice and was reduced by pre-incubation with an ecto-5’-nucleotidase inhibitor. This suggested that enhancement was primarily due to a metabolic breakdown product acting on another purinergic receptor subtype. Further studies revealed that ciliary beat frequency enhancement was also induced by adenosine receptor agonists, and pharmacological studies revealed that ciliary beat frequency enhancement was primarily due to A2B receptor activation. A2B expression by ependymal cells was subsequently confirmed using A2B−/−/β-galactosidase reporter gene knock-in mice. CONCLUSION: This study demonstrates that A2B receptor activation enhances ciliary beat frequency in lateral ventricle ependymal cells. Ependymal cell ciliary beat frequency regulation may play an important role in cerebral fluid balance and cerebrospinal fluid dynamics.

Post-lumbar puncture (LP) headache may be due to "low CSF pressure", leading to stretching of pain sensitive intracranial structures. The low intracranial pressure is secondary to net loss of intracranial CSF. It has, however, not been possible to measure intracranial CSF volume accurately during life until recently. Intracranial CSF volume can now be measured non-invasively by a MRI technique. The changes in intracranial CSF volume were studied in 20 patients who had LP. Total intracranial CSF volume was reduced in 19 of the 20 patients 24 hours after LP (range -1.8 mls to -158.6 mls). Most of the CSF was lost from the cortical sulci. Very large reductions in intracranial CSF volume were frequently related to post-LP headache but some patients developed headache with relatively little alteration in the intracranial CSF volume. There was not a measurable change in position of the intracranial structures following LP.

It is almost a century since Dandy made the first experimental studies on hydrocephalus, but its underlying mechanism has been unknown up to now. The conventional view is that cerebrospinal fluid (CSF) malabsorption due to hindrance of the CSF circulation causes either obstructive or communicating hydrocephalus. Analyses of the intracranial hydrodynamics related to the pulse pressure show that this is an over-simplification. The new hydrodynamic concept presented here divides hydrocephalus into two main groups, acute hydrocephalus and chronic hydrocephalus. It is still accepted that acute hydrocephalus is caused by an intraventricular CSF obstruction, in accordance with the conventional view. Chronic hydrocephalus consists of two subtypes, communicating hydrocephalus and chronic obstructive hydrocephalus. The associated malabsorption of CSF is not involved as a causative factor in chronic hydrocephalus. Instead, it is suggested that increased pulse pressure in the brain capillaries maintains the ventricular enlargement in chronic hydrocephalus. Chronic hydrocephalus is due to decreased intracranial compliance, causing restricted arterial pulsations and increased capillary pulsations. The terms “restricted arterial pulsation hydrocephalus" or “increased capillary pulsation hydrocephalus" can be used to stress the hydrodynamic origin of both types of chronic hydrocephalus. The new hydrodynamic theories explain why third ventriculostomy may cure patients with communicating hydrocephalus, a treatment incompatible with the conventional view.

BACKGROUND: Circulation of cerebrospinal fluid (CSF) through the ventricular system is driven by motile cilia on ependymal cells of the brain. Disturbed ciliary motility induces the formation of hydrocephalus, a pathological accumulation of CSF resulting in ventricle dilatation and increased intracranial pressure. The mechanism by which loss of motile cilia causes hydrocephalus has not been elucidated. The aim of this study was: (1) to provide a detailed account of the development of ciliation
in the brain of the African clawed frog *Xenopus laevis*; and (2) to analyze the relevance of ependymal cilia motility for CSF circulation and brain ventricle morphogenesis in *Xenopus*. METHODS: Gene expression analysis of *foxj1*, the bona fide marker for motile cilia, was used to identify potentially ciliated regions in the developing central nervous system (CNS) of the tadpole. Scanning electron microscopy (SEM) was used to reveal the distribution of mono- and multiciliated cells during successive stages of brain morphogenesis, which was functionally assessed by bead injection and video microscopy of ventricular CSF flow. An antisense morpholino oligonucleotide (MO)-mediated gene knock-down that targeted *foxj1* in the CNS was applied to test the role of motile cilia in the ventricles. RESULTS: RNA transcripts of *foxj1* in the CNS were found from neurula stages onwards. Following neural tube closure, *foxj1* expression was seen in distinct ventricular regions such as the zona limitans intrathalamica (ZLI), subcommissural organ (SCO), floor plate, choroid plexus (CP), and rhombomere boundaries. In all areas, expression of *foxj1* preceded the outgrowth of monocilia and the subsequent switch to multiciliated ependymal cells. Cilia were absent in *foxj1* morphants, causing impaired CSF flow and fourth ventricle hydrocephalus in tadpole-stage embryos. CONCLUSIONS: Motile ependymal cilia are important organelles in the *Xenopus* CNS, as they are essential for the circulation of CSF and maintenance of homeostatic fluid pressure. The *Xenopus* CNS ventricles might serve as a novel model system for the analysis of human ciliary genes whose deficiency cause hydrocephalus.


Hidaka, M., et al. (2001). "Dynamic measurement of the flow rate in cerebrospinal fluid shunts in hydrocephalic patients." *Eur J Nucl Med* 28(7): 888-893. We compared clinical outcomes in hydrocephalic patients and observed variation in the rate of flow in ventriculoperitoneal shunts with changes in posture in 231 separate examinations of shunt flow in 148 patients. A small cadmium telluride detector was placed over the shunt reservoir, and clearance of radioisotope injected into the reservoir was recorded as a measure of flow. Flow rate tended to increase during head elevation. Four patterns of radioisotope clearance were seen: type I, no flow; type II, adequate flow with moderate opening pressure; type III, adequate flow with low opening pressure; and type IV, excessive flow. This categorisation reflected clinical shunt function. Our method effectively assesses flow rate with the patient in a variety of postures or during movement, yielding useful information for adjustment of shunt valve pressure.

Hodel, J., et al. (2012). "Imaging of the entire cerebrospinal fluid volume with a multistation 3D SPACE MR sequence: feasibility study in patients with hydrocephalus." *Eur Radiol*. OBJECTIVES: To evaluate the feasibility of imaging the entire cerebrospinal fluid (CSF) volume using the SPACE MR sequence. METHODS: The SPACE sequence encompassing the brain and spine was performed at 1.5 T in 12 healthy volunteers and 26 consecutive patients with hydrocephalus. Image contrast was estimated using difference ratios in signal intensity between CSF and its background. Segmentation of CSF was performed using geometrical features and a topological assumption of CSF shapes. Subarachnoid and ventricular CSF space volumes were assessed in volunteers and patients and linear discriminant analysis was performed. RESULTS: Image contrast was 0.94 between the CSF and the brain and 0.90 between the CSF and the spinal cord. According to the phantom study, the accuracy of CSF volume measurement was 98.5 %. A clear distinction between patients and healthy volunteers was obtained using the linear discriminant analysis. Significant linear regression was found in healthy volunteers between ventricular (Vv) and the whole subarachnoid CSF volume (Vs) with Vv = 0.083 Vs. CONCLUSIONS: Imaging of the entire CSF volume is feasible in healthy volunteers and patients with hydrocephalus. CSF volume can be obtained on a whole-body scale. This approach may be of use for the diagnosis and follow-up of patients with hydrocephalus. KEY POINTS: * MRI assessment of CSF volume is feasible in healthy volunteers/hydrocephalus patients. * CSF volume can be obtained on a whole-body scale. * The ratio of subarachnoid and ventricular CSF is constant in healthy volunteers. * CSF linear discriminant analysis can distinguish between patients and healthy volunteers. * Entire CSF volume imaging is useful for diagnosing and following hydrocephalus.

The glymphatic system is a recently defined brain-wide paravascular pathway for cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange that facilitates efficient clearance of solutes and waste from the brain. CSF enters the brain along para-arterial channels to exchange with ISF, which is in turn cleared from the brain along para-venous pathways. Because soluble amyloid beta clearance depends on glymphatic pathway function, we proposed that failure of this clearance system contributes to amyloid plaque deposition and Alzheimer’s disease progression. Here we provide proof of concept that glymphatic pathway function can be measured using a clinically relevant imaging technique. Dynamic contrast-enhanced MRI was used to visualize CSF-ISF exchange across the rat brain following intrathecal paramagnetic contrast agent administration. Key features of glymphatic pathway function were confirmed, including visualization of para-arterial CSF influx and molecular size-dependent CSF-ISF exchange. Whole-brain imaging allowed the identification of two key influx nodes at the pituitary and pineal gland recesses, while dynamic MRI permitted the definition of simple kinetic parameters to characterize glymphatic CSF-ISF exchange and solute clearance from the brain. We propose that this MRI approach may provide the basis for a wholly new strategy to evaluate Alzheimer’s disease susceptibility and progression in the live human brain.


This review integrates eight aspects of cerebrospinal fluid (CSF) circulatory dynamics: formation rate, pressure, flow, volume, turnover rate, composition, recycling and reabsorption. Novel ways to modulate CSF formation emanate from recent analyses of choroid plexus transcription factors (E2F5), ion transporters (NaHCO3 cotransport), transport enzymes (isoforms of carbonic anhydrase), aquaporin 1 regulation, and plasticity of receptors for fluid-regulating neuropeptides. A greater appreciation of CSF pressure (CSFP) is being generated by fresh insights on peptidergic regulatory servomechanisms, the role of dysfunctional ependyma and circumventricular organs in causing congenital hydrocephalus, and the clinical use of algorithms to delineate CSFP waveforms for diagnostic and prognostic utility.

Increasing attention focuses on CSF flow: how it impacts cerebral metabolism and hemodynamics, neural stem cell progression in the subventricular zone, and catabolite/peptide clearance from the CNS. The pathophysiological significance of changes in CSF volume is assessed from the respective viewpoints of hemodynamics (choroid plexus blood flow and pulsatility), hydrodynamics (choroidal hypo- and hypersecretion) and neuroendocrine factors (i.e., coordinated regulation by atrial natriuretic peptide, arginine vasopressin and basic fibroblast growth factor). In aging, normal pressure hydrocephalus and Alzheimer’s disease, the expanding CSF space reduces the CSF turnover rate, thus compromising the CSF sink action to clear harmful metabolites (e.g., amyloid) from the CNS. Dwindling CSF dynamics greatly harms the interstitial environment of neurons. Accordingly the altered CSF composition in neurodegenerative diseases and senescence, because of adverse effects on neural processes and cognition, needs more effective clinical management. CSF recycling between subarachnoid space, brain and ventricles promotes interstitial fluid (ISF) convection with both trophic and excretory benefits. Finally, CSF reabsorption via multiple pathways (olfactory and spinal arachnoidal bulk flow) is likely complemented by fluid clearance across capillary walls (aquaporin 4) and arachnoid villi when CSFP and fluid retention are markedly elevated. A model is presented that links CSF and ISF homeostasis to coordinated fluxes of water and solutes at both the blood-CSF and blood-brain transport interfaces. OUTLINE: 1 Overview2 CSF formation2.1 Transcription factors2.2 Ion transporters2.3 Enzymes that modulate transport2.4 Aquaporins or water channels2.5 Receptors for neuropeptides3 CSF pressure3.1 Servomechanism regulatory hypothesis3.2 Ontogeny of CSF pressure generation3.3 Congenital hydrocephalus and periventricular regions3.4 Brain response to elevated CSF pressure3.5 Advances in measuring CSF waveforms4 CSF flow4.1 CSF flow and brain metabolism4.2 Flow effects on fetal germinal matrix4.3 Decreasing CSF flow in aging CNS4.4 Refinement of non-invasive flow measurements5 CSF volume5.1 Hemodynamic factors5.2 Hydrodynamic factors5.3 Neuroendocrine factors6 CSF turnover rate6.1 Adverse effect of ventriculomegaly6.2 Attenuated CSF sink action7 CSF composition7.1 Kidney-like action of CP-CSF system7.2 Altered CSF biochemistry in aging and disease7.3 Importance of clearance transport7.4 Therapeutic manipulation of composition8 CSF recycling in relation to ISF dynamics8.1 CSF exchange with brain interstitium8.2 Components of ISF movement in brain8.3 Compromised ISF/CSF dynamics and amyloid retention9 CSF reabsorption9.1 Arachnoidal outflow resistance9.2 Arachnoid villi vs. olfactory drainage routes9.3 Fluid reabsorption along spinal nerves9.4 Reabsorption across capillary aquaporin channels10 Developing translationally effective models for restoring CSF balance11 Conclusion.
This article reviews the range of hydrodynamic disorders affecting the CSF circulation. Initially consideration is given to questions of definition and classification. A scheme for the practical, clinical analysis for the diagnosis of such disorders is then presented. The physiology and pathophysiology of the CSF circulation is reviewed, with particular emphasis on issues that remain unresolved. This provides a background to consideration of the adverse consequences of abnormal CSF hydrodynamics, again focusing on areas where further information is required. Methods of clinical investigation of CSF hydrodynamics are reviewed, followed by general considerations of treatment. Finally, each of the main, clinically important, forms of disordered CSF hydrodynamics is briefly considered, with particular emphasis, again, on areas where current knowledge is deficient. The conditions considered include hydrocephalus of various forms (childhood, adult, arrested, multi-compartment), infantile macrocephaly, arachnoid and gliopependymal cysts, syringo- and hydromyelia, pseudotumour cerebri, impaired cranial venous outflow, altered CSF composition, shunt obstruction without ventricular enlargement and low-CSF-pressure states.

The textbook view that projections of the arachnoid membrane into the cranial venous sinuses represent the primary cerebrospinal fluid (CSF) absorption sites seems incompatible with many clinical and experimental observations. On balance, there is more quantitative evidence suggesting a function for extracranial lymphatic vessels than exists to support a role for arachnoid villi and granulations in CSF transport.

BACKGROUND: The parenchyma of the brain does not contain lymphatics. Consequently, it has been assumed that arachnoid projections into the cranial venous system are responsible for cerebrospinal fluid (CSF) absorption. However, recent quantitative and qualitative evidence in sheep suggest that nasal lymphatics have the major role in CSF transport. Nonetheless, the applicability of this concept to other species, especially to humans has never been clarified. The purpose of this study was to compare the CSF and nasal lymph associations in human and non-human primates with those observed in other mammalian species. METHODS: Studies were performed in sheep, pigs, rabbits, rats, mice, monkeys and humans. Immediately after sacrifice (or up to 7 hours after death in humans), yellow Microfil was injected into the CSF compartment. The heads were cut in a sagittal plane. RESULTS: In the seven species examined, Microfil was observed primarily in the subarachnoid space around the olfactory bulbs and cribriform plate. The contrast agent followed the olfactory nerves and entered extensive lymphatic networks in the submucosa associated with the olfactory and respiratory epithelium. This is the first direct evidence of the association between the CSF and nasal lymph compartments in humans. CONCLUSIONS: The fact that the pattern of Microfil distribution was similar in all species tested, suggested that CSF absorption into nasal lymphatics is a characteristic feature of all mammals including humans. It is tempting to speculate that some disorders of the CSF system (hydrocephalus and idiopathic intracranial hypertension for example) may relate either directly or indirectly to a lymphatic CSF absorption deficit.

OBJECTIVES: To study the effect of blood osmolarity on cerebrospinal fluid (CSF) volume and CSF pressure in cats. METHODS: Three types of methods were used on anesthetized cats. The first, ventriculo-cisternal perfusion (12.96 muL/min) before and after i.v. application of 20% mannitol; the second, measuring the outflow of CSF by cisternal free drainage; and the third, measuring CSF pressure in the ventricles of an intact CSF system, with the second and third method being performed before and after the i.p. application of a hypo-osmolar substance (distilled water). RESULTS: In the first group, the application of 20% mannitol led to a significantly reduced (p < 0.005) outflow volume (from 12.60 +/- 0.29 to 0.94 +/- 0.09 muL/min). In the second group, the outflow CSF volume significantly increased (p < 0.001) after the application of distilled water (from 18.8 +/- 0.3 to 28.2 +/- 0.7 muL/min). In the third group, after the application of distilled water, the CSF pressure also significantly increased (p < 0.05; from 8.3 +/- 0.8 to 16.1 +/- 0.14 cm H(2)O). CONCLUSION: We conclude that changes in serum osmolarity change the CSF volume because of the osmotic gradient between the blood and all of the
CSF compartments, and also that the change in CSF pressure is closely associated with changes in CSF volume.


Cerebrospinal fluid (CSF) in a shunt does not have a constant flow rate. The flow fluctuates from 0.01 ml min to 1.93 ml/min according to each patient’s own daily supine rhythmic pattern. We determined and evaluated the factors influencing CSF flow in a shunt in 19 cases of hydrocephalus. Postural changes, such as head elevation, led to increases by over 0.04 ml/min in inshunt CSF flow, while inshunt CSF flow in the supine position was less than 0.04 ml/min. Respiratory changes, such as coughing and apnea-hyperventilation, also influenced inshunt CSF flow. Changes in intracranial pressure (ICP) corresponded to changes in inshunt CSF flow. Inshunt CSF flows were higher than average during the night, the flows being stimulated by increases in ICP especially during REM sleep.


OBJECT: Intracranial hypertension remains a common complication of traumatic brain injury (TBI). Ventriculostomy drainage is a recommended therapy to decrease intracranial pressure (ICP), but little empirical evidence exists to guide treatment. The authors conducted a study to examine systematically the effect of cerebrospinal fluid (CSF) drainage on ICP and indices of cerebral perfusion. METHODS: Intracranial pressure, cerebral perfusion pressure (CPP), cerebral blood flow velocity (CBFV), and near-infrared spectroscopy-determined regional cerebral oxygenation (rSO2) were measured in 58 patients (with Glasgow Coma Scale scores ≤ 8) before, during, and after ventriculostomy drainage. Three randomly ordered CSF drainage protocols varied in the volume of CSF removed (1 ml, 2 ml, and 3 ml). Physiological variables were time averaged in 1-minute blocks from baseline to 10 minutes after cessation of ventricular drainage. There was a significant dose-time interaction for ICP with the three-extraction volume protocol, with incremental decreases in ICP (F [20, 1055] = 6.10; p = 0.0001). There was a significant difference in the CPP depending on the amount of CSF removed (F [2, 1787] = 3.22; p = 0.040) and across time (F [10, 9.58] = 11.9; p = 0.0003) without a significant dose-time interaction. A 3-ml withdrawal of CSF resulted in a 10.1% decrease in ICP and a 2.2% increase in CPP, which were sustained for 10 minutes. There was no significant dose, time or dose-time interaction with CBFV or rSO2. CONCLUSIONS: Cerebrospinal fluid drainage (3 ml) significantly reduced ICP and increased CPP for at least 10 minutes. Analysis of these findings supports the use of ventriculostomy drainage as a means of at least temporarily reducing elevated ICP in patients with TBI.


AIMS: To describe the anatomy and the arrangement of the arachnoid trabeculae, pillars, and septa in the subarachnoid space of the human optic nerve and to consider their possible clinical relevance for cerebrospinal fluid dynamics and fluid pressure in the subarachnoid space of the human optic nerve. METHODS: Postmortem study with a total of 12 optic nerves harvested from nine subjects without ocular disease. All optic nerves used in this study were obtained no later than 7 hours after death, following qualified consent for necropsy. The study was performed with transmission (TEM) and scanning electron microscopy (SEM). RESULTS: The subarachnoid space of the human optic nerve contains a variety of trabeculae, septa, and stout pillars that are arranged between the arachnoid and the pia layers of the meninges of the nerve. They display a considerable numeric and structural variability depending on their location within the different portions of the optic nerve. In the bulbar segment (ampulla), adjacent to the globe, a dense and highly ramified meshwork of delicate trabeculae is arranged in a reticular fashion. Between the arachnoid trabeculae, interconnecting velum-like processes are observed. In the mid-orbital segment of the orbital portion, the subarachnoid space is subdivided, and can appear even loosely chambered by broad trabeculae and velum-like septa at some locations. In the intracanalicular segment additionally, few stout pillars and single round trabeculae are observed. CONCLUSION: The subarachnoid space of the human optic nerve is not a homogeneous and anatomically empty chamber filled with cerebrospinal fluid, but it contains a complex system of arachnoid trabeculae and septa that divide the subarachnoid space. The trabeculae, septa, and pillars, as well as their arrangement described in this study, may have a role in the cerebrospinal fluid dynamics between the subarachnoid space of the optic nerve and the chiasmal cistern and may contribute to the understanding of the pathophysiology of asymmetric and unilateral papilloedema. All the structures
described are of such delicate character that they can not even be visualised with high resolution
magnetic resonance imaging (MRI).


**OBJECTIVE:** To determine by cerebral venography and manometry in patients with idiopathic intracranial 
hypertension the cause of the previously demonstrated venous hypertension in the superior sagittal and 
proximal transverse sinuses. **METHODS:** Cerebral venous sinus pressure was measured before and 
immediately after C1-2 puncture with removal of 20 to 25 mL of CSF. **RESULTS:** Lowering the intracranial 
pressure by lateral C1-2 puncture during manometry has shown that the venous hypertension resolves 
immediately. **CONCLUSION:** These studies indicate that the venous hypertension is due to compression 
of the transverse sinuses by raised intracranial pressure and not due to a primary obstructive process in 
the cerebral venous sinuses.


The effect of head-down tilt during general anesthesia on intracranial pressure (ICP) dynamics was 
examined in eight cats. Changes in lateral ventricular pressure (LVP), sagittal sinus pressure (SSP), and 
effective CSF pressure (ECSFP), which is the driving pressure of cerebrospinal fluid (CSF) absorption, 
were studied in association with a shift from the horizontal prone position to the 20 degrees head-down 
tilt position. Both LVP and SSP values were significantly (P < 0.01) increased at 10 min in the head-down 
tilt position as compared with the control position, remained elevated during the next 110 min, and 
returned to baseline when the horizontal position was restored. However, ECSFP (expressed by LVP - 
SSP) was not significantly different from the control value, because changes in LVP and SSP were similar. 
These results suggest that head-down tilt does not impair CSF absorption.

Kroin, J. S., et al. (2002). "The mechanisms of intracranial pressure modulation by epidural blood and other 

The epidural blood patch is considered effective in treating postdural puncture headache. We have 
developed a postdural puncture model in rats for quantitative evaluation of the magnitude and duration 
of changes in cerebrospinal fluid (CSF) pressure in the cisterna magna in response to the administration 
of epidural blood or other moieties. This model was used to compare the efficacy of various methods of 
epidural injection for restoring and maintaining CSF pressure for up to 240 min. After lumbar dural 
puncture, CSF pressure declined 3.6 +/- 0.2 mm Hg. Epidural saline (100 microL) injected at the 
puncture site initially increased pressure by 7.2 +/- 0.7 mm Hg, but it rapidly (7.8 +/- 0.6 min) returned 
to postdural puncture baseline. A similar initial increase of CSF pressure was observed with equal 
volumes of all other epidural injectates, but the duration of pressure increase varied greatly. Hetastarch 
and dextran 40 produced results similar to saline. Only whole blood or fibrin glue consistently increased 
CSF pressure for the entire 240-min observation period. Whole blood mixed with anticoagulant or 
injected 20-mm cephalad to the puncture site did not sustain pressure. After laminectomy, direct 
application of blood or adhesive to the dural defect caused no pressure increase. Continuous infusion of 
saline after bolus could maintain pressure increase for 180 min, but within 60 min of stopping infusion, 
pressure returned to baseline. These results confirm the efficacy of the epidural administration of blood 
or fibrin glue to correct CSF hypotension after dural puncture and also provide insight into the 
mechanisms of intracranial pressure modulation. Sealing the dural defect does not effectively correct 
CSF pressure unless an epidural tamponade effect is also maintained. **IMPLICATIONS:** A rat model was 
developed to evaluate different drugs that may be injected epidurally to treat postdural puncture 
headache. Epidural injection of blood or fibrin glue was the most effective method of maintaining 
increased cerebrospinal fluid pressure after dural puncture. Sealing the dural defect does not effectively 
correct cerebrospinal fluid pressure unless an epidural tamponade effect is maintained.

Kuczkowski, K. M. and J. L. Benumof (2003). "Decrease in the incidence of post-dural puncture headache: 

The incidence of epidural needle-induced post-dural puncture headache (PDPH) in parturients following 
dural puncture with a large bore (18-gauge) needle has been reported to range 76-85%. We describe 
seven cases in which the performance of epidural anesthesia in parturients was complicated by an 
unintentional dural puncture with an 18-gauge epidural needle. In all seven cases, the unintentional 
dural puncture was followed by (i) injection of the CSF in the glass syringe back into the subarachnoid
space through the epidural needle, (ii) insertion of a epidural catheter into the subarachnoid space (now referred to as an intrathecal catheter), (iii) injection of a small amount of preservative free saline (3-5 ml) into the subarachnoid space through the intrathecal catheter, (iv) administration of bolus and then continuous intrathecal labor analgesia through the intrathecal catheter and then (v) leaving the intrathecal catheter in-situ for a total of 12-20 h. PDPH occurred in only one of these cases (14%).


Preface. After publication of the presented hypothesis some predictions were verified independently by other authors: (1) Monro-Kellie “four compartments” doctrine, (2) relation between cerebrospinal fluid (CSF) formation and CSF removal in physiological phase as presented with illustrative curves, (3) hypovolemia during intracranial hypotension syndrome, (4) increased CSF proteins in decreased CSF flow and (5) influence of neuro-vegetative system on CSF pressure. The predictions not yet verified: (1) turning points B-low and B-high that represent physiological borders, (2) pathophysiological self-sustaining phases of very low (around -10mmHg) and very high (around +30mmHg) CSF pressure with corresponding minimal or maximal CSF volume (maximal dural sac collapse or distension) and no CSF transport, (3) compensated and de-compensated conditions. None of the predictions were disproved yet. There are three types of CSF hydrodynamic processes according to their duration in time: (1) rapid changes (in second(s), e.g., hydrodynamic changes caused by arterial pulsations in craniospinal space, etc), (2) homeostatic changes (in minutes to hours, e.g., as described in this article) and (3) long-term changes and adaptations, e.g., chronic hydrocephalus, etc. This article is not discussing (1) and (3) processes. The purpose of this presentation on the INTERNET is to promote further discussions about unverified predictions and to encourage clinical research and experimenting in this direction.

Summary. Physiological and pathophysiological processes in the intracraniovertebral space are specific because of its rigid and constant volume (Monro-Kellie doctrine). The hypothesis presents how the homeostasis of the intracraniovertebral compartments’ volumes, cerebrospinal fluid (CSF) flow and CSF pressure is physically regulated. The hypothesis takes into account the quantitative and qualitative relations regulating CSF formation and CSF removal on which the homeostasis is based.


Obstacles involved in resolving the enigma of the third circulation.

FAF CSF is released into BV during the diastolic phase of the cardiac cycle when net caudal CSF flow exists.


The pathophysiology of lumbar puncture headache (LPH) is still unclear. There is evidence that leakage of cerebrospinal fluid (CSF) leads to CSF hypotension, which causes dilation of intracranial veins, resulting in LPH. However, CSF leaks at the skull base are not associated with orthostatic headache; there is poor correlation between recumbent CSF pressure and LPH; and there has been no satisfactory explanation of how venous dilation causes orthostatic headache. We propose the hypothesis that LPH is caused by an abnormal distribution of craniospinal elasticity. Increased compliance at the lumbar end of the spinal CSF space, resulting both from anatomic joining of the subarachnoid to the epidural space and from reduced CSF filling pressure, causes the hydrostatic indifferent point to move caudally, creating additional intracranial hypotension and venous dilation in the erect position. We are, thus, able to explain the orthostatic character of LPH, the fact that spinal but not cranial sites of leakage produce orthostatic headache and the imperfect correlations both between recumbent CSF pressure and LPH and between reduced CSF volume and LPH. The near absence of LPH in the very young and in the elderly relates to the relative stiffness of the epidural space at these ages. Epidural injections of blood or saline give immediate relief by reducing epidural distensibility.


CINE phase-contrast MRI (CINE-MRI) was used to measure cerebrospinal fluid (CSF) velocities and flow rates in the brain of six normal subjects and five patients with communicating hydrocephalus. Mathematical brain models were created using the MRI images of normal subjects and hydrocephalic patients. In our model, the effect of pulsatile vascular expansion is responsible for pulsatile CSF flow between the cranial and the spinal subarachnoidal spaces. Simulation results include intracranial pressure gradients, solid stresses and strains, and fluid velocities throughout the cranio-spinal system. Computed velocities agree closely with our in vivo CINE-MRI CSF flow measurements. In addition to normal intracranial dynamics, our model captures the transition to acute communicating hydrocephalus. By increasing the value for reabsorption resistance in the subarachnoid villi, our model predicts that the poroelastic parenchyma matrix will be drained and the ventricles enlarge despite small transmantle pressure gradients during the transitional phase. The poroelastic simulation thus provides a plausible explanation on how reabsorption changes could be responsible for enlargement of the ventricles without large transmantle pressure gradients.


Increased intracranial pressure can result in irreversible injury to the central nervous system. Among the many functions of the cerebrospinal fluid, it provides protection against acute changes in venous and arterial blood pressure or impact pressure. Nevertheless, trauma, tumors, infections, neurosurgical procedures, and other factors can cause increased intracranial pressure. Both surgical and nonsurgical therapeutic modalities can be used in the management of increased intracranial pressure attributable to traumatic and nontraumatic causes. In patients with cerebral injury and increased intracranial pressure, monitoring of the intracranial pressure can provide an objective measure of the response to therapy and the pressure dynamics. Intraventricular, intraparenchymal, subarachnoid, and epidural sites can be used for monitoring, and the advantages and disadvantages of the various devices available are discussed. With the proper understanding of the physiologic features of the cerebrospinal fluid, the physician can apply the management principles reviewed herein to minimize damage from intracranial hypertension.


Ventriculocisternal perfusion is regarded as a precise method of measuring the rate of formation of cerebrospinal fluid (CSF) but it possesses inherent potential sources of error. Using the technique to
measure CSF formation rate in the rhesus monkey, we have observed rate changes when none were expected. Most puzzling has been the steady decline of CSF formation rate at 4 percent each hour during the final five hours of a seven hour perfusion although variables known to affect CSF formation remained stable. In addition, alterations in rate caused by artefacts were observed in experiments in which craniospinal blood volume was changed by sudden changes of either PCO2 or central venous pressure. Mobilisation or sequestration of incompletely equilibrated CSF is believed responsible. In other experiments, a small increase of intracranial pressure produced by increasing outflow resistance was quickly followed by an apparent reduction of CSF formation. We have concluded that to assess accurately the effect a variable has on the rate of CSF formation, one must control perfusion time and craniospinal blood volume as well as intracranial pressure.


Object New approaches for understanding CSF motion in healthy individuals and patients with hydrocephalus and Chiari malformation are presented. The velocity and the pressure gradient of CSF motion were determined using phase contrast (PC) MRI. Methods The authors examined 11 healthy control subjects and 2 patients (1 with hydrocephalus and 1 with Chiari malformation), using 4-dimensional PC (4D-PC) MRI and a newly developed computer analysis method that includes calculation of the pressure gradient from the velocity field. Sagittal slices including the center of the skull and coronal slices of the foramen of Monro and the third ventricle were used. Results In the ventricular system, mixing and swirling of the CSF was observed in the third ventricle. The velocity images showed that the CSF was pushed up and back down to the adjacent ventricle and then returned again to the third ventricle. The CSF traveled bidirectionally in the foramen of Monro and sylvian aqueduct. Around the choroid plexus in the lateral ventricle, the CSF motion was stagnant and the CSF pressure gradient was lower than at the other locations. An elevated pressure gradient was observed in the basal cistern of the subarachnoid space. Sagittal imaging showed that the more prominent pressure gradients originated around the cisterna magna and were transmitted in an upward direction. The coronal image showed a pressure gradient traveling from the central to the peripheral subarachnoid spaces that diminished markedly in the convexity of the cerebrum. The 2 patients, 1 with secondary hydrocephalus and 1 with Chiari malformation, were also examined. Conclusions The observed velocity and pressure gradient fields delineated the characteristics of the CSF motion and its similarities and differences among the healthy individuals and between them and the 2 patients. Although the present results did not provide general knowledge of CSF motion, the authors' method more comprehensively described the physiological properties of the CSF in the skull than conventional approaches that do not include measurements of pressure gradient fields.


OBJECTIVE: To establish the current viewpoint with regards to the role of arachnoid villi/granulations in cerebrospinal fluid (CSF) absorption. DESIGN: Retrospective study. SUBJECTS: Journal articles published between 1913 and 1993. MAIN OUTCOME MEASURE: The contribution of arachnoid villi/granulations to CSF absorption from the subarachnoid space. RESULTS: From available literature, it is yet to be proved that arachnoid villi/granulations are the major sites for CSF absorption from the subarachnoid space into the venous system. They may, however, play an important role in the absorption of CSF's waste products of neuronal metabolism (mainly CSF proteins) under normal physiological conditions. Furthermore, it would appear that, under pathological conditions, the absorption of CSF proteins can take place at other CSF absorption sites. CONCLUSION: The paucity of data on the relationship between the development of arachnoid villi, the superior sagittal sinus, the superficial cortical vessels and the subarachnoid space warrants that an ontogenic study be conducted in order to achieve a better understanding of the function of arachnoid villi which is currently speculative.


In order to study age-related differences in cerebrospinal fluid (CSF) production in humans, we measured the rate of CSF production in 7 young (age 21 to 36 years) and 7 elderly (age 67 to 84 years) healthy volunteers, using a modified Masserman method. In addition, we evaluated CSF protein gradients by collecting CSF in serial fractions up to the 30th ml and assaying for total protein concentration. The mean rate of CSF production was significantly less in the elderly than in the young subjects. Mean CSF total protein concentrations were higher in the elderly than in the young, and
significant rostrocaudal protein gradients with similar slopes were present in both groups. However, there was no correlation between CSF production and CSF total protein concentrations or protein gradient slopes. Age-related reductions in CSF production, together with the ventricular dilatation that occurs with aging, should presumably result in reduced CSF turnover and therefore influence measured concentrations of lumbar CSF constituents.


We report on a case of spontaneous intracranial hypotension (SIH) presenting with classic MR findings, such as diffuse smooth thickening and intense contrast enhancement of the dura matter, increased size of the pituitary gland and downward displacement of the brain. In this case an engorgement of the cavernous sinuses is reported as an additional imaging finding of SIH. Moreover, phase-contrast MR study of the CSF flow dynamics revealed at the level of the aqueduct a decrease of the systolic and diastolic flow volume of CSF. A normalization of the flow volume was observed when SIH subsided.


BACKGROUND: It has long been known that cerebrospinal fluid (CSF), its composition and flow, play an important part in normal brain development, and ependymal cell ciliary beating as a possible driver of CSF flow has previously been studied in mammalian fetuses in vitro. Lower vertebrate animals are potential models for analysis of CSF flow during development because they are oviparous. Albino Xenopus laevis larvae are nearly transparent and have a straight, translucent brain that facilitates the observation of fluid flow within the ventricles. The aim of these experiments was to study CSF flow and circulation in vivo in the developing brain of living embryos, larvae and tadpoles of Xenopus laevis using a microinjection technique. METHODS: The development of Xenopus larval brain ventricles and the patterns of CSF flow were visualised after injection of quantum dot nanocrystals and polystyrene beads (3.1 or 5.8 mum in diameter) into the fourth cerebral ventricle at embryonic/larval stages 30-53. RESULTS: The fluorescent nanocrystals showed the normal development of the cerebral ventricles from embryonic/larval stages 38 to 53. The polystyrene beads injected into stage 47-49 larvae revealed three CSF flow patterns, left-handed, right-handed and non-biased, in movement of the beads into the third ventricle from the cerebral aqueduct (aqueduct of Sylvius). In the lateral ventricles, anterior to the third ventricle, CSF flow moved anteriorly along the outer wall of the ventricle to the inner wall and then posteriorly, creating a semicircle. In the cerebral aqueduct, connecting the third and fourth cerebral ventricles, CSF flow moved rostrally in the dorsal region and caudally in the ventral region. Also in the fourth ventricle, clear dorso-ventral differences in fluid flow pattern were observed. CONCLUSIONS: This is the first visualisation of the orchestrated CSF flow pattern in developing vertebrates using a live animal imaging approach. CSF flow in Xenopus albino larvae showed a largely consistent pattern, with the exception of individual differences in left-right asymmetrical flow in the third ventricle.


Tracer studies indicate that cerebrospinal fluid (CSF) transport can occur through the cribriform plate into the nasal submucosa, where it is absorbed by cervical lymphatics. We tested the hypothesis that sealing the cribriform plate extracranially would impair the ability of the CSF pressure-regulating systems to compensate for volume infusions. Sheep were challenged with constant flow or constant pressure infusions of artificial CSF into the CSF compartment before and after the nasal mucosal side of the cribriform plate was sealed. With both infusion protocols, the intracranial pressure (ICP) vs. flow rate relationships were shifted significantly to the left when the cribriform plate was blocked. This indicated that obstruction of the cribriform plate reduced CSF clearance. Sham surgical procedures had no significant effects. Estimates of the proportional flow through cribriform and noncribriform routes suggested that cranial CSF absorption occurred primarily through the cribriform plate at low ICPs. Additional drainage sites (arachnoid villi or other lymphatic pathways) appeared to be recruited only when intracranial pressures were elevated. These data challenge the conventional view that CSF is
absorbed principally via arachnoid villi and provide further support for the existence of several anatomically distinct cranial CSF transport pathways.


Cerebrospinal fluid (CSF) drains through the cribriform plate (CP) in association with the olfactory nerves. From this location, CSF is absorbed into nasal mucosal lymphatics. Recent data suggest that this pathway plays an important role in global CSF transport in sheep. In this report, we tested the hypothesis that blocking CSF transport through this pathway would elevate resting intracranial pressure (ICP). ICP was measured continuously from the cisterna magna of sheep before and after CP obstruction in the same animal. To block CSF transport through the CP, an external ethmoidectomy was performed. The olfactory and adjacent mucosa were removed, and the bone surface was sealed with tissue glue. To restrict our analysis to the cranial CSF system, CSF transport into the spinal subarachnoid compartment was prevented with a ligature tightened around the thecal sac between C1 and C2. Sham surgical procedures had no significant effects, but in the experimental group CP obstruction elevated ICP significantly. Mean postobstruction steady-state pressures (18.0 +/- 3.8 cmH(2)O) were approximately double the preobstruction values (9.2 +/- 0.9 cmH(2)O). These data support the concept that the olfactory pathway represents a major site for CSF drainage.


BACKGROUND: We recently reported a lymphatic cerebrospinal fluid (CSF) absorption deficit in a kaolin model of communicating hydrocephalus in rats with ventricular expansion correlating negatively with the magnitude of the impediment to lymphatic function. However, it is possible that CSF drainage was not significantly altered if absorption at other sites compensated for the lymphatic defect. The purpose of this study was to investigate the impact of the lymphatic absorption deficit on global CSF absorption (CSF outflow resistance). METHODS: Kaolin was injected into the basal cisterns of Sprague Dawley rats. The development of hydrocephalus was assessed using magnetic resonance imaging (MRI). In one group of animals at about 3 weeks after injection, the movement of intraventricularly injected iodinated human serum albumin (125I-HSA) into the olfactory turbinates provided an estimate of CSF transport through the cribriform plate into nasal lymphatics (n = 18). Control animals received saline in place of kaolin (n = 10). In a second group at about 3.5 weeks after kaolin injection, intraventricular pressure was measured continuously during infusion of saline into the spinal subarachnoid space at various flow rates (n = 9). CSF outflow resistance was calculated as the slope of the steady-state pressure versus flow rate. Control animals for this group either received no injections (intact: n = 11) or received saline in place of kaolin (n = 8). RESULTS: Compared to saline injected controls, lateral ventricular volume in the kaolin group was significantly greater (0.087 +/- 0.013 ml, n = 27 versus 0.015 +/- 0.001 ml, n = 17) and lymphatic function was significantly less (2.14 +/- 0.72% injected/g, n = 18 versus 6.38 +/- 0.60% injected/g, n = 10). Additionally, the CSF outflow resistance was significantly greater in the kaolin group (0.46 +/- 0.04 cm H2O microL(-1) min, n = 9) than in saline injected (0.28 +/- 0.03 cm H2O microL(-1) min, n = 8) or intact animals (0.18 +/- 0.03 cm H2O microL(-1) min, n = 11). There was a significant positive correlation between CSF outflow resistance and ventricular volume. CONCLUSIONS: The data suggest that the impediment to lymphatic CSF absorption in a kaolin-induced model of communicating hydrocephalus has a significant impact on global CSF absorption. A lymphatic CSF absorption deficit would appear to play some role (either direct or indirect) in the pathogenesis of ventriculomegaly.


The CSF is often regarded as merely a mechanical support for the brain, as well as an unspecific sink for waste products from the CNS. New methodology in receptor autoradiography, immunohistochemistry and molecular biology has revealed the presence of many different neuroendocrine substances or their corresponding receptors in the main CSF-forming structure, the choroid plexus. Both older research on the sympathetic nerves and recent studies of peptide neurotransmitters in the choroid plexus support a neurogenic regulation of choroid plexus CSF production and other transport functions. Among the endocrine substances present in blood and CSF, 5-HT, ANP, vasopressin and the IGFs have high receptor concentrations in the choroid plexus and have been shown to influence choroid plexus function. Finally, the choroid plexus produces the growth factor IGF-II and a number of transport proteins, most importantly transthyretin, that might regulate hormone transport from blood to brain.
These studies suggest that the choroid plexus-CSF system could constitute an important pathway for neuroendocrine signalling in the brain, although clearcut evidence for such a role is still largely lacking.


A circadian variation in human cerebrospinal fluid (CSF) production has recently been demonstrated using magnetic resonance phase imaging. A nightly peak in CSF production was found at approximately 0200, when production is approximately twice the daytime values. In the present study, we have investigated the effect of a beta 1-receptor antagonist, atenolol, on the production of CSF, specifically the nocturnal production peak. CSF production was measured in fourteen healthy volunteers of both sexes in the time interval 1500-1800, with or without drug administration (100 mg orally) at 1800, and a second measurement was made in the time interval 2300-0200. In the absence of drug administration, all nine volunteers showed a significant increase in CSF production at night, from 0.34 +/- 0.06 ml/min in the time interval 1500-1800 to 0.61 +/- 0.05 (SE) ml/min (P < 0.005), confirming the presence of a circadian variation in these individuals. One week later, the experiment was repeated in five of these volunteers, plus an additional five volunteers, but with the administration of 100 mg atenolol orally immediately after the first measurement (at 1800). In five of the volunteers a decrease in CSF production was seen at midnight compared with daytime production values; in two volunteers CSF production remained unchanged, while three volunteers showed increased production. The average CSF production was 32% lower at night (0.27 +/- 0.10 ml/min) compared with the afternoon (0.40 +/- 0.07 ml/min), after administration of atenolol (P = 0.37). (ABSTRACT TRUNCATED AT 250 WORDS)


Recent advances in magnetic resonance imaging have made it possible to visualize and quantify flow of cerebrospinal fluid (CSF) in the brain. The net flow of CSF through the cerebral aqueduct was used to measure CSF production in six normal volunteers at different times during a 24-h period. CSF production varied greatly both intra- and interindividually. The average CSF production in each time interval showed a clear tendency to circadian variation, with a minimum production 30% of maximum values (12 +/- 7 ml/h) approximately 1800 h and a nightly peak production approximately 0200 h of 42 +/- 2 ml/h. The total CSF production during the whole 24-h period, calculated as an average of all measurements, was 650 ml for the whole group and 630 ml for repeated measurements in each time interval in one of the volunteers.


OBJECT: The aim of this study was to analyze physiological changes in cerebrospinal fluid (CSF) dynamics following endoscopic third ventriculostomy (ETV) for shunt-dependent noncommunicating hydrocephalus. METHODS: Clinical data obtained in 15 patients treated with ETV for shunt malfunction were analyzed. Magnetic resonance imaging studies demonstrated the obstruction of the ventricular system preoperatively. After ETV, the existing shunt system was removed and a continuous extraventricular drain, set at 30 cm H2O in height, was installed to measure daily amounts of CSF outflow. Cerebrospinal fluid dynamics after ETV were also evaluated using 111In-diethylenetriamine pentaacetic acid radioisotope cisternography in six of 15 patients within 1 month of the procedure. Three patients underwent cisternography at 6 months after ETV. Cisternograms were obtained at 1, 5, 24, and 48 hours after injection of the radioisotope. To study CSF absorptive capacity, ratios of radioisotope counts at 48 and 5 hours after injection were calculated (C48:C5). Seven of 15 patients had daily outflows of CSF of less than 20 ml; this volume decreased quickly within a few days. The other eight patients maintained an outflow of more than 150 ml of CSF for several days, three of whom had signs of transiently increased intracranial pressure. Their CSF outflow volume decreased gradually and symptoms improved within 1 week. Ratios of C48:C5 were within normal limits in five of six patients who had undergone cisternography 1 month after ETV. These ratios were decreased in all three patients who had undergone cisternography at 6 months after ETV compared with that measured at 1 month after the procedure. CONCLUSIONS: Our data suggest that CSF dynamics convert from a shunt-dependent state to a shunt-independent state within 1 week following ETV in patients with shunt-dependent noncommunicating hydrocephalus. Nonetheless, intraventricular pressure does not decrease quickly in certain cases. Cerebrospinal fluid absorptive capacity or CSF circulation through the subarachnoid space may show further improvement several months after ETV.

Formation and circulation of cerebrospinal fluid (CSF) have been studied in the isolated brain ventricles of anesthetized cats by a new approach and under direct observation. A plastic cannula was introduced into the aqueduct of Sylvius through the vermis cerebelli and the outflow of CSF from the cannula was used as the CSF formation and circulation index. During the 60 min of observation at a physiological CSF pressure not a single drop of CSF escaped out of the end of the cannula. This indicates that CSF net formation and circulation inside the brain ventricles, proposed by classical hypothesis regarding CSF dynamics, should be at least re-evaluated.


Aquaporin-1 (AQP1) is a water channel expressed strongly at the ventricular-facing surface of choroid plexus epithelium. We developed novel methods to compare water permeability in isolated choroid plexus of wild-type vs. AQP1 null mice, as well as intracranial pressure (ICP) and cerebrospinal fluid (CSF) production and absorption. Osmotically induced water transport was rapid in choroid plexus from wild-type mice and reduced by fivefold by AQP1 deletion. AQP1 deletion did not affect choroid plexus size or structure. By stereotaxic puncture of the lateral ventricle with a microneedle, ICP was 9.5 +/- 1.4 cm H2O in wild-type mice and 4.2 +/- 0.4 cm H2O in AQP1 null mice. CSF production, an isosmolar fluid secretion process, was measured by a dye dilution method involving fluid collections using a second microneedle introduced into the cisterna magna. CSF production in wild-type mice was (in microl min(-1)) 0.37 +/- 0.04 (control), 0.16 +/- 0.03 (acetazolamide-treated), and 1.14 +/- 0.15 (forskolin-treated), and reduced by approximately 25% in AQP1 null mice. Pressure-dependent CSF outflow, measured from steady-state ICP at different ventricular infusion rates, was not affected by AQP1 deletion. In a model of focal brain injury, AQP1 null mice had remarkably reduced ICP and improved survival compared with wild-type mice. The reduced ICP and CSF production in AQP1 null mice provides direct functional evidence for the involvement of AQP1 in CSF dynamics, suggesting AQP1 inhibition as a novel option for therapy of elevated ICP.


PURPOSE: To quantify the cerebrospinal fluid (CSF) dynamics in the aqueduct of children with normal and dilated ventricles using MR phase-contrast technique. MATERIAL AND METHODS: Eighteen patients (6 months to 17 years of age) with various neurological symptoms underwent routine brain MR imaging and CSF flow measurement in the aqueduct. Nine patients had normal ventricles, 5 had dilated ventricles and 4 had a ventriculoperitoneal shunt. RESULTS: The CSF velocity and flow rates in the aqueduct in patients with normal and dilated ventricles showed marked inter-individual variation and clear overlap. In a patient with tight aqueductal stenosis and increased ventricular pressure, pronounced CSF flow in the aqueduct was measured. Absence of flow in another patient with aqueductal stenosis was detected. Measurable although low flow in the aqueduct in 4 patients with a ventriculoperitoneal shunt was found. CONCLUSION: Quantitative phase MR flow measurement in the aqueduct demonstrated aqueductal stenosis; these patients had either pronounced flow or no flow in the aqueduct.


A 51-year-old man had a 4-month history of progressive headache and gradual onset of somnolence. MRI suggested spontaneous intracranial hypotension (SIH) with diencephalic compression, but he did not improve after three epidural blood patches. He became alert following intrathecal saline infusion that normalized his CSF pressure. A CSF leak was noted on spinal MRI and confirmed with CT contrast myelography. Surgical ligation of a torn dural root sleeve isolating a ruptured Tarlov's cyst resulted in permanent cure.

Current techniques for intracranial pressure (ICP) measurement are invasive. All require a surgical procedure for placement of a pressure probe in the central nervous system and, as such, are associated with risk and morbidity. These considerations have driven investigators to develop noninvasive techniques for pressure estimation. A recently developed magnetic resonance (MR) imaging-based method to measure intracranial compliance and pressure is described. In this method the small changes in intracranial volume and ICP that occur naturally with each cardiac cycle are considered. The pressure change during the cardiac cycle is derived from the cerebrospinal fluid (CSF) pressure gradient waveform calculated from the CSF velocities. The intracranial volume change is determined by the instantaneous differences between arterial blood inflow, venous blood outflow, and CSF volumetric flow rates into and out of the cranial vault. Elastance (the inverse of compliance) is derived from the ratio of the measured pressure and volume changes. A mean ICP value is then derived based on a linear relationship that exists between intracranial elastance and ICP. The method has been validated in baboons, flow phantoms, and computer simulations. To date studies in humans demonstrate good measurement reproducibility and reliability. Several other noninvasive approaches for ICP measurement, mostly nonimaging based, are also reviewed. Magnetic resonance imaging-based ICP measurement may prove valuable in the diagnosis and serial evaluation of patients with a variety of disorders associated with alterations in ICP.


Extremes of intracranial pressure commonly cause headache. Benign intracranial hypertension is a rare syndrome of increased intracranial pressure manifesting as headache, intracranial noises, transient visual obscurcation, and palsy of the sixth cranial nerve. Endocrine disorders such as obesity and hypoparathyroidism, hypervitaminosis A, tetracycline use and thyroid replacement are probable causes of benign intracranial hypertension. In the majority of cases, however, it is idiopathic. Benign intracranial hypertension is though to be caused by cerebral edema, high cerebrospinal fluid outflow resistance and high cerebral venous pressure, or a combination of the three. The management of benign intracranial hypertension includes, symptomatic headache relief, removal of offending risk factor(s), and medical or surgical reduction of intracranial pressure. Spontaneous intracranial hypotension is more rare than benign intracranial hypertension. Postural headache (worse in the upright position) is the hallmark of spontaneous intracranial hypotension. Typically, the cerebrospinal fluid pressure is less than 60 mm H2O. Diminished cerebrospinal fluid production, hyperabsorption, and leak are postulated mechanisms of spontaneous intracranial hypotension. Empirical treatment includes bed rest, administration of caffeine, corticosteroids or mineralocorticoids, epidural blood patch, and epidural saline infusion.


The role of human choroid plexus (CP) epithelium in the transport of solutes between the blood and the cerebrospinal fluid and/or in secretion processes may be studied by employing several experimental approaches. There are a number of in vitro techniques for human CP epithelium (CPE) and all have limitations that do not exclude them a priori, but that should be carefully taken into consideration. Developmental and morphological studies have been largely performed on human choroid plexus samples of either embryonic or post-mortem origin. Functional uptake studies may be performed on pathologically unaltered CP samples obtained during surgical removal of choroid plexus tumors. This approach can be used to explore transport processes mainly across the apical side of the CPE, but cannot be used to study vectorial transport across the CPE. Also, these samples have limited viability. A monolayer of CPE in culture, grown on permeable supports, provides the best available tool to study transport processes or polarized secretion by the CP, but thus far only limited attempts to culture these cells have been published and they mainly include data from neoplastic CPE. A study that used a human papilloma-derived cell line in culture showed that it forms a monolayer with barrier properties, although the cells express pleomorphic and neoplastic features and lack contact inhibition. Other cell cultures express some CPE markers but do not develop tight junctions/barrier properties. This article reviews the main characteristics and limitations of available in vitro methods to study human CPE, which could help researchers choose an appropriate experimental approach for a particular study.

Cerebrospinal fluid (CSF) routine analysis for diagnosis of neurological diseases is based on the concepts for discrimination of blood-derived and brain-derived immunoglobulin fractions in CSF. The actual molecular flux/CSF flow theory of the blood/CSF barrier function, which founded the hyperbolic discrimination lines in quotient diagrams, is derived from the laws of molecular diffusion combined with CSF flow rate. It emerged from this theory that the decrease of CSF flow rate is sufficient to explain quantitatively the increase of CSF protein concentrations as observed in many neurological diseases. With this concept of CSF flow rate as the modulator of the normal and pathological blood-CSF barrier function, we got for the first time a theoretical frame work to explain also quantitatively the dynamics of brain-derived proteins and their source related (neurons and glial cells or leptomeningal cells) differences. The review of the anatomical, physiological and biophysical knowledge points to the new interpretations: The changing albumin quotient is an indicator of changing CSF flow rate and not for a morphological "leakage" of the blood-brain barrier. As an application of these concepts the dynamics of brain-derived molecules in blood are discussed with two examples: beta trace protein, flowing with CSF into venous blood, and neuron-specific enolase, passing from tissue into blood the opposite direction of serum proteins, again a gradient-dependent protein diffusion across the intact blood vessel wall.


BACKGROUND: Mannan-binding lectin (MBL), a protein of the innate immune response is attracting increasing clinical interest, in particularly in relation to its deficiency. Due to its involvement in brain diseases, identifying the source of MBL in CSF is important. Analysis of cerebrospinal fluid (CSF) can provide data that discriminates between blood-, brain-, and leptomeninges-derived proteins. To detect the source of MBL in CSF we need to consider three variables: the molecular size-dependent concentration gradient between CSF and blood, the variation in transfer between blood and CSF, and the CSF MBL concentration correlation with the albumin CSF/serum quotient (QAlb), i.e., with CSF flow rate. METHODS: MBL was assayed in samples of CSF and serum with an ELISA, coated with anti MBL antibodies. Routine parameters such as albumin-, immunoglobulin- CSF/serum quotients, oligoclonal IgG and cell count were used to characterize the patient groups. Groups comprised firstly, control patients without organic brain disease with normal CSF and normal barrier function and secondly, patients without inflammatory diseases but with increased QAlb, i.e. with a blood CSF barrier dysfunction. RESULTS: MBL concentration in CSF was at least five-fold higher than expected for a molecular-size-dependent passage from blood. Secondly, in a QIgM/QAlb quotient diagram (Reibergram) 9/13 cases showed an intrathecal fraction in some cases over 80% of total CSF MBL concentration 3) The smaller inter-individual variation of MBL concentrations in CSF of the control group (CV = 66%) compared to the MBL concentrations in serum (CV = 146%) indicate an independent source of MBL in CSF. 4) The absolute MBL concentration in CSF increases with increasing QAlb. Among brain-derived proteins in CSF only the leptomeningeal proteins showed a (linear) increase with decreasing CSF flow rate, neuronal and glial proteins are invariant to changes of QAlb. CONCLUSIONS: MBL in CSF is predominantly brain-derived and all results pointed to the leptomeningeal cells as the source of the protein. The evaluation of this protein requires the interpretation of its absolute concentrations in CSF as a function of the albumin quotient, QAlb. This recognition of MBL in brain cells opens a new field of discussion about the function of the innate immune response in CNS in cases of acute and chronic neurological diseases.


PURPOSE: Determining acute intracranial hydrodynamic changes after subarachnoid hemorrhage through an analysis of the CSF stroke volume (SV) as measured by phase-contrast MRI (PC-MRI) in the mesencephalon aqueduct. METHOD: A prospective study was performed in 33 patients with subarachnoid hemorrhage. A PC-MRI imaging study was performed n the acute phase (< 48 hours). CSF flow was measured in the aqueduct. The appearance of acute hydrocephalus (HCA) was then compared with data on CSF flow, and the location of the intraventricular and perimesencephalic bleeding. RESULTS: CSF analysis was performed on 27 patients, 11 of whom presented with an acute HCA. All 11 patients had an abnormal SV in the aqueduct: patients with a communicating HCA had an increased SV (n=8); and patients with a noncommunicating HCA had a nil SV (n=3). Patients with a normal SV in the aqueduct did not develop an acute HCA. Intraventricular bleeding significantly led to HCA (P=0.02),
which was of the communicating type in 70% of cases. CONCLUSION: Subarachnoid hemorrhage leads to intracranial CSF hydrodynamic modifications in the aqueduct in the majority of patients. CSF flow can help us to understand the mechanism of the appearance of acute HCA. Indeed, hydrocephalus occurred - of the communicating type in most cases - even in the presence of intraventricular bleeding.


In this paper, phase contrast magnetic resonance flow measurements of the foramina of Monro and the aqueduct of Sylvius of seven healthy volunteers are presented. Peak volume flow rates are of the order of 150 mm3/s for the aqueduct of Sylvius and for the foramina of Monro. The temporal shift between these volume flows is analyzed with a high-resolution cross-correlation scheme which reveals high subject-specific phase differences. Repeated measurements show the invariability of the phase differences over time for each volunteer. The phase differences as a fraction of one period range from -0.0537 to 0.0820. A mathematical model of the pressure dynamics is presented. The model features one lumped compartment per ventricle. The driving force of the cerebrospinal fluid is modeled through pulsating choroid plexus. The model includes variations of the distribution of the choroid plexus between the ventricles. The proposed model is able to reproduce the measured phase differences with a very small (5%) variation of the distribution of the choroid plexus between the ventricles and, therefore, supports the theory that the choroid plexus drives the cerebrospinal fluid motion.


OBJECTIVES: To estimate the mean influence of the main determinants of the cerebrospinal fluid (CSF) concentration of albumin and plasma-derived immunoglobulin G (IgG). METHODS: Correlations of serum and CSF concentrations of albumin and IgG and assumptions of the mode of action of the determinants (plasma concentration, barrier permeability, and CSF flow) are used to quantify the determinants’ influences in a sample of 1700 patients. RESULTS: We estimated in patients with normal CSF albumin that the serum concentrations of albumin and IgG explained 3.3% and 23% of the variation of the respective CSF concentrations, whereas the barrier permeability accounted for 41.9% and 22.2%, and CSF flow for 54.8%. In patients with pathologic CSF albumin concentration, the serum concentrations were estimated to explain 0.2% and 8.2% of the variation of the respective CSF concentrations, the barrier permeability 19.7% and 11.7%, and CSF flow 80.1%. CONCLUSIONS: CSF flow had the strongest mean influence, especially at elevated CSF albumin levels. The serum concentrations and barrier permeabilities of albumin and IgG influenced the respective CSF concentrations quite differently, which should be due to the different physicochemical properties of the two molecules. Mean influences from large patient samples, as explored here, can give only an overview. Understanding the determinants in individuals will need further specific measurements, especially of CSF flow.


OBJECTIVE: To determine factors influencing the wide variation of protein concentration in lumbar cerebrospinal fluid (CSF). METHODS: Patient variables with potential influence on spinal CSF flow and
resorption were measured in different patient settings and compared with albumin and IgG CSF/serum quotients. RESULTS: In patients whose diagnostic lumbar puncture produces normal CSF the albumin quotient increased with body mass index (r = 0.408), abdominal circumference (r = 0.399), and body weight (r = 0.317), age-corrected with partial correlation. Body motion before lumbar puncture showed only marginal influence on albumin quotient. In patients with radiculography the albumin quotient decreased with iodine contrast medium elimination from spinal subarachnoid space (r = -0.598) and increased with narrowing of lumbosacral spinal canal (r = 0.515). CONCLUSION: Correlation of albumin quotient with body mass index and related variables may be mediated by spinal CSF resorption, which should be impaired in overweight patients with elevated venous pressure. Negative correlation of albumin quotient with iodine resorption from spinal CSF supports this assumption. Correlation of albumin quotient with narrowing of lumbosacral canal should be due to slowed spinal CSF flow which does increase protein concentration. Tested variables explain part of variation of CSF protein concentration. Other variables like blood-CSF barrier permeability and pulsatile spinal CSF flow should have additional influence.


Spontaneous intracranial hypotension is a rare disease characterized by orthostatic headache, low cerebrospinal fluid pressure and diffuse dural enhancement in brain MRI. German neurologist Schaltenbrand reported that orthostatic headache by low cerebrospinal fluid pressure in 1938. This disease came to be known after development of radiological diagnosis in 1990. The author reported that cerebrospinal fluid leak is induced in the whiplash sequelae after traffic accident in 2003. Cerebrospinal fluid hypovolemia got into the news social. A lot of doctors deny the cerebrospinal fluid leak after mild traffic accident. The Cerebrospinal Fluid Hypovolemia Society is started up in 2003 and 11 research meeting held until today. The research group of Ministry of Health, Labour and Welfare was made in 2007. The image diagnostic criteria of cerebrospinal fluid leakage syndrome model were made in 2012. Neither the mechanism of the cerebrospinal fluid leak nor the mechanism of symptoms are understood well. The pathophysiology of cerebrospinal fluid hypovolemia is expected by researching the cerebrospinal fluid circulation.


Recent studies in sheep suggest that a significant proportion of global cerebrospinal fluid (CSF) drainage (50% or greater) occurs through the cribiform plate into nasal mucosal lymphatics. If this is true, obstructing CSF clearance through the cribiform plate should have an impact on the ability of the intracranial pressure regulating systems to compensate for volume infusions. To test this concept, bolus infusions of artificial CSF were administered into one lateral ventricle in sheep and the intracranial pressure monitored from the contralateral side. Peak intracranial pressures (ICP) were measured and CSF outflow resistances were calculated from the pressure patterns observed in response to bolus infusions administered before and after the cribiform plate was sealed in the same animal. To obstruct the cribiform plate, a portion of nasal bone was removed to expose the nasal mucosa. The olfactory mucosa, a portion of the nasal mucosa and all soft tissue on the extracranial surface of the cribiform plate were scraped away with a curette and the bone surface sealed with bone wax. Obstruction of CSF transport through the cribiform plate increased the peak ICP after infusion (P = 0.016) and augmented the time required for ICP to return to baseline. CSF outflow resistance was elevated approximately 2.7 times (P = 0.006). When the cribiform plate was left intact (sham surgery), no significant changes in peak ICP or CSF outflow resistance were observed. We conclude that the cribiform plate represents an important site for CSF clearance. Obstruction of this pathway reduces volumetric CSF transport significantly.


The lattice Boltzmann method is used to model oscillatory flow in the spinal subarachnoid space. The effect of obstacles such as trabeculae, nerve bundles, and ligaments on fluid velocity profiles appears to be small, when the flow is averaged over the length of a vertebra. Averaged fluid flow in complex models is little different from flow in corresponding elliptical annular cavities. However, the obstacles stir the flow locally and may be more significant in studies of tracer dispersion.

Head-down tilt (HDT) causes a fluid shift towards the upper body, which increases intracranial pressure (ICP). In the present study, the time course of ICP changes during prolonged exposure to HDT was investigated in conscious rabbits through a catheter chronically implanted into the subarachnoid space. The production of cerebrospinal fluid (CSF) after exposure to 7-days HDT was also examined by a ventriculo-cisternal perfusion method. The ICP increased from 4.3 +/- 0.4 (mean +/- S.E.M.) mmHg to 8.0 +/- 0.8 mmHg immediately after the onset of 45 degrees HDT, reached a peak value of 15.8 +/- 1.9 mmHg at 11 h, and then decreased to 10.4 +/- 1.1 mmHg at 24 h. During 7-days HDT, it also increased from 4.8 +/- 0.9 mmHg to 9.2 +/- 1.6 mmHg immediately after the onset of 45 degrees HDT, reached a peak value of 12.8 +/- 2.5 mmHg at 12 h of HDT, and then decreased gradually towards the pre-HDT baseline value for 7 days. The rate of CSF production was 10.1 +/- 0.6 microl/min in rabbits exposed to 7-days HDT, and 9.7 +/- 0.5 microl/min in control rabbits. These results suggest that the rabbits begin to adapt to HDT within a few days and that the production of CSF is preserved after exposure to 7-days HDT. The time course of ICP changes during HDT in conscious rabbits seems to be considerably different from that in anesthetized rabbits.


**BACKGROUND:** Sheep are seasonal breeders. The key factor governing seasonal changes in the reproductive activity of the ewe is increased negative feedback of estradiol at the level of the hypothalamus under long-day conditions. It has previously been demonstrated that when gonadotropin secretions are inhibited during long days, there is a higher concentration of estradiol in the cerebrospinal fluid (CSF) than during short days. This suggests an involvement of the CSF and choroid plexus in the neuroendocrine regulatory loop, but the mechanisms underlying this phenomenon remain unknown. One possible explanation of this difference in hormonal content is an effect of concentration or dilution caused by variations in CSF secretion rate. The aim of this study was thus to investigate changes in the CSF turnover rate related to light-dark cycles. **METHODS:** The turnover rate of the CSF was estimated by measuring the time taken for the recovery of intraventricular pressure (IVP) after removal of a moderate volume (0.5 to 2 ml) of CSF (slope in mmHg/min). The turnover rate was estimated three times in the same group of sheep: during a natural period of decreasing day-length corresponding to the initial period when gonadotropin activity is stimulated (SG1), during a long-day inhibitory period (IG), and finally during a short-day stimulatory period (SG2). **RESULTS:** The time taken and the speed of recovery of initial IVP differed between groups: 8 min 30 sec, 0.63 +/- 0.07 mmHg min(SG1), 11 min 1 sec, 0.38 +/- 0.06 mmHg/min (IG) and 9 min 0 sec, 0.72 +/- 0.15 mmHg/min (SG2). Time changes of IVP differed between groups (ANOVA, p < 0.005, SG1 different from IG, p < 0.05). The turnover rate in SG2: 183.16 +/- 23.82 microl/min was not significantly different from SG1: 169.23 +/- 51.58 microl/min (Mann-Whitney test, p = 0.41), but was significantly different from IG: 71.33 +/- 16.59 microl/min (p = 0.016). **CONCLUSION:** This study shows that the turnover rate of CSF in ewes changes according to the light-dark cycle; it is increased during short day periods and reduced in long day periods. This phenomenon could account for differences in hormonal concentrations in the CSF in this seasonal species.


There is substantial anatomical and functional continuity between the veins, venous sinuses, and venous plexuses of the brain and the spine. The term "cerebrospinal venous system" (CSVS) is proposed to emphasize this continuity, which is further enhanced by the general lack of venous valves in this network. The first of the two main divisions of this system, the intracranial veins, includes the cortical veins, the dural sinuses, the cavernous sinuses, and the ophthalmic veins. The second main division, the vertebral venous system (VVS), includes the vertebral venous plexuses which course along the entire length of the spine. The intracranial veins richly anastomose with the VVS in the suboccipital region. Caudally, the CSVS freely communicates with the sacral and pelvic veins and the prostatic venous plexus. The CSVS constitutes a unique, large-capacity, valveless venous network in which flow is bidirectional. The CSVS plays important roles in the regulation of intracranial pressure with changes in posture, and in venous outflow from the brain. In addition, the CSVS provides a direct vascular route for the spread of tumor, infection, or emboli among its different components in either direction.

The effects of an anti-siphon device (ASD) on shunt flow and intracranial pressure (ICP) in 16 children with hypertensive hydrocephalus were examined using quantitative radionuclide shuntography (99mTc) with the children in supine and sitting positions. The average age of these patients was 9.5 years. Results were compared with those recorded in 36 patients with adult normal-pressure hydrocephalus (NPH). The closing pressure levels of shunt valve used were low in 8 cases, medium in 7 and high in 1. Half the children (8) had shunt systems with, and the other 8 without, ASD. In the children who had the shunt system without ASD, sitting shunt flow was significantly greater than supine shunt flow, which indicated overdrainage. Conversely, in children who had the shunt system with ASD, supine shunt flow was greater than sitting shunt flow. Because ASD prevented overdrainage, ICP was higher with the shunt system with ASD than with the shunt system without ASD. Without ASD, sitting shunt flow of children was lower than that of adult patients with NPH because of the lower hydrostatic pressure, which correlated with their height. Conversely, in the presence of a shunt system with ASD, sitting shunt flow of children was greater than that of adults, because of the higher ICP and lower hydrostatic pressure. The effect of ASD was smaller in children than in adults, because positive pressure over the ASD was greater (hypertension vs normal pressure) and negative pressure under the ASD was less (short vs tall) in children than in adults. Thus, in children the ASD was effective in preventing overdrainage.


Gait instability, urinary incontinence, and dementia are the signs and symptoms typically found in patients who have normal pressure hydrocephalus. Estimated to cause no more than 5 percent of cases of dementia, normal pressure hydrocephalus often is treatable, and accurate recognition of the clinical triad coupled with radiographic evidence most commonly identifies likely responders. Magnetic resonance imaging or computed tomography typically demonstrates ventricular dilation with preservation of the surrounding brain tissue. The abnormality in normal pressure hydrocephalus occurs secondary to an abnormality in fluid removal, leading to an increase in ventricular size and encroachment of enlarged ventricles on adjacent brain tissue. The pressure exerted on the cerebral parenchyma by immense fluid-filled cavities deforms white matter tracts, instigating gait abnormalities and incomplete control of the bladder, as well as difficulties in processing incoming stimulation and in producing expeditious responses. Signs and symptoms often occur as sequelae to an imbalance between the expected ongoing production of cerebrospinal fluid and continuous efflux. Ventriculoperitoneal shunting is used to relieve excess ventricular fluid not absorbed by normal physiologic channels. Multiple studies have explored various techniques to identify patients with normal pressure hydrocephalus in an effort to predict likely benefit from shunting. However, the effectiveness of cerebrospinal fluid diversion has never been proven in a randomized controlled trial comparing use of a shunt versus no shunt.


Recent investigations confirm the importance of nonsynaptic signal transmission in several functions of the nervous tissue. Present in various periventricular brain regions of vertebrates, the system of cerebrospinal fluid (CSF)-contacting neurons seems to have a special role in taking up, transforming and emitting nonsynaptic signals mediated by the internal and external CSF and intercellular fluid of the brain. Most of the CSF-contacting nerve cells send dendritic processes into the internal CSF of the brain ventricles or central canal where they form terminals bearing stereocilia and a 9+0- or 9+2-type cilium. Some of these neurons resemble known sensory cells of chemoreceptor-type, others may be sensitive to the pressure or flow of the CSF, or to the illumination of the brain tissue. The axons of the CSF-contacting neurons transmit information taken up by dendrites and perikarya to synaptic zones of various brain areas. By forming neurohormonal terminals, axons also contact the external CSF space and release various bioactive substances there. Some perikarya send their axons into the internal CSF, and form free endings there, or synapses on intraventricular dendrites, perikarya and/or on the ventricular surface of ependymal cells. Contacting the intercellular space, sensory-type cilia were also demonstrated on nerve cells situated in the brain tissue subependymally or farther away from the ventricles. Among neuronal elements entering the internal CSF-space, the hypothalamic CSF-contacting neurons are present in the magnocellular and parvicellular nuclei and in some circumventricular organs like the...
paraventricular organ and the vascular sac. The CSF-contacting dendrites of all these areas bear a solitary 9 x 2 +0-type cilium and resemble chemoreceptors cytologically. In electrophysiological experiments, the neurons of the paraventricular organ are highly sensitive to the composition of the ventricular CSF. The axons of the CSF-contacting neurons terminate not only in the hypothalamic synaptic zones but also in tel-, mes- and rhombencephalic nuclei and reach the spinal cord as well. The supposed chemical information taken up by the CSF-contacting neurons from the ventricular CSF may influence the function of these areas of the central nervous system. Some nerve cells of the photoreceptor areas form sensory terminals similar to those of the hypothalamic CSF-contacting neurons. Special secondary neurons of the retina and pineal organ contact the retinal photoreceptor space and pineal recess respectively, both cavities being embryologically derived from the 3rd ventricle. The composition of these photoreceptor spaces is important in the photochemical transduction and may modify the activity of the secondary neurons. Septal and preoptic CSF-contacting neurons contain various opsins and other compounds of the phototransduction cascade and represent deep encephalic photoreceptors detecting the illumination of the brain tissue and play a role in the regulation of circadian and reproductive responses to light. The medullo-spinal CSF-contacting neurons present in the oblongate medulla, spinal cord and terminal filum, send their dendrites into the fourth ventricle and central canal. Resembling mechanoreceptors of the lateral line organ, the spinal CSF-contacting neurons may be sensitive to the pressure or flow of the CSF. The axons of these neurons terminate at the external CSF-space of the oblongate medulla and spinocerebellar system and form neurohormonal nerve endings.

Based on information taken up from the CSF, a regulatory effect on the production or composition of CSF was supposed for bioactive materials released by these terminals. Most of the axons of the medullospinal CSF-contacting neurons and the magnocellular neurosecretory nuclei running to neurohemal areas (neurohypophysis, median eminence, terminal lamina, vascular sac and urophysis) do not terminate directly on vessels, instead they form neurohormonal nerve terminals attached by half-desmosomes on the basal lamina of the external and vascular surface of the brain tissue. Therefore, the bioactive materials released from these terminals primarily enter the external CSF and secondarily, by diffusion into vessels and the composition of the external CSF, may have a modulatory effect on the bioactive substances released by the neurohormonal terminals. Contacting the intercellular space, sensory-type cilia were also demonstrated on nerve cells situated subependymally or farther away from the ventricles, among others in the neurosecretory nuclei. Since tight-junctions are lacking between ependymal cells of the ventricular wall, not only CSF-contacting but also subependymal ciliated neurons may be influenced by the actual composition of the CSF besides that of the intercellular fluid of the brain tissue. According to the comparative histological data summarised in this review, the ventricular CSF-contacting neurons represent the phylogenetically oldest component detecting the internal fluid milieu of the brain. The neurohormonal terminals on the external surface of the brain equally represent an ancient form of nonsynaptic signal transmission.


Intracranial pressure (ICP) is often measured from intraventricular catheters, a technique that allows therapeutic drainage of ventricular cerebrospinal fluid (CSF) as an aid in controlling ICP and circumventing obstruction. Drainage of CSF simultaneously with ongoing ICP measurement has been advocated as safe and efficient, and devices are commercially available to permit this practice; however, this concept has been seriously challenged, based on clinical observations. The inaccuracy induced by simultaneous CSF drainage and ICP monitoring is quantitated in this report in a mechanical brain model using a standard ventricular catheter. The following conclusions have been confirmed: 1) rapid CSF drainage induces a severe artifactual reduction in measured ICP, more extreme at higher pressures; 2) calibrated slower rates of CSF drainage produce a severe, although less immediate, reduction in measured ICP; 3) severe artifact appears even in the presence of continuous CSF outflow, so a system that measures ICP only in the presence of CSF flow does not prevent artifact; 4) with simultaneous CSF drainage, measured ICP is determined more by the outflow pressure setting than by actual brain pressure; 5) Since ICP elevation of 25 to 30 mm Hg blocks CSF production, even slow fluid drainage at high pressures should ultimately lead to ventricular collapse and severe artifact.

Previously there have been no methods for directly tracing the flow of cerebrospinal fluid (CSF) under physiological conditions, and the circulation of CSF has therefore been studied and visualized by injecting a radioactively labeled tracer or contrast medium visible in x-ray images. The newly developed Time-Spatial Inversion Pulse (Time-SLIP) method makes it possible to directly visualize the flow of CSF using magnetic resonance imaging (MRI), permitting CSF dynamics to be depicted in a certain time frame. The CSF dynamics visualized using Time-SLIP has been found to differ markedly from the classical CSF circulation theory described in medical textbooks. It can be said that research on CSF dynamics has advanced to the next stage with the use of this innovative imaging method. Obtaining a more accurate understanding of normal CSF physiology and pathophysiology should lead to improved diagnostic accuracy, permit the identification of new etiological factors in a variety of diseases, and promote the development of new therapeutic approaches.


The functional ultrastructure of the human arachnoid villi was studied to clarify drainage channels of cerebrospinal fluid (CSF). The apical portion of each villus was usually covered by the arachnoid cell layer alone with no endothelial investment, whereas most of the stromal central core was further encompassed by a fibrous capsule with an endothelial investment. Accordingly, the CSF-blood interface was assumed to be in both the endothelial cells and the arachnoid cell layer. The former were characterized by abundant micropinocytotic vesicles and occasional intracytoplasmic vacuoles, whereas the latter was characterized by numerous extracellular cisterns measuring 10 micron in maximal diameter. There were no free communications such as endothelial open junctions or endothelium-lined tubules. In the villi affected by subarachnoid hemorrhage, endothelial cells were intact and continuous despite the erythrocyte-packed subendothelial space, which appeared to be on the verge of rupturing. Intracytoplasmic vacuoles, measuring less than 1 micron diameter, sometimes contained serum protein-like substance. Furthermore, the extracellular cisterns were distended by intact or disintegrating erythrocytes that served as a natural tracer, suggesting CSF drainage channels. It is conceivable that, in human arachnoid villi, the extracellular cisterns of the arachnoid cell layer contribute to the passive transport of CSF, whereas micropinocytosis and vacuolization mechanisms of the endothelial cells are available for active transport.


Spontaneous intracranial hypotension (SIH) is characterized by orthostatic headache. Typical abnormal magnetic resonance imaging (MRI) findings have been considered to be the sine qua non of SIH, but a sizeable minority of patients has normal results using conventional MRI. The purpose of this study was to evaluate the difference in cerebrospinal fluid (CSF) flow dynamics between patients and healthy people using cine phase contrast (PC) MRI, and to assess the CSF flow dynamics in patients before and after treatment. From November of 2007 to December of 2012, twenty patients with SIH (10 men and 10 women, mean age=40.9±7.77 years) and 31 age- and gender- matched healthy subjects (15 men and 16 women, mean age=46.3±7.53 years) were enrolled in this retrospective study. Cine PC MRI was performed on the patients and on the healthy subjects to measure the CSF flow in cerebral aqueduct. Patients underwent repeated cine PC MRI at 24 hours and at one month after treatment respectively. Five parameters including peak positive and negative velocity, average flow, and average positive and negative flow were recorded to evaluate their differences. Seventeen patients (85%) received epidural blood patching (EBP) owing to the failure of conservative treatment. All patients experienced resolution of symptoms after treatment. Before treatment, the patients had a significantly lower average CSF flow than the healthy subjects ($p<0.001$). The average CSF flow was elevated in patients with SIH at 24 hours after treatment and was significantly increased one month after treatment ($p=0.003$). By establishment of the receiver operating characteristic (ROC) curve, the best cutoff value for the average CSF flow was determined to be 14.0μl/beat, while the sensitivity and specificity were determined to be 90.3% and 72.2%, respectively. Patients with SIH showed lower CSF flow compared to healthy subjects, but this decreased CSF flow was shown by cine PC MRI to be gradually recovered after treatment. This study provides evidence that cine PC MRI is useful for assessing the dynamic changes of CSF flow in the cerebral aqueduct noninvasively and for demonstrating the effectiveness of treatment in patients with SIH reliably.

BACKGROUND: Physiological studies suggest that a major portion of cerebrospinal fluid (CSF) drainage is associated with transport along cranial and spinal nerves with absorption taking place into lymphatic vessels external to the central nervous system. Especially important is CSF transport through the cribriform plate in association with the olfactory nerves. This study examined the anatomical connections that link the CSF and extracranial lymphatics at the base of the brain. METHODS AND RESULTS: The contrast agent, Yellow Microfil, was infused into the cranial sub-arachnoid compartment of 2- to 7-day-old lambs postmortem. In some animals, Blue Microfil was perfused into the carotid arteries. Yellow Microfil was observed in extensive lymphatic networks in the submucosa associated with the olfactory and respiratory epithelium. Since little of the contrast agent was present within the interstitium of the olfactory submucosa, there appeared to be direct continuity between the subarachnoid space, the perineurial spaces of the olfactory nerve fibers that penetrate the cribriform plate, and the lumens of the lymphatic vessels within the olfactory submucosa. Lymphatics encircled the olfactory nerves at the level of the emerging nerve rootlets (in many cases providing the outer limit of the perineurial space) and then dispersed freely in the submucosa at greater distance from the cribriform plate. These vessels converged into larger collecting ducts that emptied into various lymph nodes in the head and neck. CONCLUSIONS: Lymphatic vessels gain access to the brain extracellular fluid (CSF) in an unusual anatomical association with the olfactory nerves external to the cranial vault. This study highlights the important role played by lymphatic vessels in CSF absorption.


At relatively low cerebrospinal fluid (CSF) pressures, the majority of CSF drainage in 6- to 8-month-old sheep occurs through the cribriform plate into lymphatic vessels in the nasal submucosa. As CSF pressures are elevated, other absorption sites are recruited and these may include transport through arachnoid projections. To test for the transport of CSF directly into the venous sinus, the concentration of a tracer (131I-human serum albumin [HSA]) administered into the CSF compartment was measured in the confluence of the intracranial venous sinuses (torcular) and in the peripheral blood (inferior vena cava). CSF pressures were adjusted to favor absorption. Enrichment of the CSF tracer in the cranial venous system was most evident when the CSF-venous sinus pressure gradients were high. Peak concentration differences occurred 90 s after the CSF pressures were elevated. When pressure gradients approached 30 cm H(2)O, tracer concentrations in the torcular were approximately twofold higher than those observed in peripheral blood. The greatest concentration differences favoring the torcular were obtained when the CSF-venous sinus pressure gradients were elevated to high levels (20- to 40 cm H(2)O) and when CSF access to the paranasal lymphatics and CSF transport into the spinal subarachnoid compartment were prevented. In conjunction with previous studies, these results are compatible with the view that CSF absorption in the adult animal can occur directly into the cranial venous system. However, contrary to the established view, this pathway may represent a secondary system that is recruited to complement lymphatic transport when global absorption capacity is stressed or compromised.


Transmission and scanning electron microscopical observations in the rat indicate a considerable capacity of the spinal meninges to reabsorb cerebrospinal fluid. The density of blood vessels and lymphatics in the duramater is extremely high, particularly in the areas of meningeal funnels and spinal nerve root sleeves. Arterioles with closely related unmyelinated nerve fibres, many fenestrated capillaries and venules predetermine these areas as sites where absorption processes could take place. At certain sites of the meningeal angle region, the arachnoid membrane, mostly multilayered, is reduced to only three or four layers. Intercellular discontinuities and cytoplasmic fenestrations occurring in the arachnoid lining cell layer result in direct communications between the subarachnoid space and cisterns of the arachnoid "reticular layer". These cisterns are partly fluid-filled, partly occupied by a net of collagen fibre bundles. Some cisterns harbour macrophages that often project filiform processes through the lining cell layer into the subarachnoid space, contacting cerebrospinal fluid. Desmosomes and gap junctions are present in all layers of the arachnoid. However, tight junctions and the continuous electrondense intercellular gap, known to occur normally within the "arachnoid barrier layer", were not seen in many
sites of the meningeal angle region. Numerous arachnoid cells display a high degree of vesiculation. Cationized ferritin, introduced in vivo into the rat subarachnoid space, passes inter- and intracellularly from the cerebrospinal fluid compartment through the arachnoid membrane, reaching dural blood vessels and lymphatics. Tracer could be visualized both in the cytoplasm of the endothelium and on the luminal surface of the cells. Tracer also passed through pial cell layers into pial vessels, through leptomeningeal sheaths into vessels crossing the subarachnoid space, into the connective tissue compartment and into vessels of spinal dorsal root ganglia. In the angle region, a particularly large number of macrophages can be found on the surface of leptomeninges, within the arachnoid reticular layers, and in close relation to dural and epidural capillaries, venules and lymphatics. Their possible role in the process of cerebrospinal fluid reabsorption is discussed.


PURPOSE: To develop quantitative MRI techniques to measure, model, and visualize cerebrospinal fluid (CSF) hydrodynamics in normal subjects and hydrocephalic patients. MATERIALS AND METHODS: Velocity information was obtained using time-resolved (CINE) phase-contrast imaging of different brain regions. A technique was developed to measure the change of lateral ventricle (LV) size. The temporal relationships between the LV size change, CSF movement, and blood flow could then be established. The data were incorporated into a first-principle CSF hydrodynamic model. The model was then used to generate specific predictions about CSF pressure relationships. To better-visualize the CSF flow, a color-coding technique based on linear transformations was developed that represents the magnitude and direction of the velocity in a single cinematic view. RESULTS: The LV volume change of the eight normal subjects was 0.901±0.406%. Counterintuitively, the LV decreases as the choroid plexus expands, so that they act together to produce the CSF oscillatory flow. The amount of oscillatory flow volume is 21.7±10.6% of the volume change of the LV from its maximum to its minimum. CONCLUSION: The quantification and visualization techniques, together with the mathematical model, provide a unique approach to understanding CSF flow dynamics.


A severe complication, c. s. f. hypotension (CSFH), developed in 9 patients after intracranial manipulations for meningioma (4), intracranial aneurysm (3), and subdural hematoma (2). It occurred on the second or third postoperative day and was characterized by rapid development of general cerebral disorders (even to deep loss of consciousness) and aggravation of focal disorders. An important role in the differential diagnosis of the hypotensive and the hypertensive syndromes is attached to lumbar puncture which in cases of CSFH reveals very low c. s. f. pressure or none at all. Effective therapy for the disease includes subarachnoid infusion of up to 50-80 ml of physiological solution through a lumbar puncture and daily intravenous infusions of fluio (2 500-3 000 ml).