Changes in temporal flow characteristics of CSF in Chiari malformation Type I with and without syringomyelia: implications for theory of syrinx development

Clinical article

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Object. The pathogenesis of syringomyelia in association with Chiari malformation Type I (CM-I) is unclear. Studies of patients with CM-I have shown alterations in the CSF velocity profile using cardiac-gated cine phase-contrast MRI, and computational simulations have demonstrated that temporal features of the CSF pulse could contribute to syrinx development or enlargement. Few studies have reported temporal characteristics of the CSF profile, and few studies have reported on CM-I patients with and without syringomyelia separately. This study was performed to determine whether specific temporal features of the CSF flow profile may underlie the development or enlargement of a syrinx in patients with CM-I.

Methods. Ten healthy volunteers and 18 patients with CM-I with (8 patients) and without (10 patients) syringomyelia were studied using cardiac-gated cine phase-contrast MRI, measuring the maximum CSF velocities in the cranial and caudal directions, the timing of these maximums relative to the cardiac cycle time, the timing of caudal flow onset, timing of cranial flow onset, and the duration of caudal flow.

Results. The caudal CSF flow was significantly faster (p ≤ 0.01) and earlier (p < 0.02) in patients without syringomyelia than in healthy volunteers and patients with syringomyelia. There were no significant differences in the CSF velocities between patients with syringomyelia and healthy volunteers. Patients with CM-I who had syringomyelia had a significantly later start of caudal CSF flow (p < 0.01) and earlier maximum cranial velocity (p = 0.03) than healthy volunteers, but the relative durations of caudal and cranial flow were not significantly different between any of the groups.

Conclusions. The significantly earlier arrival and earlier peak velocity of caudal CSF flow may underlie the development of syringomyelia in patients with CM-I, and after a syrinx develops the CSF flow profile appears to stabilize.

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Key Words • syringomyelia • Chiari malformation • cerebrospinal fluid • magnetic resonance imaging

CHIARI malformation Type I is an abnormality characterized by inferior protrusion of the cerebellar tonsils through the foramen magnum. Approximately two-thirds of patients with CM-I also develop syringomyelia, but it is not clear why some patients with CM-I develop syringomyelia and others do not. The possibility of prevention of syringes and the optimal treatment of resistant syringes is unclear because the pathogenesis of syringomyelia remains unknown.

Several theories on the pathogenesis of syringomyelia have been formed over the years. Experimental studies have demonstrated that syrinx fluid flows into the central canal via the perivascular spaces, and it is proposed that the driving force of syrinx fluid into the central canal is arterial pulsation-dependent CSF flow from the perivascular spaces into the cord from the SAS. Subsequent experimental studies investigated which features of arterial and CSF pulsation may contribute to syrinx development or enlargement, for example, arterial pulse pressure and the relative timing of the arterial and SAS pulses. The study by Bilston et al. demonstrated that even a moderate shift in the timing of the CSF pulse relative to arterial pulse could influence the mass flow rate of CSF into the perivascular spaces due to changes in perivascular space size during the cardiac cycle acting as...
a “leaky one-way valve.” This study altered the timing offset of a simulated CSF pressure wave, but it did not investigate which specific temporal features of the CSF pressure wave may be responsible for syrinx development (for example, the timing of the peak cranial and caudal velocities, the timing of reverse between cranial and caudal flows, and the relative durations of cranial and caudal flow).

Clinical MRI studies in syringomyelia and CM-I have demonstrated alterations in CSF pulse profiles relative to the cardiac pulse; however, some important information about the CSF pulses in CM-I patients with and without syringomyelia is lacking. For example, patients with CM-I have earlier onset and reduced duration of caudally directed CSF flow than healthy volunteers; however, these studies either did not separate CM-I patients with and without syringomyelia or only included patients with syringomyelia. Therefore, it is still not clear whether the relative timing or duration of caudal CSF flow may be implicated in the development of syringomyelia in association with CM-I. To date, only one clinical study has performed quantitative comparisons of CSF profiles in healthy volunteers compared with patients with CM-I, separating the patients into groups with and without syringomyelia. That study reported that, in some spinal regions, CM-I patients without syringomyelia had a shorter duration of caudally directed CSF flow than those with CM-I with syringomyelia. Unfortunately that study did not measure other temporal features of the CSF flow profiles that may be related to the causes of syrinx development. Other studies have investigated changes in CSF velocity of patients with CM-I compared with healthy volunteers. However, neither of these studies separated patients with CM-I into those with and without syringomyelia. Therefore, it is still not clear whether the velocity of CSF flow may be implicated in the development of syringomyelia in association with CM-I. It is important to better understand the role of peak CSF velocity and the role of various temporal features of the CSF wave in CM-I patients with and without syringomyelia.

This study aims to quantitatively compare the peak velocities and temporal features of the CSF velocity-time profiles relative to the cardiac pulse in healthy volunteers and CM-I patients with and without syringomyelia. Specifically, we aimed to determine the timing of the onset of cranially and caudally directed CSF flow and the magnitude and timing of the peak cranial and caudal CSF flow, because it is not currently known whether these features are different in CM-I patients with and without syringomyelia, and some of these features have been suggested as possible factors in syrinx formation and enlargement. Furthermore, these features may provide useful information for further computer simulations to investigate systematically altering these features to study their effect on the likelihood of syrinx formation.

**Methods**

**Participants**

The University of New South Wales Human Research and Ethics Committee approved all experimental protocols, and all participants gave written informed consent to enter the study. There were 10 healthy volunteers (7 women and 3 men, age range 24–60 years, weight 55–85 kg) and 18 patients with symptomatic CM-I: 10 patients without syringomyelia (8 women and 2 men, age range 22–60 years, weight 55–78 kg, mean tonsillar descent 10.1 ± 4.2 mm [± SD]) and 8 patients with syringomyelia (5 women and 3 men, age range 27–58 years, weight 58–100 kg, mean tonsillar descent 10.7 ± 2.1 mm). There was no significant difference in the magnitude of tonsillar descent for the 2 CM-I groups (p = 0.73, unpaired t-test). All patients experienced headaches; some experienced numbness, dizziness and pain; and 1 patient had partial paralysis. There was also a range of symptom duration; however, there was no consistent difference between the 2 groups of patients in terms of the duration and range of symptoms.

**Imaging Protocol**

Cardiac-gated cine phase-contrast MRI was performed using a 3-T MRI scanner (Philips Achieva TX). Cardiac gating was achieved using vectorcardiogram leads, and 30 cardiac phase images were collected and measured from the onset of the R wave. Four images were obtained at the following cranial/spinal levels and encoding velocities (V<sub>enc</sub>) using an (axial) imaging plane aligned perpendicular to the CSF flow: 5 mm cranial to the tip of the cerebellar tonsils (V<sub>enc</sub> 10 cm/sec), at the foramen magnum (V<sub>enc</sub> 12 cm/sec), midvertebral C-2 (V<sub>enc</sub> 9 cm/sec), and midvertebral C-5 (V<sub>enc</sub> 13 cm/sec) (Fig. 1A). The spatial resolution of the phase-contrast MR images was 0.694–0.977 mm<sup>2</sup>. Encoding velocities were determined during pilot studies to prevent aliasing. Other typical imaging parameters were flip angle 10°, matrix 240 × 176, FOV 250 × 250, TR 21 msec, TE 6.8 msec, and slice thickness 5 mm.

**Data Analysis**

The CSF velocity profiles were measured from the phase-contrast MR images using the freely available analysis software Segment. For each of the 4 spinal level images, segmentation was performed using up to 10 regions of interest (2 mm in diameter) spaced evenly around the SAS (Fig. 1B and C). This resulted in left-right symmetrical placement of anterior, anterolateral, lateral, posterolateral, and posterior velocity monitoring points (except where posterior monitors were prevented due to the presence of the tonsils at the higher spinal levels). The data for corresponding left and right monitoring points were averaged.

Quantitative measurements of the velocity-time profiles were performed for each of the monitoring points at each of the 4 spinal levels. The following features were measured from each CSF velocity-time profile (Fig. 2): the maximum velocities in the cranial and caudal directions, the timing of these maximums relative to the cardiac cycle time, the timing of the reverse from cranial-to-caudal flow and from caudal-to-cranial flow relative to the cardiac cycle time, and the relative duration of the caudally directed flow. All temporal measurements were made relative to the cardiac cycle time (R-R wave inter-
val). The timing of the onset of caudal flow and return to cranial flow were calculated using linear interpolation between the temporally adjacent cranial/caudal velocities, and duration of caudal flow was calculated as the difference between these 2 interpolated values.

Two-way repeated-measures ANOVAs were performed for each velocity parameter using STATA (version 11.1, StataCorp). The 2 effects tested were CM-I/syringomyelia status (Group 1, healthy volunteers; Group 2, CM-I without syringomyelia; and Group 3, CM-I with syringomyelia) and location of velocity measurement (separately for each region of each spinal level, that is, anterior and lateral regions at tonsil and foramen levels, and anterior, lateral, and posterior regions at the C-2 and C-5 levels). The measurement region was modeled as a repeated-measures variable. Differences were considered significant with p < 0.05. When the ANOVA model returned a significant effect of CM-I/syringomyelia status, a Bonferroni post hoc test for multiple comparisons was performed to identify any significant differences between the 3 CM-I/syringomyelia status groups.

Results

A representative CSF velocity-time curve from a healthy volunteer (anterior mid-C2 region) is shown in Fig. 2. In general, the CSF velocity profiles followed a similar pattern for all participants and all measurement regions, where CSF flow was initially cranially directed (positive velocity), then reversed to caudal flow (negative velocity), and then reversed again to cranial flow.

The means and 95% confidence intervals for each velocity parameter are shown in Fig. 3 for the 3 groups, and the corresponding p values from the statistical analyses are summarized in Table 1.

Velocity of CSF

Figure 3 upper shows the peak caudal and cranial velocities for each group. There was no effect of CM-I or syringomyelia on the maximum velocity of CSF in the cranial direction; however, CM-I/syringomyelia status did have a significant effect on the maximum velocity of CSF in the caudal direction (p < 0.01). Patients without syringomyelia had significantly faster CSF flow in the caudal direction (0.7 cm/sec, a 24% increase) than healthy volunteers (p < 0.01) and patients with syringomyelia (p = 0.01). There was no significant difference in the maximum velocity of CSF in the caudal direction between patients with syringomyelia and healthy volunteers.

Time of Maximum CSF Velocity

The lower panel in Fig. 3 shows the time at which the CSF flow is fastest for each group. When CSF was flowing in the cranial direction, the peak flow occurred earlier in patients with CM-I than in healthy volunteers, and this difference was significant for those with syringomyelia (p = 0.03). When CSF was flowing in the caudal direction, the peak flow occurred significantly earlier in patients without syringomyelia than in patients with syringomyelia and healthy participants (p < 0.01).

Time and Duration of Caudal and Cranial CSF Flow

The lower panel in Fig. 3 also shows the time at which...
the CSF started to flow in the caudal direction and then returned to the cranial direction for each group, and also the relative duration of the pulse where CSF flowed in the caudal direction. The time at which the CSF started to flow in the caudal direction was significantly earlier in the CM-I group without syringomyelia than in healthy participants (p = 0.02), and significantly later in the CM-I group with syringomyelia than in healthy participants (p < 0.01). Also the time at which the CSF started to return to flow in the cranial direction was significantly earlier in patients with syringomyelia than in patients without syringomyelia (p < 0.01). There were no significant differences in the relative duration of the caudal flow between any of the groups.

**Discussion**

This is the first clinical evidence of significant differences in the temporal features of the CSF pulse in CM-I patients with and without syringomyelia. Computational simulations have suggested that even a modest shift in the timing of the CSF pressure profile with respect to the

**TABLE 1: Summary from the ANOVA and the Bonferroni multiple comparisons tests**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ANOVA CM-I/Sx Status Overall</th>
<th>Bonferroni Multiple Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>max cranial velocity</td>
<td>0.05</td>
<td>Healthy vs CM-I w/o Sx</td>
</tr>
<tr>
<td>max caudal velocity</td>
<td>&lt;0.01†</td>
<td>CM-I w/o Sx vs CM-I w/ Sx</td>
</tr>
<tr>
<td>time peak cranial velocity</td>
<td>0.04†</td>
<td>Healthy vs CM-I w/ Sx</td>
</tr>
<tr>
<td>time peak caudal velocity</td>
<td>&lt;0.01†</td>
<td></td>
</tr>
<tr>
<td>time cranial flow onset</td>
<td>&lt;0.01†</td>
<td></td>
</tr>
<tr>
<td>time caudal flow onset</td>
<td>&lt;0.01†</td>
<td></td>
</tr>
<tr>
<td>caudal flow duration</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

* Refer to Fig. 3 for graphical comparisons. Abbreviation: Sx = syringomyelia.
† Significant comparisons (p < 0.05).
arterial pressure profile may enhance CSF flow through the perivascular spaces into the central canal of the spinal cord, and this may contribute to formation or enlargement of a syrinx.

Implications of Results for Syringomyelia Development in CM-I

This study shows that CM-I patients without syringomyelia had a significantly faster and earlier caudal phase of CSF flow than healthy volunteers and CM-I patients with syringomyelia. The results also show that patients with syringomyelia had significantly later onset of caudal CSF flow than normal, and the maximum CSF flow in the cranial direction occurred significantly earlier than normal. The computational simulations by Bilston et al. suggested that a modest shift toward earlier arrival of the peak CSF pressure compared with the arrival of the peak arterial pressure may enhance CSF flow into the cord, thus contributing to a syrinx. That study suggested that CSF flow into the perivascular spaces steadily increased when the CSF pulse was shifted temporally between 0% and 30% of the cardiac cycle time, then decreased for greater temporal offsets. It is therefore curious that the timing of the peak caudal velocity (which relates to the timing of peak CSF pressure) in CM-I patients without syringomyelia was earlier than those with syringomyelia. For patients without syringomyelia the peak CSF velocity was also significantly earlier than for healthy volunteers, but this was not the case for patients with syringomyelia. First, it is interesting to note that the only other clinical study to our knowledge that has reported significant differences in temporal patterns of CSF flow in CM-I patients with and without syringomyelia also found a greater difference between healthy volunteers and CM-I patients without syringomyelia than in those with syringomyelia. In terms of the relationship between fluid flow and spinal SAS anatomy, CM-I may have the effect of restricting flow at the foramen magnum in the region of the tonsils but allowing relatively unrestricted flow in the spinal SAS caudally. The results of this study suggest that this is associated with earlier caudal flow in the spinal SAS below the CM-I. The precise mechanism for this is unclear. On the other hand, once a syrinx forms and enlarges, this would act to extend the resistance to flow lower down the spinal canal, as the syrinx-affected cord encroaches on the spinal SAS. This may further alter the dynamics of the flow, resulting in the timing reverting to closer to normal.

Our results support the theory that earlier arrival of the pressure pulse in the spinal SAS might contribute to the formation of a syrinx in a patient with CM-I, since the SAS pressure pulse is associated with the earlier caudal flow and could thus enhance CSF flow into the cord through perivascular spaces. In addition, we propose that once a syrinx has formed, the characteristics of the spinal SAS are altered, which may act to stabilize the CSF flow timing and slow the syrinx formation.

Posterior fossa decompression often results in a decrease in syrinx size, although the mechanism of this effect remains unknown. It has been suggested that the effect is to allow normal flow of CSF across the foramen magnum or to eliminate the effect of the cerebellar tonsils on spinal SAS pressure. Our results, supporting a theory of relative pulse timing, suggest that the effect may be to restore a normal relationship between the CSF and arterial pulse timing, rather than by affecting the pressure amplitude in the spine. It is possible that a similar mechanism may underlie the effect of expansive duraplasty in cases of syringomyelia in association with arachnoiditis.

Limitations of the Current Study

In interpreting the results of the current study, it is important to consider some limitations and assumptions. While the current study has shown differences in the CSF velocity profiles, and using fluid dynamics principles this relates directly to the pressure profile, we cannot directly and noninvasively measure the real-time CSF pressure pulse in patients with CM-I. Another limitation of this study is that the results cannot be used directly for clinical decision making for individuals. For example, we have not performed follow-up in the cohort without syringomyelia to determine whether the earlier CSF pulse in this group may in the future lead to syringomyelia. However, the observed temporal differences in the CSF pulse of patients with CM-I in the current study is consistent with mechanisms of syringomyelia proposed through computational simulations. The current study has also not been able to control for the amount of time that any patient has experienced symptoms or had syringomyelia and cannot determine the duration of any irregularity in the CSF flow profiles. We also have no information about the CSF flow profiles of the patients with CM-I who go on to develop syringomyelia before the time of syrinx development. The only way to determine whether CSF flow changes over time in CM-I and syringomyelia would be to follow up with this cohort of patients with CM-I at a later time. Also, while several important parameters were found to have significant differences between the groups, this study was nevertheless performed in a relatively small group of participants, which should be considered when interpreting the comparisons that did not achieve statistically significant p values.

Future Research

We have found several significant differences in CSF flow timing and magnitude between CM-I patients with and without syringomyelia. While we and others hypothesize that the timing of the spinal SAS pressure pulse, which is approximately aligned with the peak caudal CSF velocity, may influence syrinx development, it is possible that other temporal features such as timing of onset of caudal flow may play a role. Computational simulation studies may be able to independently vary these features of the CSF pressure pulse relative to the arterial pulse, and this may shed further light on the development of syringomyelia. Additionally, patients with CM-I have different hindbrain anatomy and different CSF flow profiles compared with healthy individuals, and it is not known whether the anatomical or CSF flow differences are responsible for possible syrinx formation. Computational simulations could also investigate the relative effects of anatomy and CSF flow profile on the potential for syrinx formation.
It was interesting to note in this study that for all CSF flow parameters for which CM-I/syringomyelia status had an effect, the parameter values for healthy participants were between the parameter values for patients with and patients without syringomyelia (see Fig. 3). It is possible that one or a combination of these parameters may later produce syringomyelia in this group of patients with CM-I, and it would be interesting for future research to investigate whether patients without syringomyelia who have similar CSF flow characteristics later develop syringomyelia. Future research may also investigate whether surgery affects the temporal parameters of the CSF profile and how this relates to changes in symptoms and syrinx size.

Conclusions

The aim of this study was to determine if there are differences in the temporal patterns of CSF flow in CM-I patients with and without syringomyelia. Patients with CM-I who did not have syringomyelia had earlier onset and peak caudal CSF flow and earlier reverse to cranial flow compared with those with syringomyelia. The onset and peak caudal flows were significantly different for patients without syringomyelia compared with healthy volunteers. The timing of peak caudal CSF flow and/or onset timing of caudal CSF flow may underlie the development of syringomyelia in patients with CM-I, and, after a syrinx develops, the CSF flow profile appears to stabilize.

Disclosure

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