Post-Shunt Gait Improvement Correlates with Increased Cerebrospinal Fluid Peak Velocity in Normal Pressure Hydrocephalus: A Retrospective Observational Phase-Contrast Magnetic Resonance Imaging Study

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INTRODUCTION

It is estimated that 1-10% of all elderly and up to 6% of nursing home residents have normal pressure hydrocephalus (NPH).1 Our own imaging experience suggests a much larger prevalence of radiologic communicating hydrocephalus with or without the...
symptomatology of NPH. In addition, approximately 375,000 Americans with NPH are thought to be misdiagnosed with dementia or Parkinson's disease. Therefore, diagnosis of idiopathic NPH and, in particular, the identification of potential shunt responders remains a challenge. An invasive procedure, that has withstood the test of time, is lumbar puncture (LP) with high volume cerebrospinal fluid (CSF) drainage with gait testing performed before and after LP. Gait improvement after high volume LP identifies patients who are likely to respond to ventricular shunting.

Successful treatment of NPH can ameliorate symptoms in up to 80% of shunted patients and over 90% of patients at our institution (unpublished data). Identifying non-invasive means of diagnosing NPH and NPH shunt candidates is a highly desirable objective.

Phase-contrast magnetic resonance imaging (MRI) metrics, in particular, the peak velocity (PV) of CSF flow, characterizes a subset but not all NPH patients, and prior studies have shown higher group PV in NPH compared with healthy controls. Furthermore, Sharma et al. recently demonstrated the utility of measuring PV both before and after lumbar CSF drainage as a way to determine NPH patients likely to improve following ventricular shunt placement.

Bradley et al. demonstrated that pre-operative CSF stroke volume through the aqueduct of 42 uL or more was associated with shunt response in all patients (n = 12). PV was not reported to be a useful measure.

To the best of our knowledge, no phase-contrast MRI study has yet determined the association of changes in aqueductal PV with changes in symptom severity from pre- to post-shunt. We observed aqueductal flow changes through the aqueduct prior to and as a result of the ventricular shunt and related these changes to gait measures. We chose PV for flow quantification since this measure, unlike other flow parameters, varies minimally across observers, as PV always occurs at or near the center of flow in a tubular structure.

Since gait impairment is the principal symptom in many NPH patients and also the clinical parameter most likely to improve after shunt, gait function measures were used as markers of disease severity and for monitoring symptom improvement. Consequently, our goal was: (a) To establish the relationship, if any exists, between change in aqueductal PV and change in gait performance pre- to post-shunt, and (b) to test the hypothesis that aqueductal PV is correlated with gait function.

**METHODS**

**Subjects**

This retrospective, anonymized, single-center, health insurance portability, and accountability act-compliant study was exempt from Institutional Review Board approval. We reviewed patients who were referred to New York University’s (NYU) adult hydrocephalus evaluation program for symptoms of gait impairment (irrespective of the presence of cognitive or urologic dysfunction) and enlarged ventricles and who underwent ventriculoperitoneal shunting (VPS) between January of 2012 and December of 2013. All patients were examined by a board-certified study neurologist (25 years of experience) who made the initial diagnosis of NPH, and frequently followed up on patients through the post-shunt time period monitoring for disease symptoms and shunt failure. All patients underwent a standardized shunt surgery. The clinical diagnosis of probable NPH was made on the basis of enlarged ventricles, a characteristic dyspraxic gait disorder, marked improvement to either high volume CSF LP and/or continuous lumbar drainage, and exclusion of other confounding diagnoses such as Parkinson’s disease, cerebellar dysfunction, cerebrovascular disease, myelopathy, and/or metabolic disease known to cause gait problems. We reviewed retrospectively seven patients (six men/one woman) who: (a) Had available pre- and postsurgical high-resolution (1 mm) isotropic, 3D T-weighted, magnetization-prepared rapid acquisition gradient echo (MP-RAGE) MRI needed for ventricular segmentation, and (b) had pre- and post-shunt phase-contrast MRI scans. Age at pre-shunt MRI was 74.4 ± 3.5 (mean ± standard deviation), range: 68.8-78.6 years. Age at post-shunt MRI was 75.1 ± 3.4, range: 69.0-79.0 years.

**Clinical Evaluation**

Gait impairment and its subsequent improvement following ventricular shunting were assessed with two gait metrics: (i) The functional ambulation performance (FAP) score and (ii) gait time (GT), defined as the time to walk ~9 m (30 ft) and return. The FAP score is a well-validated, quantitative composite gait measure based on step length, symmetry, velocity, and ranges from 95 to 100 in healthy adults. It was determined using the GaitRite System (CIR Systems, Inc., Havertown, Pennsylvania, USA). Both GT and FAP measures consist of six individual trials that are averaged together.

Cognitive status and urinary incontinence were used for clinical characterization by the Neurologist. Cognitive function was evaluated using the Mini Mental State Examination and the global deterioration scale. The global deterioration scale score pre- and post-shunt was identical.
for each patient, with a mean of 2.9 (range: 2-6). Mean Mini Mental State Examination score was 25.4 pre-shunt (range: 15-30) and 26.6 post-shunt (range: 17-30). Urinary incontinence was queried by means of a questionnaire administered at initial clinical assessment and scored on a scale from 0 (no incontinence) to 9 (three or more incontinent episodes per day). Mean urinary incontinence score for the patients was 4.1 pre-shunt (range: 0-9) and 3.0 post-shunt (range: 0-7). Patients were clinically evaluated at the time of imaging and immediately prior to shunt placement, with no reported significant difference in impairment based on NPH symptomatology.

**MR Imaging Data Acquisition**

Patient logs of the NYU adult hydrocephalus service were reviewed to identify all patients for whom pre- and post-shunt phase-contrast MRIs were acquired and who were studied and followed up by a neurologist. Subject MRI scans were anonymized and transferred off-line for in-house processing at NYU School of Medicine. Pre-shunt MRI was performed 8-218 days before shunt (median=50 days) and 55-488 days following shunt (median=104 days).

**MRI Image Evaluation**

All subjects had T1-weighted brain MRI acquired using the 3D MP-RAGE sequence on either a Siemens 1.5 or 3T unit (Avanto, TrioTim, or Skyra; Siemens AG, Erlangen, Germany). The TR ranged from 1590 to 2200 ms, TE ranged from 2.26 to 2.48 ms, field-of-view: 256 mm, matrix size: 256 x 256, slice thickness: 1 mm. The bandwidth was set to 250 or 260 Hz across scans. PV in the aqueduct was obtained using a phase-contrast method, as described elsewhere. Prospective cardiac gating used was either finger plethysmography or electrocardiogram leads for a range of 17-42 segments of acquisition. The TR ranged from 22.25 to 28.6 ms, TE ranged from 6.08 to 8.87 ms, field-of-view ranged from 180 to 230 mm, matrix size: 256 x 256, slice thickness: 5 mm. The V_enc was set from −20 cm/s to 20 cm/s. Bandwidth was set to 130 or 201 Hz across scans. The local plane of acquisition for all subjects was midway through the aqueduct of Sylvius at 90° transverse orientation, as shown in Figure 1.

Orientation of plane of section for flow measurements. Mid-sagittal T1-weighted MRI with flow compensation off. Note the solid, white line indicates axial position of slice used for CSF PV measurements in the aqueduct of Sylvius.

**Image Analysis**

To approximate the contours of the cerebral aqueduct and to calculate the PV, a region-of-interest (ROI) was manually placed for each phase of the study using circle cardiovascular magnetic resonance (CMR) 42 software (Circle Cardiovascular Imaging, Calgary, Alberta, Canada), which approximates the dimensions of the cerebral aqueduct to optimally calculate the cross-sectional area of the ROI as shown in Figure 2a and b.

Cerebral aqueduct for flow measurements (a): Anatomical phase-contrast MR image at 90° transverse orientation relative to the plane shown in Figure 1. Right (b): A ROI was placed using CMR 42 software on the aqueduct to best match the contours of the structure. Note the bright CSF suggests craniocaudal flow.

The cross-sectional area of each ROI is averaged across all phase images of the acquisition to yield an average aqueductal cross-sectional area (ACSA). Given that prospective gating neglects, a portion of the cardiac cycle and plethysmography gating omits a different portion altogether than EKG gating, the PV graph for each phase was inspected to ensure the PV was not obtained at the first or last phase for each patient’s scan as this may have produced an erroneous result. From inspection, there was no apparent difference in the flow waveform when comparing a patient’s pre-shunt scan with his/her post-
shunt scan. This suggests a consistent craniocaudal flow direction and amplitude throughout all phase acquisitions. Total ventricular volume was generated in three steps using fire voxel:21 (a) Bridge burner algorithm was used to segment the whole brain excluding CSF;21 (b) morphologic closure of the brain mask was performed to include the ventricular spaces; (c) 3D set difference of (a) subtracted from (b) was taken as the ventricular volume.

Retrospective cardiac gating was not available in this group of patients, and stroke volumes were not obtained. Our current NPH protocol includes retrospective cardiac gating and stroke volume acquisition.

**Statistical Analyses**

The temporal change in each gait impairment metric and PV was computed for each subject as the “pre-” minus the “post-” surgery level so that a positive change reflects a decline over time. Paired sample t-tests were used to assess the temporal change in each metric pre- to post- shunt. All correlations were tested using Pearson’s correlation coefficient. Significance was set at \( P < 0.05 \) and Minitab version 14 (Minitab Inc., State College, Pennsylvania, USA) was used for all analyses.

**RESULTS**

There were no significant differences from pre- to post-shunt in dementia scores or urinary incontinence. In terms of gait impairment, metrics for all seven patients before and after shunt are compiled in Table 1. Five out of seven patients had quantifiable gait improvement following shunt while two patients had stable to decreased gait scores following shunt.

Mean FAP increased 14% (\( P = 0.05 \)), while mean GT decreased 14% (\( P = 0.3 \)), but this change was not statistically significant. There was no significant association of GT or FAP score with age (\( R = 0.03, P = 0.95; R = 0.12, P = 0.80 \), respectively).

Mean PV increased 25% (\( P < 0.01 \)).

**Relationship between Gait Impairment and Flow Velocity**

PV values for all seven subjects prior to and after ventricular shunting are provided in Table 2.

There was no significant association of pre-shunt PV with improvement in FAP score (\( R = 0.25, P = 0.59 \)). In addition, there was no significant association of pre-shunt PV with % change in GT (\( R = 0.30, P = 0.51 \)). However, % change in either FAP score or GT with absolute PV difference (pre- to post-shunt) revealed a significant association (\( R = 0.76, P < 0.05; R = 0.91, P < 0.01 \), respectively), as shown in Figure 3a and b.

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5D: Standard deviation, PV: Peak velocity, ACSA: Aqueductal cross-sectional area

**ACSA and Total Ventricular Volume**

Pre- and post-shunt ACSA and ventricular volume are provided for each subject in Table 3.
Mean ACSA decreased 24% ($P<0.05$), while the mean ventricular volume decreased 11% ($P<0.01$). No significant association was found between ACSA and ventricular volume. No significant association was found between relative % change in ventricular volume and ACSA ($R = 0.32, P = 0.48$); neither was an association found between absolute difference in ventricular volume and ACSA ($R = 0.05, P = 0.92$).

**Relationship between PV and ACSA and Total Ventricular Volume**

There was a significant association between % change in PV and % change in ACSA ($R = 0.90, P < 0.01$), as shown in Figure 4.

Pre- to post-shunt increase in PV (given as percent [%]) versus decrease in ACSA (given as %) for each patient (“•”). However, no association was found between % change in PV and % change in ventricular volume ($R = 0.38, P = 0.40$).

**DISCUSSION**

Phase-contrast CSF flow studies have been increasingly used as a tool to study patients with NPH. However, the dynamics of CSF flow at the cerebral aqueduct in patients with NPH, and how they relate to clinical symptoms, are still not well-understood. Current research is neither consistent nor abundant in terms of what the flow patterns are for NPH shunt-responders versus non-responders and how these values change following VPS. The results from our study cohort suggest a strong correlation exists between PV and gait metrics following VPS.

At first the finding that NPH patients post shunt demonstrate higher PV may appear counter-intuitive, however, only a few studies in the literature have investigated the definitive hydrodynamic treatment response after VPS, and all differ for various reasons from our current study, especially with regard to aqueductal PV in patients with idiopathic NPH, i.e. the development of NPH without prior pathological or traumatic insult.

Abbey et al.,$^{22}$ observed a decrease in PV from pre-to post-shunt in a group (N=10) with communicating hydrocephalus. Differences from our study include: (a) younger age group 17 to 50 years of age 50% of whom were under 30 years in the Abbey study and 68.8-78.6 years in our study; (b) the Abbey patient sample consists of 8 patients who developed hydrocephalus secondary to another event and 2 cases of idiopathic NPH; all our cases of NPH are idiopathic.

In secondary NPH the primary disease typically meningitis or trauma may result in cerebritis, infarcts, post-contusional gliosis, and atrophy as well as adhesions in the subarachnoid spaces, including the aqueduct all of which may have an effect on CSF dynamics and aqueductal flow.

Scans were performed 2-20 days post shunt and all scans were performed on a 1.5T scanner. In our study, the post shunt studies were performed 104 days (median value) after shunt. It is unknown whether post shunt PV is dependent on these factors: Patient age, the cause of NPH, secondary versus idiopathic, field strength of the MRI scanner and time to post shunt MRI.

A study by Kim et al.,$^{23}$ also demonstrated that PV “decreased somewhat” (significance not indicated) after shunt in 11 cases of NPH, with an average age of 50 years and age range of 20-67 years (pre-operative 6.71 ± 2.84 cm/s and post-operative 5.16 ± 3.84 cm/s). It is not stated whether the NPH was idiopathic or secondary. This age range is younger than the age in our sample and is distinctly younger than typically seen in patients.
with idiopathic NPH. The younger age in the Kim study suggests the inclusion of secondary NPH patients.

In summary, both of the above earlier studies are in younger patient populations and are in large part studies of secondary NPH. In addition, symptom improvement was only qualitatively evaluated, while in our study we found not only a quantitative increase in PV but also that this increase is linked with a quantifiable degree of symptom improvement.

Sharma et al.,11 in a pre-operative only MRI PV study before and immediately following high volume CSF LP, demonstrated, that patients with >2 cm/s decreased PV following 50 cm³ lumbar CSF drainage had symptomatic improvement the following shunt. This study of alterations in the aqueductal hydrodynamics immediately after large volume CSF drainage may not reflect aqueductal hydrodynamics several months after permanent ventricular shunt placement. The effects on PV of the temporal progression of the disease, and alterations in CSF hydrodynamics over time in response to VPS are unknown at this time.

Prior studies24-27 suggest that pre-shunt elevated flow measures in NPH, may not be reliable as a surrogate marker for response to shunt surgery for quantifying disease severity. Although Algin et al.,10 found higher flow values for NPH patients, there was no correlation between these values and patient shunt response. Moreover, Dixon et al.,27 were unable to use pre-shunt CSF flow rates as a means to predict shunt-responders. Furthermore, this group found mean aqueductal CSF flow was significantly increased in patients with negative responses to high-volume LP compared with the mean flow in LP-responders. In our current study, as well, pre-operative PV did not correlate with shunt response.

We also found that the NPH patient group had significantly decreased ventricular volume following VPS. However, there was no significant relationship between ventricular volume change and change in gait metrics. This agrees with other studies that show significant clinical improvement can occur after shunt, even without a reduction in ventricular size.28,30 Thus, although a clear reduction in ventricular size was observed in our patient group, consistent with previous studies,28,30 there may not be a measurable association between ventricular size and patient symptomatology.

Admittedly, there are several limitations to our study. The first, we demonstrated our findings with a small number of patients and with retrospective clinical and radiographic data. Future work including longitudinal assessments will focus on increasing the sample size to prospectively, replicate and confirm that increased aqueductal PV correlates with improvement in gait metrics and to investigate the relationship of PV to stroke volume.

**CONCLUSION**

In conclusion, our study shows evidence that changes in CSF PV through the aqueduct is directly related to the degree of gait improvement. The study also suggests in conjunction with previous reports that aqueductal PV and hydrodynamics are complex and likely dynamic phenomena that may change over time. The results from our study help shed light on one aspect of the physiology of the disorder. Further study is warranted and, in particular, longitudinal studies to help determine the role of aqueductal PV and hydrodynamics in the diagnosis and management of this debilitating but treatable condition.

**REFERENCES**

Miskin, et al.: Gait Improvement Correlates with CSF Velocity in NPH


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