Estimating intracranial fluid dynamics using quantitative analyses of phase contrast magnetic resonance images

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Abstract
Objective: To estimate the dynamic relations between cerebrospinal fluid (CSF) and blood in the cerebral and spinal subarachnoid spaces and in the cerebral ventricles by quantifying phase contrast magnetic resonance imaging (MRI). Material and methods: 15 healthy volunteers were analyzed during the same hourly stripe and using the same magnetic field strength (3 T). Each study consisted of four phase contrast sequences: two to calculate the CSF (aqueduct of Sylvius and the C2-C3 perimedullary space) and two to calculate the blood flow (internal carotid and vertebral arteries, superior sagittal sinus, and straight sinus). Amplitude parameters (systolic volume, mean flow, pulsatility and compliance indexes, absolute pressure gradient, and ratio of CSF stroke volume) and temporal parameters (delays respect to arterial flow) were calculated. Results: With respect to the input of arterial blood, the displacement of venous blood (22 % and 38 % of the cardiac cycle in the straight sinus and superior sagittal sinus, respectively) and of CSF (12 % and 25 % of the cardiac cycle in the C2-C3 perimedullary space and in the aqueduct of Sylvius, respectively) show the distribution of the pulsatility of the intracranial fluids. Indexes of compliance of the encephalic and medullary compartments in normal subjects were calculated.

Conclusions: It is possible to quantitatively describe the dynamic relations between intracranial fluids and infer the elastic behavior of the brain and spinal canal by using flow velocity maps obtained with phase contrast MRI.

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KEYWORDS
Magnetic resonance imaging; Cerebrospinal fluid; Blood; Compliance
Introduction

Intracranial volume is principally composed of three elements: cerebrospinal fluid (CSF), blood and the cerebral parenchyma. Blood entry into the interior of the cranium during systole raises the intracranial volume. According to the Monroe-Kellie doctrine, a decompensation should occur in the remaining volumes to keep the total volume constant when one volume is modified. Diverse neurodegenerative and cerebrovascular diseases induce disequilibrium in cerebral homeostasis.1,2 It is because of this that more complete knowledge about the dynamic relationships of intracranial liquids (CSF and blood) and contribute relevant information for the diagnosis and treatment of some diseases. The development of a quantitative methodology of imaging biomarkers to analyse these dynamic behaviours in an average population is essential before its clinical utilisation.

Dynamic magnetic resonance (MR) sequences acquired with sequences of phase contrast (PC-MRI) and cardiac synchronism have opened new channels for the study of the physiological changes that occur in fluid dynamics. The measurement of flow using PC-MRI is precise and always reproducible, provided that a protocol of acquisition and adequate post-processing are used. The post-process techniques should also take into account errors related to the effect of partial volume caused by the presence of stationary tissue, like flow in the interior of the voxels of the periphery of the region to study.17-23

After obtaining the velocity maps using appropriate methodology, it is possible to quantify the volume of blood flow and CSF displaced in the cranio-caudal direction during systole and caudocranial flow during diastole.1 This information provides a description of the regulation mechanisms of the pressure and of the intracranial compliance during a cardiac cycle. The objective of this work is to estimate, by means of the quantification of PC-MR images, the dynamics of craniospinal fluids (CSF and blood) and deduce the cerebral elastic behaviour.10,11

In order to obtain a normal dynamic model in a healthy control population, the parameters of amplitude (increase of volume of flow during systole, average flows, compliance and pulsatility indexes, pressure variations, supratentorial CSF production, and the relation of CSF fluid volume between the ventricular space and the spinal dural sac) and of temporal relations (delays opposite the entry of arterial flow to the brain) were studied.

Material and methods

Subjects

Fifteen healthy control volunteers of between 23-28 years (27 ± 4 years [mean ± standard deviation]) of age,
Consisting of 8 males and 6 females, were chosen prospectively. The average heart rate of the subjects was 68 ± 8 beats/min. None of the volunteers presented with a clinical history of neurological problems or cerebrovascular disease. All subjects were informed of the procedure and the objective of the study and their signed consent was obtained.

Acquisition of data

All the examinations were performed in the same hourly stripe (14:00 to 15:00), with the same MR equipment with a magnetic field strength of 3 teslas (Achieva Intera, Philips Medical Systems, Best, Netherlands) in order to avoid the influence of the circadian rhythm and magnetic field in the measurements.

In all cases, a sequence of PC-MRI was acquired in synchrony with the cardiac cycle using a peripheral pulse device. Twenty-five temporal points were retrospectively reconstructed per cardiac cycle. The images were obtained using a field of view of 170 mm, with a slice thickness of 5 mm and a matrix size of 512 × 512, which permitted a spatial resolution of 0.33 × 0.33 × 5 mm. Two averaged signals were acquired. The values selected for repetition time (TR = 18 ms), echo time (TE = 8 ms), and an excitation angle of 10° were constant in order to optimise the temporal resolution, the signal to noise ratio, and to reduce dispersions of the spin phase.

For every MR study, four acquisitions of PC-MRI were obtained. The first sequence was obtained perpendicular to the aqueduct of Sylvius with a velocity encoding (V_{enc}) of 80 cm/s; and a fourth sequence, also parallel to the level of intervertebral disc C2-C3, for the calculation of perimedullary CSF, with a V_{enc} of 15 cm/s; the second, parallel to the level of intervertebral disc C2-C3 for the calculation of arterial entry (both internal carotids and the two vertebral arteries) with a V_{enc} of 80 cm/s; and a fourth sequence, 2 cm above the C2-C3 level, for the calculation of perimedullary CSF, with a V_{enc} of 15 cm/s; a third sequence, also parallel to the level of intervertebral disc C2-C3 for the calculation of perimedullary CSF, with a V_{enc} of 80 cm/s; and a fourth sequence, 2 cm above the level of intervertebral disc C2-C3 for the calculation of arterial entry (both internal carotids and the two vertebral arteries) with a V_{enc} of 80 cm/s; and a fourth sequence, 2 cm above the

Quantification of parameters and dynamic relations of intracranial fluids

Eight parameters of amplitude were quantified from the curves of arterial and venous blood flow and of CSF reconstructed with the temporal information obtained thanks to the cardiac synchronism:

1. Systolic volume, measured in microliters, is calculated as the area under the curve of flow in the systole. This value represents the increase of flow volume that occurs during the systole above the mean flow volume.
2. Mean flow, calculated as the mean of the absolute values of the measurements obtained in the systole and the diastole. It is expressed in ml/min.
3. Pulsatility index, calculated as the ratio between the difference of peak systolic and diastolic flow compared with the mean flow.
4. Amplitude of pressure gradient resulting from changes in flow rate applying the theory of fluid mechanics (equations of Navier-Stokes). This method estimates the variations of absolute pressure in the flow and, therefore, in the walls during the cardiac cycle. It is calculated through the following equation:

\[ VP = -\delta \frac{\partial v}{\partial t} + v \cdot \nabla v + \mu \cdot \nabla^2 v \]  

(1)

where \( \delta \) is the fluid density, \( \mu \) is the fluid viscosity (in centipoise, cP), and \( v \) and \( P \) are the vectors of velocity and pressure, respectively. For CSF, \( \delta = 1.0007 \text{g/ml} \), and \( \mu = 1.1 \text{cP} \); for blood, \( \delta = 1.0007 \text{g/ml} \), and \( \mu = 4.3 \text{cP} \).

5. Compliance index (CI). This provides an indirect measurement of the intracranial deformability analysing the arteriocerebral relationship. It is analysed with respect to the increase of arterial volume in the systole and is calculated using the following equation:

\[ DI = \frac{SV_{artery} - SV_{region}}{SV_{region}} \]  

(2)

\[ SV_{artery} \] is the flow volume in the systole. This

\[ SV_{region} \] is the flow volume.

\[ SV_{artery} \] is the

\[ SV_{region} \] is the flow volume.

\[ SV_{artery} \] is the

\[ SV_{region} \] is the flow volume.

Figure 1 Locators for the four acquisitions of PC-MRI. a) Sagittal slice of a T1 weighted turbo inversion recovery sequence used to determine flow acquisition level for the cerebral aqueduct (1) and C2-C3 space (2). b) Fast coronal angiography used to determine the acquisition level for the internal carotid, vertebral arteries and jugular veins (3). c) Fast sagittal angiography to determine the acquisition level for the straight and superior sagittal sinuses.
where SV is the systolic volume and region refers to the
systolic volume in the aqueduct or C2-C3 perimedullary
space.
6. Supratentorial CSF production in ml/min, measured as
the difference between the volume of systolic and
diastolic flow in the aqueduct of Sylvius per unit of
time.
7. Ratio of volume of CSF displaced from the ventricular
system to the subarachnoid space during a cardiac cycle,
which is expressed as a percentage. The volume per
cycle, in μl/cycle, is calculated as the mean of the
displaced volume in the systole and diastole. This value
is different from the previously mentioned systolic
volume.
8. In addition to the amplitude parameters, a temporal
relationship of the delay of the outflows (venous and
CSF) versus arterial entry to describe the temporal
distribution of the intracranial fluids along the
craniospinal axis was calculated. The cardiac cycle is
expressed as a percentage, measured between systolic
peaks, and is calculated with the systolic peak of the
arterial entry (identified as the initial point of the cycle)
as the reference.

A post-processing image-analysis tool developed in-house,
implemented in Matlab R7 (The Math-Works, Inc., Natick,
MA, USA) was used for the quantitative measurement of the
different parameters. This tool incorporates algorithms of
semiautomatic segmentation to delineate for regions with
laminar flow patterns (aqueduct of Sylvius and vascular
structures) as well as turbulent flow patterns (perimedullary
spaces). For the first regions, thresholding techniques were
employed, whereas k-means techniques were
employed for the more complex regions. By using the
k-means method the pixels that conform to the ROI are
classified based on three temporal attributes that
characterise the CSF flow behaviour (tendency of the flow,
spectral decompensation of the velocity signal obtained
during a cardiac cycle through the fast Fourier transform
and mean absolute velocity). Figure 2 shows the different
ROIs selected in one of the analysed volunteers. Mean
values and SD of the areas of each region were 5 ± 2 mm²
for the aqueduct of Sylvius, 12 ± 2 mm² for the carotids,
107 ± 22 mm² for the C2-C3 perimedullary space, 7 ± 2 mm²
for the straight sinus and 26 ± 7 mm² for the superior
gittal sinus.

Results
For a control population, the average values and SD of the
parameters obtained from the different vascular structures
and spaces of CSF are presented in table 1. The production
of CSF measured in the aqueduct of Sylvius was
0.24 ± 0.19 ml/min. The ratio of the volume of CSF displaced
from the ventricular system to the subarachnoid space in a
cardiac cycle was 5.24 ± 3.55%.

With respect to temporal relationships, the peak systolic
of the CSF displacement to the spinal subarachnoid space
occurs at 12 ± 10% of the cardiac cycle after the arterial
systolic peak. Then, almost simultaneously, we observed the
peak venous flow in the straight sinus and the CSF flow
through the aqueduct of Sylvius (occurring at 22 ± 4% and
25 ± 13% after the arterial peak, respectively). Finally,
maximum displacement of blood is produced through the
superior sagittal sinus, at approximately 38 ± 16% after the
arterial peak (fig. 3).

Discussion
Neuroimaging techniques and quantification of biomarkers
have opened new ways for the study of the changes on the
dynamics of fluids, which can either produce, or to be
secondary to various neuropathological disorders. The
establishment of imaging biomarkers needs adequate
acquisition protocols and analysis methodology and the
study of reference values. Only with these will we be able
to increase knowledge about the disease states and be
reliable in diagnosing these pathologies.

Although our study is limited, its importance lies in to
methodologically analyze in a population healthy control
diverse parameters of the dynamics of fluids. These
biomarkers are related to the elastic behavior and the
compliance of the brain.

The stroke volume measured in the aqueduct of Sylvius
has been considered as a biomarker for Normal Pressure
Hydrocephalus (NPH). However, its usefulness is
questionable because this parameter does not permit
differentiation when there is an overlap by comorbidity
among patients with NPH, Alzheimer’s and vascular
dementia. Because of this caveat, this imaging biomarker
is not sufficient for conducting a reliable and precise
diagnosis between these entities. Therefore, it seems
necessary to include other parameters that reflect the state
of the intracranial dynamic in a multivariate approach.
Moreover, it is probable that other neurological entities also
produce or associate changes in the parameters of flow and
their temporal relationships. Before analysing broad series
of subjects with established diseases and grades of variable
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<table>
<thead>
<tr>
<th>Parameters</th>
<th>Arterial Input</th>
<th>Aqueduct of Sylvius</th>
<th>Space C2-C3</th>
<th>Straight Sinus</th>
<th>Superior Sagittal Sinus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic volume (mL/cycle)</td>
<td>1.300 ± 196</td>
<td>34 ± 18</td>
<td>544 ± 122</td>
<td>58 ± 18</td>
<td>247 ± 76</td>
</tr>
<tr>
<td>Mean flow (mL/min)</td>
<td>660 ± 104</td>
<td>5 ± 2</td>
<td>75 ± 12</td>
<td>90 ± 10</td>
<td>320 ± 90</td>
</tr>
<tr>
<td>Pulsatility Index</td>
<td>1.03 ± 0.15</td>
<td>0.35 ± 0.26</td>
<td>1.42 ± 0.33</td>
<td>0.33 ± 0.04</td>
<td>0.39 ± 0.10</td>
</tr>
<tr>
<td>Compliance Index</td>
<td>Reference Value</td>
<td>35 ± 10</td>
<td>1.10 ± 0.45</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Amplitude pressure gradient (mm Hg/cm)</td>
<td>0.31 ± 0.08</td>
<td>0.07 ± 0.03</td>
<td>0.07 ± 0.02</td>
<td>0.11 ± 0.03</td>
<td>0.09 ± 0.03</td>
</tr>
</tbody>
</table>

*The results are expressed as mean ± standard deviations.

# Table 1: Amplitude Parameters Values Obtained from 15 Healthy Volunteers

## Figure 3: Temporal distribution of intracranial fluids. AcS: aqueduct of Sylvius; ART: arterial input; SR: straight sinus; SS: superior sagittal sinus, and C2-C3 intervertebral disc.

Current value against reference value, respectively, stroke volume (33.43 ± 18.49 vs. 39.51 ± 18.21 mL/cycle) and CSF production (0.24 ± 0.19 vs. 0.45 ± 0.34 ml/min).

The small differences between the studies reflect the bias associated with the differences in age, hourly stripe of acquisition of the studies and magnetic field intensity of the equipment utilised. Arterial entry to the cranium in systole raises the intracranial pressure (ICP) by increasing volume. The CSF volume that is displaced in systole along the aqueduct of Sylvius and the C2-C3 perimedullary space is related to the property of the intracranial arterial tree to cushion the arterial pulse within its proximity (efecto windkessel). The dinstensibility index measured in this investigation relates the volume of CSF with the volume of arterial flow, A reduced index is caused by the displacement of elevated CSF, which, at the same time, reflects the loss of compliance of the adjacent parenchyma and its vascular tree. The great difference that exists between the CI measured in the aqueduct of Sylvius and the C2-C3 space (35 and 1.10, respectively) is related to the adjacent parenchyma (midbrain and medulla, respectively) and with the proportion of CSF outflow at the two levels. Bateman et al. previously calculated the CI in the aqueduct of Sylvius, and their mean value (32 ± 15) was similar to that obtained in this study. It is important to highlight this similarity even with subjects with marked difference in age (43 years older than our subjects) because of the loss of elasticity in the intracranial vessels. This similarity appears to be due to the multipule effects of field strength intensity (at a lower intensity decreased flow measures). The 30% increase in volume of CSF measured by Bateman et al. agrees with the aging of his population and the loss of arterial absorption. The smallest deviation of arterial flow volume of our series can be explained by the different vascular structures chosen (internal carotid arteries and vertebral arteries). This deviation justifies the similarity of the CI values obtained in subjects with different ages.

ICP is measured for the diagnosis and control of numerous diseases, both neurological and cerebrovascular. Its value is always obtained by invasive methods (lumbar puncture) but also through less risky methods. Using PC-MRI, it can be calculated based on the exponential curve between volume and pressure, in which the elastance (ability of a structure, deformed by pressure, to regain its initial form) has a linear relationship with the ICP. On the other hand, the elastance...
is the inverse of the compliance. PC-MRI can quantify the change of intracranial volume and changes in pressure flow during a cardiac cycle. Alperin et al. calculated the ICP as the quotient between the amplitude of the gradient pressure curve derived from the secondary changes of velocity and the amplitude of the curve of intracranial volume change. In the present study, we have not calculated the ICP but rather the amplitude of the absolute pressure gradient in the vascular structures and the CSF spaces, reflecting in an indirect manner the state of the ICP. Calculating the ICP as Alperin et al. is associated with the difficulty of obtaining accurately the total outflow volume.

The physiology of CSF is complex and still not well understood. Different studies have revealed transparent, chymal production and absorption of CSF. Gertz et al. have confirmed the absorption of liquid through the perivascular spaces and brain capillaries, suggesting that this mechanism occurs through the Starling principle to balance the hydrostatic pressure and the osmotic force within the capillary.

A detailed analysis of the intracranial dynamic in the different encephalic pathologies, as well as a greater knowledge of their temporal patterns and relationships, would provide information of enormous relevance for the development of reliable and reproducible diagnostic methodologies based on imaging biomarkers. Through velocity flow maps obtained with MR, it is possible to quantitatively describe the dynamic relations of the intracranial flow and infer the medullar and elastic cerebral behaviour.

Declaration of conflict of interests
The authors declare they have no conflicts of interest.

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Authorship
All the authors contributed to the conception, design study, obtaining of facts, analysis and interpretation. Each has been involved in the drafting and critical review of the work by making intellectual and relevant contributions.

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