Journal of Biomechanics xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Chiari malformation may increase perivascular cerebrospinal fluid flow into the spinal cord: A subject-specific computational modelling study

Robert A. Lloyd [a], David F. Fletcher [c], Elizabeth C. Clarke [b], Lynne E. Bilston [a,*]

[a] Neuroscience Research Australia and Prince of Wales Clinical School, University of New South Wales, Australia
[b] Murray Maxwell Biomechanics Laboratory, Institute for Bone and Joint Research, Kolling Institute of Medical Research, Sydney Medical School, University of Sydney, Australia
[c] School of Chemical and Biomolecular Engineering, University of Sydney, Australia

ARTICLE INFO

Article history:
Accepted 15 October 2017
Available online xxxx

Keywords:
Syringomyelia
Chiari malformation
Cerebrospinal fluid (CSF)
Perivascular space
Computational fluid dynamics (CFD)

ABSTRACT

Syringomyelia is associated with Chiari I malformation, although the mechanistic link is unclear. Studies have suggested that cerebrospinal fluid enters the spinal cord via the perivascular spaces, and that changes in the timing of the subarachnoid pressures may increase flow into the spinal cord. This study aims to determine how Chiari malformation and syringomyelia alter the subarachnoid space pressures and hence perivascular flow. Subject-specific models of healthy controls (N = 9), Chiari patients with (N = 7) and without (N = 8) syringomyelia, were developed from magnetic resonance imaging (MRI), to simulate the subarachnoid pressures. These pressures were input to an idealised model of the perivascular space to evaluate potential differences in perivascular flow. Peak pressures in Chiari patients without a syrinx were higher than in controls (46% increase; $p = .029$) and arrived earlier in the cardiac cycle than both controls (2.58% earlier; $p = .045$) and syrinx patients (2.85% earlier; $p = .045$). The perivascular model predicted Chiari patients without a syrinx would have the greatest flow into the cord ($p < .05$) if the arterial pulse delay was between 4 and 10% of the cardiac cycle. Using phase-contrast MRI the mean arterial delay for all subjects was similar, and was estimated as 4.7 ± 0.2%. The perivascular pumping rate showed a strong positive correlation ($R^2_{Adj} = 0.85$; $p < .0001$) with extended periods of high pressure that arrived earlier in the cardiac cycle, suggesting these pressure characteristics may play a role in syrinx development.

1. Introduction

Chiari malformation Type I is a disorder in which the cerebellar tonsils herniate through the foramen magnum. A majority (65–80%) of Chiari patients also develop a fluid filled cavity (syrinx) within the spinal cord (Speer et al., 2003). Syrinxes are associated with both sensory and motor disturbances, and occasionally with autonomic dysfunction (Sakushima et al., 2012). The mechanisms that lead to syrinx formation in only some of the population remains unknown, with current treatments for syringomyelia being unsatisfactory (Aghakhani et al., 2009).

Previous experimental studies showed that cerebrospinal fluid (CSF) flows from the spinal subarachnoid space into the spinal cord via the perivascular spaces (PVS) (Ball and Dayan, 1972), and that this flow is dependent on arterial pulsation (Stoodley et al., 1997; Stoodley et al., 1999). A simple computational model was used to demonstrate that the arteries could act as a 'leaky valve', increasing resistance to flow in the PVS by dilating during systole and vice versa (Fig. 1) (Bilston et al., 2010). Via this mechanism, modest changes in the timing of the arterial and subarachnoid pressures could lead to the enhanced influx of CSF into the spinal cord required for syrinx formation (Clarke et al., 2017).

Phase-contrast magnetic resonance imaging (PC-MRI) studies have shown that both the timing and velocity of CSF flow in the subarachnoid space are altered in Chiari patients. However, the subarachnoid pressures cannot be measured noninvasively, so computational models are used to provide an estimate. Idealised models have been used to demonstrate; how obstructions to flow in the subarachnoid space delay the onset and increase the amplitude of peak pressures (Stoverud et al., 2013), that greater tonsillar herniation increases the pressure gradient in the subarachnoid space (Linge et al., 2011), and that the presence of a syrinx in the cord may delay the pressure pulses (Cirovic and Kim, 2012).

Subject-specific models provide greater accuracy, as they rely on fewer assumptions and can be validated directly. Of the subject-specific Chiari modelling studies in the literature (Clarke et al., 2013a; Martin et al., 2013; Pahlavian et al., 2015; Shaffer et al., 2011; Shaffer et al., 2014; Støverud et al., 2016), only Clarke et al. (2013a) studied how a syrinx influenced the

* Corresponding author.
E-mail address: L.Bilston@neura.edu.au (L.E. Bilston).

https://doi.org/10.1016/j.jbiomech.2017.10.007
0021-9290/

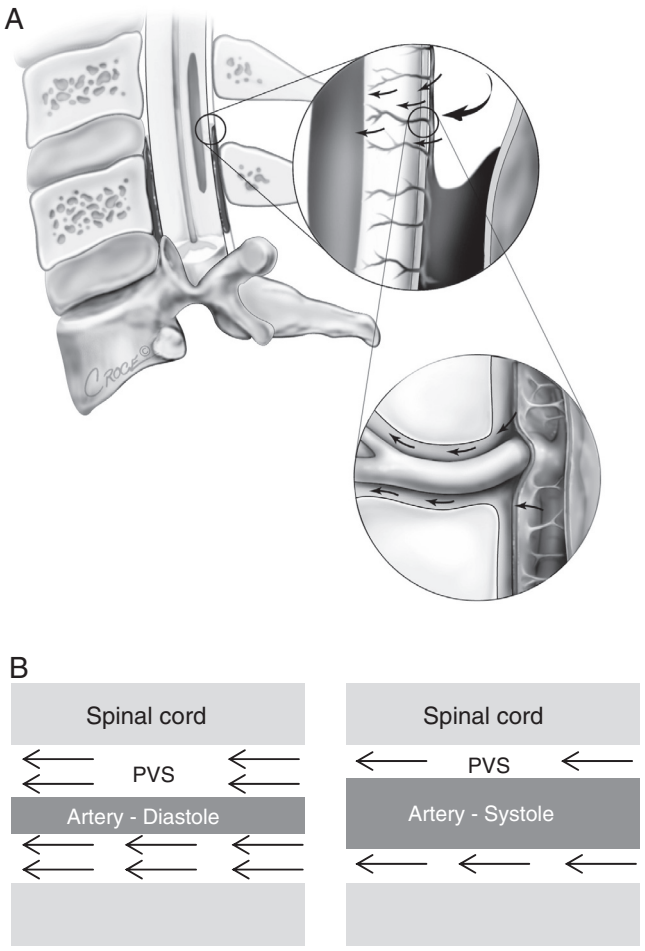

Fig. 1. (A) An illustration of the perivascular anatomy, highlighting a single penetrating vessel and the potential channel for fluid transport, *re-printed from Bilston et al., Journal of Neurosurgery, 2010, 112:808–813 with permission from http://thejns.org.* (B) A simplified diagram of the perivascular anatomy (Fig. 1A) demonstrating how the potential 'leaky valve' mechanism in the perivascular space (PVS) could alter CSF inflow, and the basis for the design of the perivascular model shown in Fig. 3G.

subarachnoid pressure–time profile, showing both timing and magnitude changes compared with healthy controls. These subject-specific pressure–time profiles were used in conjunction with a model of the PVS, to show that the increased duration of the positive pressure in syrinx patients could promote CSF flow into the spinal cord (Clarke et al., 2017). However, only one model was used per subject group, so the findings may not be representative of the patient population.

The aim of this study was to use a larger series of subject-specific models to investigate how Chiari I malformation, with and without a syrinx, affects the magnitude and timing of the subarachnoid pressure–time profiles compared with healthy controls, and to assess how characteristics of the subarachnoid pressure influence perivascular flow. We hypothesise that magnitude and timing of subarachnoid pressure in Chiari patients without a syrinx will be significantly altered, leading to a greater influx of CSF into the spinal cord.

2. Methods

2.1. MR imaging and flow measurements

This study used the MRI scan data from Clarke et al. (2013b) and reanalysed the subjects modelled in in Clarke et al. (2013a) and Clarke et al. (2017). The University of New South Wales Human Research and Ethics Committee approved all experimental protocols. All participants gave written informed consent. Twenty-four participants underwent MRI scanning of the head and neck; 9 healthy controls and 15 symptomatic Chiari I patients, 7 with and 8 without syringomyelia (Table 1).

3D isotropic T1 weighted sagittal anatomical MRI scans of the cervical spine were acquired, parameters for the scan include; 0.94 mm voxels, matrix = 288 × 288, FOV = 270 × 270, TR/TE = 5.5/2.5 ms and 180 slices of 0.94 mm thickness. Axial cardiac gated cine PC-MRI scans (30 phases/cycle) were acquired at the following locations and encoded velocities (V_{enc}); the base of the skull (V_{enc} = 12 cm s^{-1}), 5 mm cranial to the tip of the cerebellar tonsils (V_{enc} = 10 cm s^{-1}), mid C2 (V_{enc} = 9 cm s^{-1}) and mid C5 (V_{enc} = 13 cm s^{-1}). Additional scanning parameters were; matrix = 240 × 176, FOV = 250 × 250, TR/TE = 21/6.8 ms and slice thickness = 5 mm. For further details on the scanning protocol see Clarke et al. (2013a).

Blood flow measurements taken from mid-C5 were used to provide an estimate of the relative timing of the arterial and CSF pressures, by assuming that blood flow and pressure were in phase. As for a typical artery of 4 mm diameter (Reymond et al., 2009) with blood oscillating at a frequency of 60 bpm and a peak velocity of 30 cm s^{-1} (density 1054 kg m^{-3} and viscosity 4 mPa s (McDonald, 1955)), the Reynolds and the Womersley numbers would be 316 and 2.57 respectively. For a Womersley number less than 3, the boundary layer would occupy approximately half the artery's radius, reducing the inertial effects on the flow, therefore laminar flow with the pressure and flow in phase can be assumed (Lighthill, 1975). The blood flow was analysed from the C5 plane as the vertebral artery at this location runs approximately parallel to the spinal canal and therefore the flow would be primarily through-plane as required. However, the V_{enc} set to measure CSF velocities was too low to capture the blood flow, leading to phase wrapping in blood vessels (Fig. 3C, D). To remove the phase wraps (Fig. 2A, B), multiples of 2π were manually added to the affected voxels (Fig. 2C, D) (Bioucas-Dias and Valadao, 2007).

The velocity in the vertebral artery at C5 was measured from the corrected PC-MRI data using the freely available software Segment (Heiberg et al., 2010). The velocity data was fitted with cubic smoothing splines (MATLAB v8.6, The MathWorks Inc., MA) to interpolate the offset between the R wave and systolic uptake ($t_{Off-set}$; Fig. 2D).

2.2. Computational modelling of the spinal subarachnoid space

The pressure–time profiles were calculated using the modelling protocols in Clarke et al. (2013a). In summary, for each subject a 3D geometry of the subarachnoid space (Fig. 3) was constructed from point cloud data, manually segmented from the anatomical MRI. The models spanned from 5 mm cranial to the tip of the cerebellar tonsils or the base of the skull to 10 mm past mid-C5, with a 5 mm extension to the cranial inlet to provide a smooth entry zone. The models were imported into ANSYS CFX (v17.1, ANSYS Inc., PA) to calculate the CSF velocities and pressures. CSF in this study was modelled as a Newtonian fluid with 0.8 mPa s viscosity and 1000 kg m^{-3} density (Bloomfield et al., 1998). PC-MRI flow data from 5 mm cranial to the tip of the tonsils or the base of the skull was applied to the cranial end of the model as the inlet boundary condition. The caudal outlet was set to have a reference pressure of 0 Pa. The spinal cord and dura mater were treated as solid wall boundaries. The CSF flow was assumed to be laminar. All models were calculated with the measured time scales, but as there was minimal variation in heart rate between subject groups (ANOVA, p = .22), the output timescales were subsequently normalised for comparison. The models were validated by comparing features of

Please cite this article in press as: Lloyd, R.A., et al. Chiari malformation may increase perivascular cerebrospinal fluid flow into the spinal cord: A subject-specific computational modelling study. J. Biomech. (2017), https://doi.org/10.1016/j.jbiomech.2017.10.007