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A preliminary exploration of acute intracranial pressure-cerebrospinal fluid production relationships in experimental hydrocephalus

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Abstract:

CONTEXT: By occluding the fourth ventricle simultaneously obtaining telemetric data on intracranial pressure (ICP) and cerebrospinal fluid (CSF) production, the authors of this study investigate a variety of physiologic parameters in cases of experimental hydrocephalus.

AIMS: The aim of this study is to provide a new context on the disrupted homeostasis in hydrocephalus and guide toward improved treatment based on multiple physiological parameters.

MATERIALS AND METHODS: Hydrocephalus was induced in ten 21-day-old Sprague–Dawley rats by blocking the flow of CSF to the fourth ventricle with kaolin. Ten days post induction, when physical signs of ventriculomegaly reached Evan's ratio (ER) of ≥ 0.46 , CSF flow and ICP were measured while manipulating body position (0°, 45°, 90°) and heart rate.

RESULTS: In hydrocephalic animals (ER ≥ 0.46), we found a near-steady average acute ICP (13.638 ± 2.331) compared to age-matched controls (ER < 0.30) (13.068 ± 8.781), whose ICP fluctuated with the position. Hydrocephalic and controls exhibited an insignificant degree of parabolic shifts in CSF production when body position was changed from prone to 90° and again when moved back to the prone position, a trend more noteworthy in controls ($P = 0.1322$ and 0.2772). A Pearson's Correlation found CSF production and ICP to be correlated at baseline 0° posture ($P = 0.05$) in the control group, but not the hydrocephalic group. Weight appeared to play a role when animals were held at 90°. No significant changes in ICP or CSF flow patterns were observed when the heart rate was increased within either group.

CONCLUSIONS: These preliminary findings suggest that our standard assumptions of posture-dependent changes in ICP created using data from physiologic data may be inaccurate in the hydrocephalic patient, and thus describe a need to further explore these relationships.

Keywords:

Cerebrospinal fluid production, experimental hydrocephalus, hydrocephalus, intracranial pressure, ventriculomegaly

Introduction

Cerebrospinal fluid (CSF) is a clear, mildly proteinaceous plasma ultrafiltrate that bathes the brain and circulates throughout the central nervous system (CNS). Production of CSF generally takes place at

the choroid plexus— a highly vascularized tissue present in each of the CNS ventricles. CSF has a multitude of functions, including but not limited to, protection of the brain from mechanical injury, nourishment, and molecular transport.^[1] There is an estimated 150 ml of CSF circulating in an average adult at any given time, with nearly 0.3–0.4 ml being produced per minute and 430–530 ml being produced each day.^[2]

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Hydrocephalus is a condition in which CSF accumulates inside the ventricles of the brain, causing ventriculomegaly. This is commonly due to an obstruction in the ventricular system, which leads to poor circulation and subsequent ballooning of the ventricles but can also be due to congenital malformations, increased endogenous CSF production capacity by the choroid plexus, decreased CSF resorption ability, infection, and hemorrhage. The enlargement of the ventricles puts additional pressure on the surrounding brain tissue, ultimately leading to an increase in intracranial pressure (ICP) and development of symptoms, which include mild-to-severe headache, vomiting, altered mental status, visual changes, cognitive impairment, poor concentration, and gait disturbances.^[3] The most common treatment for hydrocephalus is the implantation of a shunt system, comprised typically of four components: a ventricular catheter, a reservoir, a valve, and a distal catheter.^[3] The purpose of the shunt system is to provide an avenue for excess CSF to exit the ventricles, decreasing the size of the ventricles, decreasing ICP, and restoring a physiologic balance between CSF inflow and outflow. CSF drainage through the shunt is not always physiologic. In part, this is due to the dependence of the CSF outflow through a shunt system on a standard static pressure differential. Such model only takes into account the pressure differential and wholly disregards CSF production rate dependencies such as cerebral blood flow/mean arterial pressure, thoracic respiration flow patterns, posture, endogenous brain pressure, exercise, age, and body mass index.^[4]

Despite recent advances in anti-siphon devices, we still see shunt complications arise from under- and over-drainage, including but not limited to slit ventricle syndrome, subdural hematoma, and restoration of hydrocephalus symptoms.^[5] For example, the distal pressure rapidly decreases when a patient moves from a supine to an upright position. This drop of pressure magnifies the pressure differential between the two ends of the shunt causing additional CSF to flow out of the ventricles. This siphoning effect can lead to a number of complications, including the collapse of the ventricles (slit-like ventricles or slit ventricle syndrome), hemorrhage, and/or chronic headaches.^[6] Here, we explore the pathophysiology of hydrocephalus by way of

studying dependencies between CSF production and ICP in order to ultimately advance our treatment paradigms with more physiological shunting.

Subjects and Methods

Hydrocephalus induction

All methods were approved by the Institutional Animal Care and Use Committee at Wayne State University. All animals were subjected to the experimental sequence seen in Figure 1. 10 Sprague–Dawley rats (7 males, 3 females) underwent cisternal kaolin injections at PND21, and were evenly divided into two groups: control cohort and hydrocephalic cohort. Rats were weighed before surgery and anesthetized with 2%–3% isoflurane gas. Supplemental oxygen was set at 2 L/min. Once a deep plane of anesthesia was achieved (confirmed with respiration rate equaling half normal and absence of toe pinch reflex), isoflurane was lowered to a weight-specific maintenance level. Animals were prepped for surgery on a surgical towelette; an electric shaver (Braun) was used to shave the area where the injection would take place and betadine/isopropanol were applied in triplicate in an alternating fashion. Rats were transferred to the stereotaxic head frame (Kopf, Model 900), and the ear bars were affixed to the animal's head, where the temporal bone meets the zygomatic arch. For the control cohort, a 30G needle was used to introduce 50 µl of sterile normal saline solution into the cisterna magna over 10 s, according to others.^[7] For the hydrocephalic cohort, 50 µl of 25% (w/v) kaolin solution in sterile saline (Sigma Aldrich) was introduced into the cisterna magna over 10 s. After injection in both groups, the needle was slowly withdrawn, and rats were moved to a clean cage for recovery. Postoperatively, 4% lidocaine was applied to the injection site and animals were monitored for abnormal behavior including, but not limited to head tilt, lethargy, and circling.

Mineral oil injection

To ensure CSF from both groups flowed only through the conduit formed by the flow meter tubing in the brain, molecular-grade mineral oil (Sigma Aldrich) was used to block CSF from escaping through the aqueduct of Sylvius. This was done to both groups to allow the

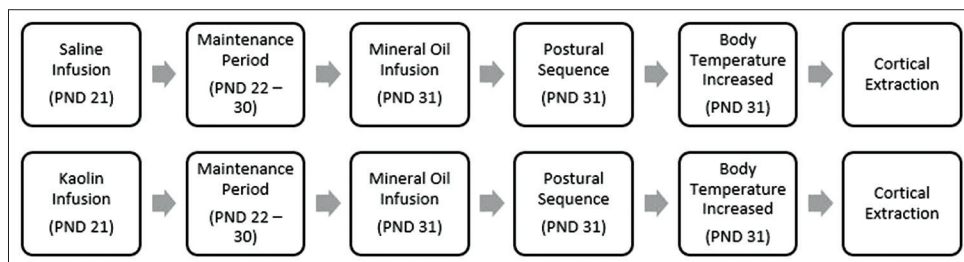


Figure 1: Experimental schematic demonstrating the sequence of events each group of animals was subjected to to harvest relevant physiologic parameters

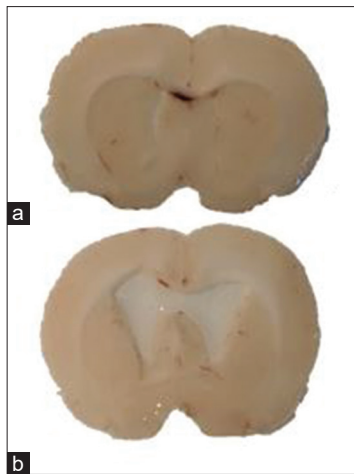


Figure 2: Evans indices representations; (a) Section of a control animal's cerebral cortex from the EI <0.3 group demonstrating normal-sized ventricles. (b) A cerebral cortex section of an animal from the EI >0.46 group demonstrated ventriculomegaly

Table 1: Experimental schematic and postural sequence

Category (body position relative to operating table surface)	Duration (min.)
0°/180°	2
Repositioning (not used in data analysis)	Variable
Re-establish baseline (not used in data analysis)	1
45°	2
Repositioning	Variable
Re-establish baseline	1
90°	2
Repositioning	Variable
Re-establish baseline	1
45°	2
Repositioning	Variable
Re-establish baseline	1
0°/180°	2

Table 2: Evans ratio analysis summary on cortices extracted from animal subjects

	Evans ratios for groupings ^a	
	Saline	Hydrocephalic
N	4	4
Range	0.28-0.32	0.44-0.63
Mean±SD	0.30±0.015	0.52±0.086

^aDistance from midline of maximal lateral ventricle width to the cortical tissue width on gross specimen sections

evaluation of CSF production through flow through the meter independent of prior aqueductal obstruction. Rats were anesthetized and placed in stereotactic head frame as described above for injection into the aqueduct of Sylvius.^[8]

Probe insertion

A midline skin incision was used to expose the surface of the skull between bregma and lambda. Alm retractors

were placed between the flaps, and connective tissue was bluntly dissected using sterile cotton swabs until bregma and lambda were visualized. The location of bregma was confirmed, and stereotactic measurements were noted. The locations of insertion were selected to allow the measurement of ICP and CSF production without compromising the integrity of nearby sinuses. A 5-mm round burr hole was drilled (center 6 mm posterior to bregma; ±2.5 mm lateral to midline; on either side), and an incision in the dura was created using angled Vannas scissors. A 27G PTFE tubing section attached to a liquid flow meter (Sensirion SLI) was gently inserted 0.38 cm, such that the tubing tip was in the right ventricle underlying the burr hole. The placement was assured through nonzero flow readings and stereotactic guidance. The tubing section was secured to the skull using Vetbond tissue adhesive (3M). Flow was recorded using a data acquisition system (Sensirion RS485). A 1.6F piezoelectric flexible pressure probe (Transonic) was inserted 2 mm into space above the left ventricle and secured using Vetbond. A baseline measurement of outflow was obtained using Sensirion's Sensor Viewer software, and baseline ICP was recorded postcalibration using a connected Transonic Scisense SP200 Data Acquisition system after the probes were situated for 2 min. A series recorder (iWorx) was used to read out the ICP oscillations. ICP was recorded at a sampling speed of 1,000 samples/second. Respiration rate, assessed by the inspiration cycles, was recorded every 5 min and anesthesia was adjusted accordingly to keep animals at one-half their normal respiration rate.

Postural adjustments

Rats were placed in ventral recumbency on an adjustable platform, and recording began. Briefly, animals were positioned at angles relative to the horizontal surface with flow and pressure recordings acquired for 2 min with no manipulation during that time. Between recordings, the platform was realigned, followed by a 1-min period to re-establish the baseline. Every animal followed a sequence of platform adjustments, re-establishment, and recordings in the order of: 0°, 45°, 90°, 45°, 0° [Table 1]. Body temperature, reflexes, and respiration rate were monitored regularly throughout the entire procedure.

Body temperature and heart rate

In an effort to increase stroke volume, plasma flow, cardiac output, cardiac index, and heart rate, body temperature was increased. Once postural testing was complete, each rat was removed from the stereotaxic headframe, then placed on a heating pad and monitored closely using a rectal thermometer until body temperature reached 40°C (approximately 15 min with intermittent removal from warming). ICP and flow were recorded over time and for 2 min following maximum body temperature.

Assessment of ventriculomegaly

To ensure the mineral oil did not lead to acute expansion of the lateral ventricles, the Evans Index of individual animal brains were assessed. Cerebral cortices were extracted from the cranium postoperatively and immersed in 4% paraformaldehyde for 24 h after which they were stored in $\times 1$ phosphate-buffered saline solution. Animals injected with kaolin but did not develop hydrocephalus ($ER < 0.46$) were removed from the study to select for the complete induction of experimental hydrocephalus and ventriculomegaly.

Statistics

After analysis for normalcy and homoscedasticity, a two-way repeat measures ANOVA was used with an alpha value set to 0.05 and sphericity assumed. Sidak's multiple comparisons test was performed to observe *post hoc* multiple comparisons. Sources of variation analyzed included interactions, position, animal temperature, degree of hydrocephalus, matching effectiveness, and residual (error). Continuous endpoint, two independent sample size analyses were conducted at varying positions and body temperatures to reveal estimates of sample size. Area under the curve was also assayed in all groups based on each individual animal. Finally, a two-tailed Pearson's r correlation was performed, when appropriate, to determine the correlation between two groups with 95% confidence interval.

Results

Hydrocephalus induction and Evan's index

We compared the saline and kaolin plus mineral oil groups for statistical variance across Evan's ratios (ERs). Figure 2 demonstrates how severely hydrocephalic animals developed strikingly large lateral ventricles that often contained evidence of blood as well as diffusely thinned septa pellucida. ERs between the kaolin ($ER = 0.525 \pm 0.086$) and saline ($ER = 0.302 \pm 0.015$) groups were compared after postural manipulation and sacrifice and were found to be significantly different ($P = 0.0125$) [Table 2].

Postural influence on intracranial pressure and cerebrospinal fluid outflow

As measured, postural change alone significantly manipulates ICP ($P = 0.0095$), but not flow alone ($P = 0.1332$). The degree of ventriculomegaly, as grouped into the saline control (Evan's Index of < 0.30) and kaolin (Evan's Index ≥ 0.46) groups, does not significantly affect baseline ICP or flow, although there was an obvious trend in both the area under the curve and mean values showing that dependence exists between ICP and postural change in nonhydrocephalic animals that is ablated in hydrocephalic animals ($P = 0.1973$).

The interaction between hydrocephalus status (kaolin versus control groups) and postural change was insignificant ($P = 0.8961$). Matching was very effective in this grouping ($P < 0.0001$), indicating that a source of variance here was deviation in each animal rather than across the group.

The trend indicating dependence on hydrocephalus status shows that sequential postural adjustment elicited a response in hydrocephalic animals differently than their control counterparts. The control group responded to the manipulations in a more predictable manner, where mean ICP is reduced following a change from recumbency to 45° as venous return is reduced. Movement from either prone recumbency to 45° or standing to 45° resulted in a decrease in mean ICP; while movement from 45° to both 90° and prone resulted in an increase in mean ICP [Figure 3]. On the other hand, the hydrocephalic group did not seem to similarly regulate ICP nor compensate for the postural changes throughout the postural adjustment sequence. Analysis

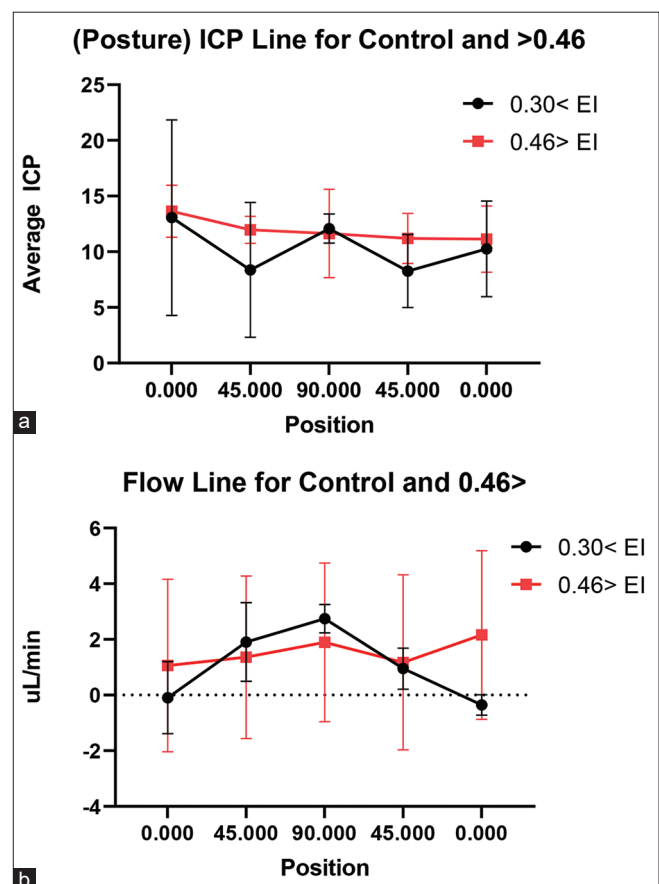


Figure 3: Intracranial pressure and cerebrospinal fluid production averages through postural sequence. (a) A steady and predictable trend for control animals with an EI < 0.3 indicating intact physiologic responses to postural sequence relative to the experimental group with an EI > 0.46 . (b) Cerebrospinal fluid production as reported through the liquid flow meter as animals went through the postural sequence showing the parabolic secretory response of control animals compared to hydrocephalic animals

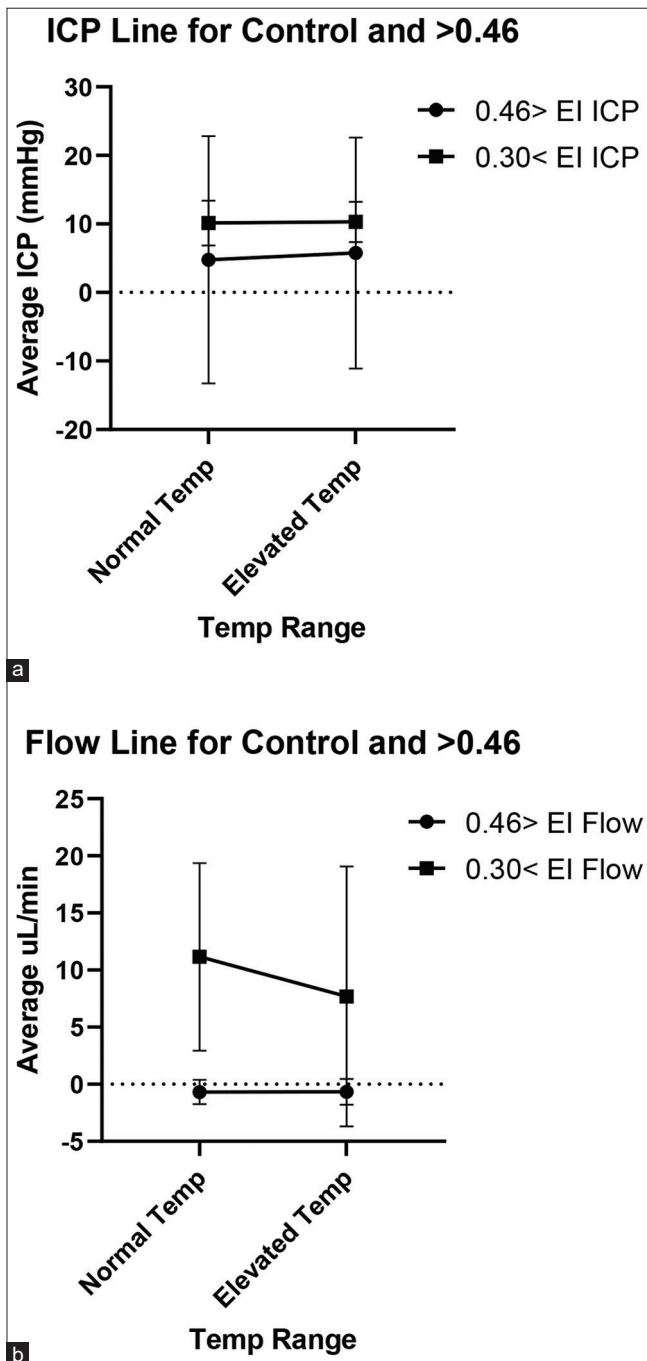


Figure 4: Intracranial pressure and cerebrospinal fluid Production Averages at normal body temperature (35.9°C–38°C) and elevated body temperature (38.5°C–40.1°C). (a) Very mild changes in intracranial pressure in both animal groups with no overall discernable trend. (b) Cerebrospinal fluid production ostensibly decreases in the normocephalic group when temperature is increased and does not significantly change in the hydrocephalic group

of ICP levels during the postural sequence demonstrated that the influence of posture on ICP is independently significant ($P = 0.0095$), but that the presence or absence of ventricular obstruction is not. This would indicate that, acutely, the positioning of animals can manipulate mean ICP without a dependency on dynamic ventricular CSF circulation. ICP-only analysis at different postures based

on the presence or absence of a ventricular obstruction shows that hydrocephalic status positively influences ICP measurements depending on the positioning of the subject ($P = <0.0001$).

Simultaneous measurement of acute CSF flow through the liquid flow sensor as proxy for CSF production in the lateral ventricles demonstrates a nonsignificant parabolic pattern in CSF production for the control group when posture is progressively changed from prone to upright and back to prone. These trends are observed, but less pronounced and not significant, in the hydrocephalic group. Significance was likely not achieved here because of the pronounced variance across the hydrocephalic group. The extent of this variance was not observed in the saline controls, showing a necessity to assume variability in CSF production in hydrocephalus more so than in others.

Dependencies of intracranial pressure and cerebrospinal fluid production on body temperature

Previous experimentation the cardiac-CNS axis has almost strictly drawn upon the dependence of heart rate on ICP whereby bradycardia is observed upon artificially increasing ICP in a variety of animal models.^[9,10] In this study, we set out to find whether the inverse (an ICP dependency on the cardiac cycle) was true. Manipulation of heart rate was made without the use of any pharmacological agents; this was done to ensure no confounding sympathomimetic effects were instantiated on the baseline physiology. The use of a microwavable heating pad allowed for a progressive increase in heart rate, like what would be observed in an exercising patient. Mean acute ICP of control animals did not significantly change when body temperature was increased from the normal range (35.9°C–38°C) to the elevated range (38.5°C–40.1°C), contrary to what would be expected if more blood is circulating through the capillaries of the choroid plexus. The hydrocephalic group's ICP also did not significantly change when the heart rate was increased [Figure 4].

Discussion

Evaluation of the model for acute intracranial pressure and cerebrospinal fluid flow testing

ERs were used to show the degree of ventriculomegaly and indicate the presence or absence of this physical sign of hydrocephalus. While of course, this is not the only indicator of hydrocephalus or ventriculomegaly, it served as an appropriate guide for evaluation of animals with and without initial pathologic sequelae of hydrocephalus. The cutoff of 0.46 aligns with other literature of severe hydrocephalus in the rodent model.^[7,11] The model of measuring CSF production from the lateral ventricles

by Karimy *et al.* demonstrated that occlusion of the ventricular system using molecular-grade mineral oil at the level of the aqueduct of Sylvius can serve to provide a conduit for CSF production measurement on canalization of the cerebral cortex at the lateral ventricles; however, in our experiment, an electronic measurement system was used as opposed to a capillary tube to provide real-time data on production rates.^[8] In addition, the simultaneous use of a fixed piezoelectric pressure transducer allowed for a novel technique to measure long-term physiologic parameters in anesthetized animals. Doing so ultimately minimized potential background aberrations to the data as would have been the case if animals were awake and mobile.

The complex mechanisms regulating CSF production, absorption, circulation, and ICP dynamics are multi-faceted and an area of ongoing research. Based on Starling forces alone, if CSF production was dependent on oncotic and osmotic pressure gradients, an increase in ICP would beget a decrease in CSF production. We do not see this in either animal group in acute measurements, but it is possible this is due to a delay in CSF production response to the ICP change, or simply that we were measuring bulk CSF outflow without necessary granularity. In the case of chronic change between hydrocephalic and control groups, Starling forces would not ultimately explain the pathophysiology of hydrocephalus in this experiment. The aqueductal obstruction set into the animals would not have caused such an increase in ventricular size if CSF production was only based on oncotic and osmotic pressures due to the counterbalance between the luminal and basolateral forces, rather the size of the ventricles would have been expected to not be dissimilar. Yet, what we were able to demonstrate was an increase in ventricular size after 10 days and a decompensation in regulation of the cranial vault upon postural adjustment. This could be seen to imply the presence of an extraventricular drainage system in the CNS, the discovery of which could ultimately lead to more fine-tuned drainage systems.

Relating to physiology

Data presented here demonstrate that animals with ventriculomegaly may not sufficiently self-regulate ICP following rapid, 2-min changes in posture. When animals were moved from 0° (horizontal and prone) or 90° (vertical) to 45°, hydrocephalic animals with Evan's Index >0.46 had higher average ICP than their nonhydrocephalic counterparts (Evan's index <0.30). That is, whereas the control group average ICP fluctuated with postural changes, the hydrocephalic group did not. This suggests that the hydrocephalic animals could not manage average ICP fluctuations dependent on postural changes. Perhaps, there is a disruption in the homeostatic regulation of ICP or CSF absorption and

production that is expressed as the inability to correct average ICP acutely following deviations. This is in line with a study conducted in patients by Poca *et al.* where it was demonstrated that free movement of CSF through the craniospinal junction was required for rapid reductions in average ICP.^[12] This conclusion also lends to the validity of using murine subjects (rats) as an appropriate model for evaluating hydrocephalus. Despite the limitations of their smaller cerebral cortex, relatively slow CSF production, and disparate head-body orientation, the evaluation of CSF dynamics in rats may be consistent in some ways with studies conducted in humans^[12,13] However, the decompensated change in ICP in hydrocephalic animals did not fall in line with the physical framework Venkataraman *et al.* validated against the study by Chapman *et al.* on the relationship between ICP and body position.^[14] This could be due to the relative invasiveness of the experiment or due to the differentially high Evans indices, in which the Chapman study did not relate.

An analysis of CSF production rate shows insignificant dependence on posture, but with a trend demonstrating average flow rate increasing at 90°. This increase at 90° is not observed with hydrocephalic animals. This trend indicates that what little dependence CSF production has on position, it is ameliorated under our kaolin-induced hydrocephalic conditions. Perhaps, there is a dependency between CSF production and average ICP in nonhydrocephalic controls, where CSF production increases, causing a latent decrease in average ICP. Alternatively, these data may be driven by experimental approach since a 90° orientation may have led to additional gravity-dependent CSF outflow. Certainly, a variance in the hydrocephalic animals contributed to the lack of significance between the two groups. This variance is anticipated, as CSF production may be related to the degree of ventriculomegaly. The addition of alternative physiological parameters in future work could inform us more about their relative impacts on both CSF production rate as well as ICP; this would include measurement of cerebral perfusion pressure, respiratory flow patterns, and endogenous brain pressure.

Several reports, especially the recent work by Dreha-Kulaczewski *et al.*, indicate that inspiration is a major regulator of human CSF flow.^[4] The respiration rate was not controlled during the experimental portion of the study. The only time respiration rate was adjusted was to establish and maintain a deep plane of anesthesia (half of the animal's normal rate with isoflurane); furthermore, we did not intubate animals to minimize any influence of breathing patterns.

In previous studies, exercise has been said to impact ICP; however, the mechanism remains unclear.^[15,16] In this

experiment, temperature elevation as proxy for exercise stimulation showed no significant change in ICP for either group. The elevated temperature did ostensibly decrease CSF production in the control group; however, this decrease was not significant, and no correlation was observed in the experimental group.

Obesity has been previously shown to positively impact ICP in rats,^[17] and even normal weight gain has been shown to increase mean daily ICP.^[18] Using linear regression analysis on the dependence of ICP on weight, we saw only a weak relationship for either group at most positions, with the exception of 90°. In this study, we saw a general insignificant decrease in ICP as weight increased. However, there was a strong trend in the hydrocephalic group when rats were at 90° ($P = 0.0004$), indicating that in hydrocephalic animals, the mean ICP decreased as weight increased. This again highlights a discontinuity in physiologic output between hydrocephalic and control groups. Additional investigations on different levels of obesity and weight ranges should be conducted in order to conclusively discern whether weight is a significant contributor to elevated ICP.

Relating to shunting

The irregular flow patterns from a shunt system are still poorly understood, partially a result of our ever-expanding understanding of CSF regulation in the hydrocephalic patient and how it relates to ICP. Standard of care shunting, with a fixed or programmable pressure valve, assumes a constant, set pressure for CSF outflow. Our data suggest that an active hydrocephalic patient may meet the valve's opening pressure more consistently than what would be expected under normal, physiologic conditions. Conceivably, this may cause over-drainage from the shunt system, since a postural change between upright and horizontal should be met with a decrease in average ICP, but is not. We can assume that a hydrocephalic patient requires more draining because their ICP does not decrease with postural changes. However, we do not see similar fluctuations in the CSF production rate. Therefore, we conclude that we may be over-draining– or at least not being consistent with physiological CSF dynamics when we shunt. Adding an anti-siphon device may eliminate these issues, but this temporizing procedure is outside the scope of this work. Perhaps, the utilization of CSF production rates may be a more robust solution in the treatment of hydrocephalus, potentially making way for a more patient-centered, personalized approach.

Limitations of the study

Measuring parameters in the brain involves inherently invasive access procedures. The study was done in such a way so as to control as many confounding variables

as possible, still this proved to be difficult given the sensitive nature of both the instrumentation involved and the animal subjects themselves. Despite the limited sample size and the variability across animals, it is our belief that these results should only serve to provide background for further studies on the pathophysiology of hydrocephalus, as clear trends are apparent when one considers how the measured parameters change in relation to the position; while this does study alone does not merit more than a preliminary analysis, it does warrant a discussion that pressure dependencies on the position may not map equally in hydrocephalic animals compared to their nonhydrocephalic counterparts. To accelerate the discovery of improved treatment methods, we must elucidate on physiological relationships that push the envelope past the ICP-CSF volume axis. Such studies should be conducted on larger model animals to validate the current findings and elucidate on the possibility that the geometry of the ventricular system influences the physiology of CSF and ICP dynamics.

Conclusions

Investigations on body dynamics of the CNS and CSF have been sporadic and are increasingly difficult to synthesize; this is even more so the case when it comes to the physical pathophysiology of CNS disorders. In this study, we elucidate the physical manifestation of hydrocephalus and how the dynamic body may compensate (or not) in an afflicted state. In the case of the posture-ICP relationship through our movement sequence, it was shown that hydrocephalic animals with an obstructed CSF circulation route show a trend that they could not accommodate postural changes by altering ICP in a compensatory manner that correlated with the deviation from normal body position (the severity of the postural change from baseline). This alludes to a disruption in the homeostatic regulation of ICP or CSF absorption and production that is expressed as the inability to correct parameters acutely following deviations. This is in line with the study conducted by Poca *et al.* where it was demonstrated that free movement of CSF through the craniospinal junction was required for more rapid reductions in ICP.^[12] This conclusion also lends to the validity of using murine subjects (rats) as an appropriate model for evaluating hydrocephalus. Despite the limitations of their smaller cerebral cortex, relatively slow CSF production, and disparate head-body orientation, the evaluation of physiological parameters in rats is not incongruous with studies conducted on humans.^[12,13]

While more work needs to be done in this area, it is our opinion from these data that we are not mimicking CSF physiology with pressure regulated shunting. Still, this data should serve to give context for further studies.

Future work done in our lab is exploring the use of flow regulated valves and more patient-specific care models.

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Conflicts of interest

There are no conflicts of interest.

References

- Adigun OO, Al-Dhahir MA. Anatomy, Head and Neck, Cerebrospinal Fluid. StatPearls Publishing, Treasure Island (FL); 2019. Available from: <http://europepmc.Org/books/NBK459286>. [Last accessed on 2019 Dec 13].
- Brown PD, Davies SL, Speake T, Millar ID. Molecular mechanisms of cerebrospinal fluid production. *Neuroscience* 2004;129:957-70.
- Thompson DNP. Hydrocephalus. *Surgery* 2007;25:522-5.
- Dreha-Kulaczewski S, Joseph AA, Merboldt KD, Ludwig HC, Gärtner J, Frahm J. Inspiration is the major regulator of human CSF flow. *J Neurosci* 2015;35:2485-91.
- Czosnyka M, Czosnyka ZH. Overdrainage of cerebrospinal fluid and hydrocephalus shunts. *Acta Neurochir (Wien)* 2017;159:1387-8.
- Mattei TA, Morris M, Nowak K, Smith D, Yee J, Goulart CR, *et al.* Addressing the siphoning effect in new shunt designs by decoupling the activation pressure and the pressure gradient across the valve. *J Neurosurg Pediatr* 2012;11:181-7.
- Nagra G, Li J, McAllister JP 2nd, Miller J, Wagshul M, Johnston M. Impaired lymphatic cerebrospinal fluid absorption in a rat model of kaolin-induced communicating hydrocephalus. *Am J Physiol Regul Integr Comp Physiol* 2008;294:R1752-9.
- Karimy JK, Kahle KT, Kurland DB, Yu E, Gerzanich V, Simard JM. A novel method to study cerebrospinal fluid dynamics in rats. *J Neurosci Methods* 2015;241:78-84.
- Krasney JA, Koehler RC. Heart rate and rhythm and intracranial pressure. *Am J Physiol* 1976;230:1695-700.
- Schmidt EA, Despas F, Pavy-Le Traon A, Czosnyka Z, Pickard JD, Rahmouni K, *et al.* Intracranial pressure is a determinant of sympathetic activity. *Front Physiol* 2018;9:11.
- Ragan DK, Cerqua J, Nash T, McKinstry RC, Shimony JS, Jones BV, *et al.* The accuracy of linear indices of ventricular volume in pediatric hydrocephalus: Technical note. *J Neurosurg Pediatr* 2015;15:547-51.
- Poca MA, Sahuquillo J, Topczewski T, Lastra R, Font ML, Corral E. Posture-induced changes in intracranial pressure: A comparative study in patients with and without a cerebrospinal fluid block at the craniovertebral junction. *Neurosurgery* 2006;58:899-906.
- Andresen M, Hadi A, Petersen LG, Juhler M. Effect of postural changes on ICP in healthy and ill subjects. *Acta Neurochir (Wien)* 2015;157:109-13.
- Venkataraman P, Browd SR, Lutz BR. A physical framework for implementing virtual models of intracranial pressure and cerebrospinal fluid dynamics in hydrocephalus shunt testing. *J Neurosurg Pediatr* 2016;18:296-305.
- Brimioulle S, Moraine JJ, Norrenberg D, Kahn RJ. Effects of positioning and exercise on intracranial pressure in a neurosurgical intensive care unit. *Phys Ther* 1997;77:1682-9.
- Thelander A, Nellgård B, Ricksten SE, Cider Å. Effects of Early Bedside Cycle Exercise on Intracranial Pressure and Systemic Hemodynamics in Critically Ill Patients in a Neurointensive Care Unit. *Neurocrit Care* 2016;25:434-9.
- Uldall M, Bhatt DK, Kruuse C, Juhler M, Jansen-Olesen I, Jensen RH. Choroid plexus aquaporin 1 and intracranial pressure are increased in obese rats: Towards an idiopathic intracranial hypertension model? *Int J Obes (Lond)* 2017;41:1141-7.
- Eftekhari S, Westgate CSJ, Johansen KP, Bruun SR, Jensen RH. Long-term monitoring of intracranial pressure in freely-moving rats; impact of different physiological states. *Fluids Barriers CNS* 2020;17:39.