In a large cine MR imaging study of 28 healthy volunteers and 11 patients with hydrocephalus, Kim et al.\textsuperscript{10} noted that patients with NPH had a net flow of CSF through the aqueduct from the fourth ventricle into the third, which they noted is opposite to that found in healthy volunteers. The “retrograde” net flow reversed to the normal “anterograde,” cranial-caudal flow pattern after VP shunt placement. This observation has important implications for an understanding of fluid dynamics of hydrocephalus and the effect of CSF shunting. It means that, in hydrocephalus, the brain parenchyma absorbs CSF via a transependymal route rather than producing it. Shunting is able to reverse this abnormality and allow flow again in the normal brain-to-ventricle route. We have confirmed the findings of Kim et al. in healthy volunteers and in a small group of patients with NPH and provide a computational model based on fluid dynamics to explain their findings and our own. To see whether the hyperdynamic flow patterns that they found in hydrocephalus cause abnormal ventricle wall movements, we also measured lateral ventricular wall displacement in our healthy volunteers and in the patients with NPH. We found that wall movements were slightly larger in the NPH patients but did not change significantly with shunting, a result predicted by our fluid dynamic modeling. This finding has clinical implications for shunt design. If the pulsating CSF flow were the root cause of ventricular wall movements and cerebrospinal fluid flow in hydrocephalus

Clinical article

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Object. The dynamics of fluid flow in normal pressure hydrocephalus (NPH) are poorly understood. Normally, CSF flows out of the brain through the ventricles. However, ventricular enlargement during NPH may be caused by CSF backflow into the brain through the ventricles. A previous study showed this reversal of flow; in the present study, the authors provide additional clinical data obtained in patients with NPH and supplement these data with computer simulations to better understand the CSF flow and ventricular wall displacement and emphasize its clinical implications.

Methods. Three NPH patients and 1 patient with aqueductal stenosis underwent cine phase-contrast MR imaging (cine MR imaging) for measurement of CSF flow and ventricle wall movement during the cardiac cycle. These data were compared to data previously obtained in 8 healthy volunteers.

The CSF flow measurements were obtained at the outlet of the aqueduct of Sylvius. Calculation of the ventricular wall movement was determined from the complete set of cine MR images obtained axially at the middle of the lateral ventricle. The data were obtained before and after CSF removal with a ventriculoperitoneal shunt with an adjustable valve. To supplement the clinical data, a computational model was used to predict the transmural pressure and flow.

Results. In healthy volunteers, net CSF aqueductal flow was 1.2 ml/minute in the craniocaudal direction. In patients with NPH, the net CSF flow was in the opposite direction—the caudocranial direction—before shunt placement. After shunting, the magnitude of the abnormal fluid flow decreased or reversed, with the flow resembling the normal flow patterns observed in healthy volunteers.

Conclusions. The authors’ MR imaging–based measurements of the CSF flow direction and lateral ventricle volume size change and the results of computer modeling of fluid dynamics lead them to conclude that the directional pattern and magnitude of CSF flow in patients with NPH may be an indication of the disease state. This has practical implications for shunt design and understanding the mechanisms that produce hydrocephalus.

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Keywords • hydrocephalus • normal pressure hydrocephalus • ventricular wall movement • CSF flow • mathematical model

Abbreviations used in this paper: cine MR imaging = cine phase-contrast MR imaging; NPH = normal pressure hydrocephalus; VP = ventriculoperitoneal.
dilation, then reducing such flow could be easily achieved by constructing a mechanical system that dampens CSF oscillations. Our findings suggest such a solution would not work and that the fundamental problem to be treated is the accumulation of CSF in the ventricles and the abnormal flow into brain tissue.

Methods

The details of the cine MR imaging techniques used in the study are described in full in our previous article. The scans were performed using the 3T GE Sigma system (GE Medical Systems) equipped with a standard quadrature birdcage head coil. Measurements previously obtained in 8 healthy volunteers (4 men and 4 women, mean age 35 years, range 23–52 years) were used as control data.

Three patients diagnosed with NPH and one with congenital aqueductal stenosis were studied before and after treatment with VP shunt placement (adjustable valve Strata Shunt; Medtronic Inc.). The diagnosis of NPH was made on the basis of clinical criteria, primarily gait disturbance and early meningeal changes, and confirmed by a positive response to 3 or 4 days of continuous lumbar drainage. In retrospect, the third patient with the diagnosis of NPH did not have the syndrome. He did not improve clinically with shunting, his ventricular size did not decrease, and his dementia progressed without further gait problems. The patient with aqueductal stenosis underwent shunt placement because of headaches and memory problems 12 years after a previous shunt revision. This case is included because it provides an opportunity to study ventricle wall dynamics after shunt treatment of obstructive hydrocephalus and not because of issues related to aqueductal flow. The patients underwent cine MR imaging 1 week before shunt placement and 2–6 months postoperatively. They all signed consent forms for the additional MR imaging, and the study was approved by the institutional review board of the University of Chicago. Some of the data obtained in the healthy volunteers were previously published, but these data have been reanalyzed for this paper.

The cine MR images were collected at an axial slice across the middle of the lateral ventricles to investigate the lateral ventricle volumetric change and an axial slice across the junction between the aqueduct of Sylvius and the fourth ventricle to measure the CSF flow rate. For the slice across the lateral ventricles, velocities in 3 directions were measured; images obtained at 16 equidistant time frames were reconstructed per cardiac cycle. For the slice at the other location, only the velocity perpendicular to the slice plane was measured; images were acquired at 32 equidistant time frames per cardiac cycle. Flow compensation and peripheral gating were applied for the 2 cine MR imaging measurements. A low maximum measurable velocity of 5 cm/second was chosen as the limit to achieve a reasonable velocity resolution. Other MR imaging parameters were as follows: TR 18 msec, TE 8.3 msec, flip angle 20°, FOV 240 mm, slice thickness 5 mm, matrix size 256 × 192, and 75% phase field of view to achieve an effective matrix resolution of 256 × 256. The pixel velocity in regions of CSF was corrected by subtrac-

tion of the time-average “velocity” of a nearby solid brain tissue within a 29 × 29 mm² region having this pixel at its center.

The CSF flow at the junction of the aqueduct of Sylvius and the fourth ventricle was estimated by the product of the average velocity through the region multiplied by the cross-sectional area. To estimate lateral ventricle wall movement, the edge between solid brain tissue and the lateral ventricle was first manually drawn based on an image that showed the best cross-section from a T1-weighted image that was acquired at exactly the same scan plane. This drawing marks the initial pixel positions during a full cardiac cycle. The position shift of each pixel at the edge of the lateral ventricle was then estimated for each time frame of the cardiac cycle by integrating the velocity over time, including all 3 components of the velocity.

Results

Flow data previously obtained in 8 healthy volunteers were reanalyzed to calculate the net flow per cycle and then the net flow per minute. Every one of these individuals had net flow out through the aqueduct, cranial to caudal (Table 1). According to our standardized technique, the mean flow (±SD) was 1.14 ± 0.599 ml/minute (range 0.5–1.9 ml/minute). The mean value for ventricle wall movement in these same controls was 0.168 ± 0.038 mm (range 0.12–0.18 mm).

In contrast, 2 of the 3 patients who had the initial clinical diagnosis of NPH had a net flow into the third ventricle and lateral ventricles. The third patient, who by later clinical course proved not to have NPH, had flow in the normal direction. After VP shunting using an adjustable valve on a low pressure setting, the retrograde flow reversed in the first case and was markedly reduced in the second. In the patient who did not actually have NPH, the cranio-caudal flow increased. Table 1 also shows calculations of the displacement of the ventricle wall and lateral ventricle volume before and after shunting. The ventricle wall displacement was higher in hydrocephalic patients than in the controls, 0.21–0.30 mm compared with a mean value of 0.17 mm. Shunting had no significant effect on this movement. In the 2 patients who had excellent clinical responses to shunting, with major improvements in gait and mentation, the ventricle size decreased and the caudocranial flow pattern reversed to the normal direction. In the patient with minimal clinical improvement (the patient in Case 3), there was no change in ventricle size, and flow was initially cranio-caudal; with shunting, the cranio-caudal flow increased. The patient with congenital aqueductal stenosis responded to shunting with a complete remission of his symptoms of mental confusion and headaches. His ventricle size decreased, and the ventricle wall movement slightly increased after shunt placement.

Models of CSF Flow and Ventricle Wall Movement

In a recently published paper, we modeled the combined blood flow, CSF flow, and brain tissue dynamics of healthy individuals and patients with hydrocephalus. Figure 1 shows the model and areas of interest for the current
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The direction of flow is schematically shown, as well as wall displacement. The model predicted a reversal in the aqueduct net flow as the ventricle size enlarges due to impaired CSF absorption in the subarachnoid space. That model also predicted that, as the ventricles enlarge, the movement of the ventricular wall increases. This was shown as a graph of wall movement versus percentage change of ventricle size (Fig. 6 in Linninger et al.14).

To predict the effect of VP shunting on CSF flow, we added a drainage function with a valve set at a low resistance in the right lateral ventricle of the model. After producing hydrocephalus by an absorption block, opening the drain resulted in the normalization of the flow pattern. Figure 2 shows the predicted transmural pressures calculated from the flow in healthy volunteers and in patients with hydrocephalus before and after shunt treatment. The magnitude of the average ventricular pressure (dashed line) varies in comparison with the average parenchymal pressure (solid line). In the healthy volunteers and the shunt-treated patients, ventricular pressure was lower than brain parenchymal pressure; this relationship is reversed in untreated hydrocephalus.

**Discussion**

Our cine MR imaging studies show changes in the direction or magnitude of the net CSF flow in patients after shunting but no significant change in the ventricle wall movement. In our healthy volunteers, the net flow is outward through the aqueduct. This flow pattern was shown by Greitz et al.8 and confirmed by Huang et al.9 Kim et al.10 also found outward net flow in 28 healthy volunteers and what they call “retrograde” or reverse net flow, caudal to cranial, into the ventricles in 11 NPH patients. The flow normalized after shunting. Our findings in our NPH patients confirm this reversal of flow with shunting. The flow of CSF into the ventricular system in hydrocephalus should not be a surprise. Cisternography with 111In-EDTA was one of the early methods used to try to differentiate cerebral atrophy from clinically significant hydrocephalus. Distribution of the marker into the ventricular system from the basal cisterns and only later over the convexities was taken as an indication of communicating hydrocephalus. While the test is poorly predictive of the outcome of shunting, it still indicates a profoundly abnormal flow.

<table>
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<tr>
<th>Case or Group</th>
<th>Dx</th>
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<th>Wall Displacement (mm)</th>
<th>LV Vol (ml)</th>
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<td>8 healthy volunteers†</td>
<td></td>
<td>1.14 ± 0.599</td>
<td>0.168 ± 0.038</td>
<td>33 ± 9.4</td>
</tr>
</tbody>
</table>

* The patient in Case 4 did not have improvement with shunting and did not in retrospect have true NPH. Abbreviations: AS = congenital aqueductal stenosis; LV = lateral ventricle; NP = measurement not performed.
† Group mean values (± SD) are given for the 8 healthy volunteers.

**Table 1: Observations of net flow and wall displacement during cardiac cycle and calculation of ventricle volume in patients with NPH before and after treatment and in healthy volunteers***

**Fig. 1.** Schematic of the model highlighting areas of interest. Note that the normal pattern of CSF flow is from the third ventricle (3V) to the fourth ventricle (4V) and that this reverses in hydrocephalus. The obstruction to flow out of the subarachnoid space (SAS) to the venous sinus (vSinus) causes a reversal of the pressure gradient from the brain parenchyma to the lateral ventricles (LV), which in turn results in the flow direction change. The model predicts this reversal. The shunt reduces the gradient and brings the flow pattern back to normal. cAr = carotid artery; Ar = artery; Al = arteriole; Cp = capillary; V = vein; VI = venule. Superscript L and R refer to left and right, respectively. The thickness of the arrows indicates volume of flow and the relative size of the boxes indicate degree of wall displacement relative to the normal size.
pattern in many patients with hydrocephalus. Prior physiological measurements on normal production and convection of interstitial fluid by the brain parenchyma clearly established flow into the ventricles from the brain.\textsuperscript{1,5} This fluid contributes up to one-third of the total amount of CSF exiting through the aqueduct. Increasing ventricular pressure slows this convective flow.\textsuperscript{5} The net cranial-to-caudal flow in healthy individuals is seen with cine MR imaging\textsuperscript{9,10} and it is within the range measured by earlier physiological tracer studies. All 8 of our healthy volunteers had this net outward flow pattern.

Shunting has a major effect on CSF dynamics and, in particular, on the pressure-volume relationship.\textsuperscript{3,4} The CSF compartment becomes more compliant after shunting. Even though the shunt is placed into the ventricle and removes CSF, after shunting, the flow pattern in our patients reversed to normal. Most likely, fluid drainage reduces the small pressure gradient from the ventricle to the brain tissue. The restitution of net CSF production of the brain parenchyma can then occur. Current MR imaging measurements are not sensitive enough to show such slow net fluid movements within the brain parenchyma, so oth-

**Fig. 2.** Computer simulation showing the pressure across the ventricle and brain parenchyma. The normal case (Frame A) shows a higher average brain pressure (solid line), which indicates flow from the brain to the ventricles. Frame B shows higher ventricular pressure (dashed line) due to hydrocephalus, which indicates flow reversal. Frame C shows the effect of fluid removal from the right ventricle and the reversal of pressure to normal.

**Fig. 3.** Computer simulation of CSF net flow in the normal and hydrocephalic brain. Net flow is from the parenchyma to the ventricles in the normal case (left); net flow is from the ventricles to the brain parenchyma in the hydrocephalic case (right).
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er types of methods will be necessary to demonstrate this in humans. The cine MR imaging measurements show only a small increase in ventricle wall displacement during hydrocephalus. Shunting did not decrease this movement, and in our only obstructive case the movement appeared to increase after shunting. In view of the small submillimeter wall movement and its lack of change when ventricle volume decreases, theories that postulate wall movement as a cause of hydrocephalus may have to be reconsidered.

Computational models provide quantitative and qualitative information critical to the understanding of the disease. Our computational model suggests a net flow of CSF into the brain parenchyma during hydrocephalus, as shown in Fig. 3. The fluid flow throughout the brain is plotted, showing that, in hydrocephalus, the net flow is into the brain, but reverses or decreases in the treated patient.

The slight increase in wall movement is also predicted by our model. The measurements that we have made on ventricle wall movement before and after CSF shunting are difficult to interpret without an understanding of the forces at play at the ventricular wall during the cardiac cycle. For this, the stresses on the wall need to be modeled using the known flow patterns of CSF and the laws of fluid dynamics. Using a number of modeling techniques, we have simulated CSF and ventricle wall movements in the normal condition and in communicating hydrocephalus. The simulation results are consistent with our cine MR imaging measurements. As would be expected, as hydrocephalus develops, fluid increases in the ventricles, and the entire compliance of the intracranial space is reduced and pressure increases. This increase is reflected also in an elevated pulse pressure. The maximum driving force on the ventricle wall due to the expansion of the less compliant brain is greater and results in a larger excursion of the wall. Because the ventricles are enlarged, the tone and fro movement of CSF through the aqueduct is significantly increased. This increased flow velocity has been taken as a measure of hydrocephalus and reflects larger ventricles and reduced intracranial compliance. Our cine MR imaging measurements show an approximately 50% increase in flow velocity in our patients with hydrocephalus compared to that of healthy volunteers. It should be noted that these movements are very small, only tenths of a millimeter. Using a viscoelastic model of the brain parenchyma, Wilkie et al. estimated that for a pulse pressure of 10 mm Hg, simulating early hydrocephalus, the wall movement would be approximately 100 nm. For healthy individuals, the movement would be even less, perhaps 50 nm.

Our computational model has been extended to show the effect of shunting on aqueductal flow and ventricle wall movement. The results of this modeling are consistent with our MR imaging measurements of ventricle size and wall movement. Of note is how small the calculated forces acting on the ventricle wall are during the cardiac cycle. The model predicts a transmural pressure in normals ranging from 0.6 mm Hg in systole to minus 0.2 mm Hg in diastole. This cycle of transmural pressure drives CSF back and forth through the aqueduct. In hydrocephalus, stroke volume is known to increase, but according to our model, the transmural pressure is no higher. This is in spite of a higher pulse amplitude and absolute CSF pressure. The larger stroke volume is most likely due to the lower compliance in the intracranial space. As others have shown, the flow through the aqueduct is directly related to its increasing size in hydrocephalic patients and also to ventricle size. Intuitively, if the ventricle surface enlarges and the ventricle wall movement is the same, more CSF will be driven to and fro in the aqueduct for the same pressures.

What are the stresses due to the cyclic pressure gradients on the ventricle wall? The distribution of stress has been estimated by means of finite element models for hydrocephalus, and these models predict that the regions of high curvature will be subjected to higher stresses than the flat areas. This modeling has been used to explain the early enlargement and edema in the frontal, temporal, and occipital horns. The wall movement we measured is an average of all the movements along the ventricle surface of the MR imaging slice through the largest area of the lateral ventricles. The technique is not sensitive enough to accurately measure different regions of the ventricle such as the flat surface along the thalamus or curved regions, such as frontal horns. However, the gradual displacement of the ventricles in hydrocephalus is in the order of centimeters, with volume changes often greater than 100 ml. This is 2 orders of magnitude higher than the cyclic wall movements of 0.1–0.3 mm. This means that the stresses as hydrocephalus develops are at least 100 times greater than those due to pulsatile movement. If shunting were to work primarily by reducing pulse pressure, one would expect the wall movements to decrease after shunt placement, but this is not the case for the 2 patients who had decreases in ventricle volume. A surgical device that dampens pulse amplitude alone would not deal with the primary pathology. The blockage to CSF absorption in the subarachnoid space must be compensated for by providing a new low-resistance pathway, one that is large enough to decrease the abnormal pressure gradient and that allows fluid flow from the brain to the ventricle.

Conclusions

The cine MR imaging findings of Kim et al. and our confirmatory observations provide an important clue to how shunts work. Shunting by removing fluid enables the brain once again to return to the normal pattern of transpennymal flow into the ventricles. A small steady pressure gradient in the wrong direction into the brain tissue is enough to enlarge the ventricles. Our measurements and those of others of the net flow reversed aqueductal flow suggest such a gradient. Recent very precise measurements of pulse pressure amplitudes over thousands of cycles in hydrocephalus patients are also consistent with this analysis. In these patients, the median pressure amplitude was 0.4 mm Hg higher in the ventricles than in the brain parenchyma. In one patient who had the monitors still in place after shunt placement, the pulse amplitude difference was reversed, the pressure becoming higher in the parenchyma than in the ventricles. These small differ-
ences in pressure among patients are consistent with our cine MR imaging measurements. Modeling based on basic fluid dynamics also supports the view that small pressure gradients create ventricular enlargement.1,13

There are clinical consequences to this view of hydrocephalus. The first is that a mechanical system that damps the increased oscillatory fluid movements found in hydrocephalus is unlikely to decrease ventricle size or reduce symptoms. Such a system would be easy to construct by providing a compliant chamber for CSF to flow into and out of. However, unless CSF is removed and the pressure gradients reversed, hydrocephalus will not change.

Another clinical consequence of this understanding is that the shunt brings the flow pattern of CSF in the brain back to normal. A shunt that continues to function when normal flow patterns are achieved may cause harm by overdrainage. Unfortunately, at present there is no easy way to adjust shunt flow precisely to the value that would produce a normal state. “Smart shunts” that adjust to physiological measurements have been suggested but have not yet been developed for use in patients.

Measurements of flow patterns of CSF as obtained by cine MR imaging may be useful for predicting the outcome of shunting. At present, such measurements are time consuming and expensive. For the measurements to be worthwhile, they would have to be more accurate than current lumbar CSF drainage testing. Larger cine MR imaging studies will have to be done to establish how well flow reversal correlates with clinical response to shunting. If proven to be accurate in predicting patient outcome, the measurements have the great advantage of being noninvasive.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Author contributions to the study and manuscript preparation include the following. Conception and design: Penn, Linninger. Acquisition of data: Basati, Guo. Analysis and interpretation of data: Sweetman, Guo. Drafting the article: Penn, Basati, Sweetman, Guo. Critically revising the article: Basati, Sweetman, Linninger. Reviewed final version of the manuscript and approved it for submission: Penn. Administrative/technical/material support: Sweetman, Linninger. Study supervision: Penn. Other: Basati (simulations).

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References


