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Research paper

Intracranial volumetric changes govern cerebrospinal fluid flow in the Aqueduct of Sylvius in healthy adults

Maria Marcella Laganà [a,*], Simon J. Shepherd [b], Pietro Cecconi [a], Clive B. Beggs [c,d]

[a] Fondazione Don Carlo Gnocchi ONLUS, IRCCS S. Maria Nascente, Milan, Italy
[b] Medical Biophysics Laboratory, University of Bradford, Bradford, BD7 1DP, UK
[c] Buffalo Neuroimaging Analysis Center, Department of Neurology, School of Medicine and Biomedical Sciences, University at Buffalo, 100 High St., Buffalo, NY 14203, NY, USA
[d] Institute for Sport, Physical Activity and Leisure, Leeds Beckett University, Leeds, LS1 3HE, UK

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ABSTRACT

Purpose: To characterize the intracranial volumetric changes that influence the cerebrospinal fluid (CSF) pulse in the Aqueduct of Sylvius (AoS).
Materials and methods: Neck MRI data were acquired from 12 healthy adults (8 female and 4 males; mean age = 30.9 years), using a 1.5 T scanner. The intracranial arterial, venous and CSF volumes changes, together with the aqueductal CSF (aCSF) volume, were estimated from flow rate data acquired at C2/C3 level and in the AoS. The correlations and temporal relationships among these volumes were computed.
Results: The aCSF volumetric changes were strongly correlated ($r = 0.967$, $p < 0.001$) with the changes in intracranial venous volume, whose peak occurred 7.0% of cardiac cycle ($p = 0.023$) before peak aCSF volume, but less correlated with the intracranial arterial and CSF volume changes ($r = -0.664$ and 0.676 respectively, $p < 0.001$). The intracranial CSF volume change was correlated with the intracranial venous volume change ($r = 0.820$, $p < 0.001$), whose peak occurred slightly before (4.2% of CC, $p = 0.059$).
Conclusion: The aCSF pulse is strongly correlated with intracranial venous volume, with expansion of the cortical veins occurring prior to aCSF flow towards the third ventricle. Both caudal-cranial aCSF flow and venous blood retention occur when arterial blood volume is at a minimum.

1. Introduction

In recent years there has been growing interest in the role that the cerebral venous system plays in regulating the biomechanics of fluids inside the cranium, with several studies demonstrating a link between cerebral venous outflow and the dynamics of the cerebrospinal fluid (CSF) in the Aqueduct of Sylvius (AoS) (aqueductal CSF, aCSF) in healthy individuals [1,2] and in multiple sclerosis (MS) patients [3,4]. However, although these studies suggest that a link exists between the venous system and the aCSF pulse, the association between the two has not yet been explained. This is largely because the functional behaviour of the cerebral venous system is poorly understood. While the presence of an intracranial windkessel mechanism linking the arterial and CSF pulses is well recognised [5–8], there is much less agreement regarding the interaction of these fluids with the cerebral venous pulse. However, the fact that venous blood exiting the cranium is pulsatile [9,10], and that an arteriovenous delay (AVD) exists between the peaks in arterial and venous flow [11], suggests that transient storage of blood occurs in the cerebral veins at some point throughout the cardiac cycle (CC). Nevertheless, much still remains unknown about the fluid volumetric changes that occur within the cranium over the CC, and the source of the compliance that causes the AVD.

In healthy young adults, blood flow through the cerebral capillary bed is constant and non-pulsatile [5], despite the considerable increase in arterial blood entering the cranium that occurs during systole. This additional blood is transiently stored during systole in the cranial arteries, including the pial arteries that run through the sub-arachnoid space (SAS), which duly expand, displacing CSF out of the cranium into the spinal column. During diastole, when the arterial flow entering the cranium drops below the mean, the blood stored in the arteries is displaced, by elastic recoil, from these vessels into the cerebral capillary bed [12] ensuring that a constant blood flow is maintained through the parenchymal capillaries [5]. As such, the system acts as a windkessel mechanism that

* Corresponding author at: IRCCS, Fondazione Don Carlo Gnocchi ONLUS, Via Capecelatro, 66, 20148, Milan, Italy.
E-mail addresses: marcella.lagana@gmail.com, mlagana@dongnocchi.it (M.M. Laganà).

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not only regulates blood flow within the cranium, but also drives the CSF pulse across the foramen magnum. In comparison to the cervical CSF pulse, the motion of the CSF pulse in the AoS is less well understood. The aCSF pulse, which is closely linked with the motion of the lateral ventricles [13], has an amplitude that is an order of magnitude less than that of the CFS pulse in the upper neck [9]. Because of its central position and proximity to the lateral ventricles, aCSF is often measured in order to assess structural changes that may be occurring in the brain parenchyma. Numerous studies have found increased pulsatility of the aCSF to be associated with MS [3,4,14,15], normal pressure hydrocephalus [16–19], and the formation of dirty appearing white matter [20], suggesting that abnormalities in this pulse may be linked to pathological changes. However, use of the aCSF pulse as a focal indicator of structural changes has been considerably hampered by a general lack of understanding of the factors that influence its motion.

In the study presented here we applied a signal processing methodology to compute the transient volumetric changes that occur in the intracranial fluids throughout the CC. Although many researchers have accurately quantified the cervical blood and CSF flows to and from the cranium using MRI [9,21–26], characterizing the intracranial interactions between these fluids has been more troublesome. However, because the cranium is a rigid container and the fluids enclosed within it are incompressible [27], in theory it should be possible to characterize the behaviour of the various intracranial fluids solely through interpretation of extracranial fluid flow signals acquired from the cervical vessels. To this end, we developed a novel volumetric model, which interpreted fluid flow signals in the neck, to characterize the temporal changes that occur in the intracranial arterial, venous and CSF volumes over the CC. We then used the model to investigate transient changes in intracranial blood and CSF volumes in healthy young adults, with the aim of gaining new insights into the fluid interactions that occur within the cranium and showing how these relate to the motion of the CSF in the AoS.

2. Materials and methods

2.1. Subjects

Twelve healthy young adults were enrolled on the study. Inclusion criteria were age <45 years and a normal neurological examination. Exclusion criteria were: history of neurological, cardiovascular or metabolic disorders and abnormalities on brain anatomical MRI.

The study was approved by the local Ethics Committee of Don Gnocchi Foundation (Milan, Italy) and a written informed consent was obtained from all subjects prior to study entry.

2.2. Magnetic resonance acquisition and processing

Brain and neck MRI were acquired from all subjects, using a 1.5 T scanner (Siemens Magnetom Avanto, Erlangen, Germany), equipped with a 8-channel head coil and a 4-channel neck coil. The acquisition protocol consisted of: 1) brain and neck T1-weighted localizer, for the slice positioning of the subsequent sequences; 2) brain 2D dual-echo turbo spin echo to assess any anatomical abnormalities (TR = 2650 ms, TE = 28/113 ms, echo train length = 5, flip angle = 150°, 50 interleaved, 2.5-mm-thick axial slices with a matrix size = 256 × 256, interpolated to 512 × 512, FOV = 250 × 250 mm); 3) 2D TOF MR venography of the neck, with a saturation band positioned caudal to the 128 axial slices (in-plane resolution = 0.5 × 0.5 mm^2, slice thickness = 3 mm, distance factor between subsequent slices = −20, FOV = 256 × 192 mm^2, TR = 26 ms, TE = 7.2 ms, flip angle = 70°); 4) three retrospective cardiac gated 2D PC MRI for the quantification of arterial and venous flows through the main cervical vessels, CSF flow at between the second and the third cervical vertebrae (C2/C3 level) (cCSF) and aCSF. The sequence parameters were respectively (blood/cCSF/aCSF): TR = 33.75/30.2/30.2 ms, TE = 5.11/7.6/7.6 ms, flip angle = 30°/10°/10°, matrix size = 288 × 384/256 × 256/256 × 256, pixel size = 0.67 × 0.67/0.62 × 0.62/0.45 × 0.45 mm^2, slice thickness = 4/4.5/4.5 mm, maximum encoding velocity (Venc) = 50/15/15 cm/s. A finger pulse oximeter was used in order to reconstruct different time points in the CC, depending on the heart rate frequency. The slice of the PC sequences were positioned perpendicularly to the flow of interest: for the cervical blood flow the sagittal neck localizer and the sagittal and coronal TOF Maximum Intensity Projection images were used for positioning the PC slice at the C2/C3 level perpendicularly to the internal jugular veins (IJVs) (Fig. 1A–C); for the cCSF flow the sagittal neck localizer was used for positioning perpendicularly to the spinal canal at C2/C3 level (Fig. 1A); for the aCSF flow the sagittal brain localizer was used (Fig. 2) for positioning perpendicularly to the AoS.

The flow data were processed with FlowQ software [28] by a single trained examiner. For every PC sequence, two kinds of regions of interest (ROIs) were manually drawn on the magnitude and phase images: in the structures of interest; for their flow quantification; and in stationary structures for the estimation of the phase offset. The internal jugular veins (IJVs), vertebral veins (VVs), internal carotid arteries, vertebral arteries were segmented on the PC images with Venc = 60 cm/s (Fig. 1d and e). The contours were drawn in the first time point and copied for every time point in the CC, adjusting them if needed. When phase aliasing was detected, pixel values were corrected with the algorithm described in a previous work [28]. The CSF (Fig. 1g) and the aCSF (Fig. 2c) were segmented on the PC images with VENC = 15 cm/s. The SAS contours were drawn on the phase image corresponding to the time point with the highest caudal flow velocity, since this shows the highest contrast. The magnitude image (Fig. 1f and b) was used to increase the confidence of the contours. For every pixel inside the segmented vessels or the CSF, and for every time point, the phase value, corrected by the offset and by the aliasing, was mapped to velocity. According to Siemens convention, positive CSF flow corresponds to cranial direction, negative CSF flow corresponds caudal direction. The flow rate (in ml/s) was computed for each time point, based on the mean velocity and on the cross sectional area of the corresponding structure.

2.3. Volumetric model and data analysis

Flow data and statistical analysis were undertaken using in-house algorithms written in Matlab (Mathworks, Natick, Mass). Arterial flow rate was computed as the sum of the flow in the internal carotid and vertebral arteries and the venous flow rate as the sum of IJVs and VVs flow rates. The arterial, venous, cCSF and aCSF flow rate signals were resampled to 32 data points over the CC. The corresponding cervical flow volume signals were computed, using the trapezoidal method for the discrete-time integration. All the timings were expressed as a fraction of the CC and as a delay from the arterial systole. For each fluid, the flow rate caudal and cranial peak amplitudes and timings were computed. The pulsatility index (*PI*) and the resistance index (*RI*) [29] were calculated as the difference between systolic and diastolic peaks normalized by the mean or the systolic peak flow rate, respectively. For the CSF, we computed a caudal and a cranial *RI*, normalizing by the systolic or diastolic peak, respectively. The cCSF and aCSF stroke volumes (i.e. the average CSF volume displaced throughout the CC) were cal-