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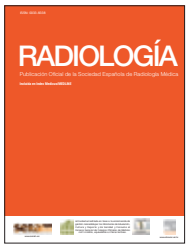

ORIGINAL

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

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KEYWORDS
Magnetic resonance imaging;
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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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PALABRAS CLAVE
Resonancia magnética;
Líquido cefalorraquídeo;
Sangre;
Distensibilidad

Estimación de la dinámica de líquidos intracraneales mediante análisis cuantitativo de imágenes de resonancia magnética de contraste de fase

Resumen
Objetivo: Estimar las relaciones dinámicas entre los fluidos craneoespinales (líquido cefalorraquídeo [LCR] y sangre) en el espacio ventricular, subaracnoideo cerebral y subaracnoideo espinal mediante la cuantificación de imágenes de resonancia magnética (RM) en contraste de fase.
Material y métodos: Se analizaron 15 sujetos voluntarios sanos en la misma franja horaria y bajo la misma intensidad de campo (3 T). Para cada estudio se realizaron 4 exploraciones en contraste de fase: 2 secuencias para el cálculo de LCR (acueducto de Silvio y espacio perimedular C2-C3) y 2 para el cálculo del flujo sanguíneo (arterias carótidas internas y vertebrales, seno sagital superior y recto). En todos los sujetos se calcularon los parámetros de amplitud (volumen sistólico, flujo promedio, índices de pulsatibilidad y distensibilidad, amplitud del gradiente de presión absoluta y relación de volumen de fluido de LCR por ciclo) y temporales (retrasos frente a la entrada de flujo arterial).
Resultados: Respecto a la entrada de sangre arterial, el desplazamiento de sangre venosa (al 22 y 38% del ciclo cardíaco en los senos recto y sagital superior, respectivamente) y del LCR (al 12 y 25% de ciclo cardíaco en el espacio perimedular C2-C3 y el acueducto de Silvio, respectivamente) describen la distribución de la pulsatibilidad de los fluidos intracraneales. Se obtienen índices de distensibilidad para los compartimientos encefálico y medular en una población normal.
Conclusiones: Mediante los mapas de velocidad de flujo obtenidos con RM es posible describir de manera cuantitativa las relaciones dinámicas de los fluidos intracraneales e inferir el comportamiento elástico encefálico y medular.

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[1] 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.[2-6] It is because of this that more complete knowledge about the dynamic relationships of intracranial liquids (CSF and blood) can contribute to relevant information for the diagnosis and follow-up 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 ought to select the regions of interest (ROI) independently of the operator. In addition, the background errors of the imperfect suppression of the induced electromagnetic currents, the contribution to the signal of the small movements of the brain because of the vascular pulse, and the aliasing must all be corrected. These analysis 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.[7,8]

After obtaining the velocity maps using appropriate methodology, it is possible to quantify the volume of blood flow and CSF displaced in the craniocaudal direction during systole and caudocranial flow during diastole.[9] 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[12] 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.[8]

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 15 cm/s; the second, parallel to the level of intervertebral disc C2-C3 for the calculation of perimedullary CSF, with a V_{enc} of 7 cm/s; a third sequence, also parallel to the C2-C3 level, 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 confluence of the venous sinuses, in order to analyse the flow in the superior sagittal sinus and in the straight sinus, with a V_{enc} of 80 cm/s (fig. 1)

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.[6,13]
4. Amplitude of pressure gradient resulting from changes in flow rate applying the theory of fluid mechanics (equations of Navier-Stokes).[10,14] 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:

$$\nabla P = -\delta\left(\frac{\partial v}{\partial t} + v\cdot\nabla v\right) + \mu\cdot\nabla^2 v \qquad (1)$$

where δ is the fluid density, μ is the fluid viscosity (in centipoise, cP), and v and P are the vectors of velocity and pressure, respectively. For CSF, δ = 1.0007 g/ml, and μ = 1.1 cP; for blood, δ = 1.0007g/ml, and μ = 4.3 cP.5.
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:[15]

$$DI = \frac{SV_{arterial} - SV_{region}}{SV_{region}} \qquad (2)$$

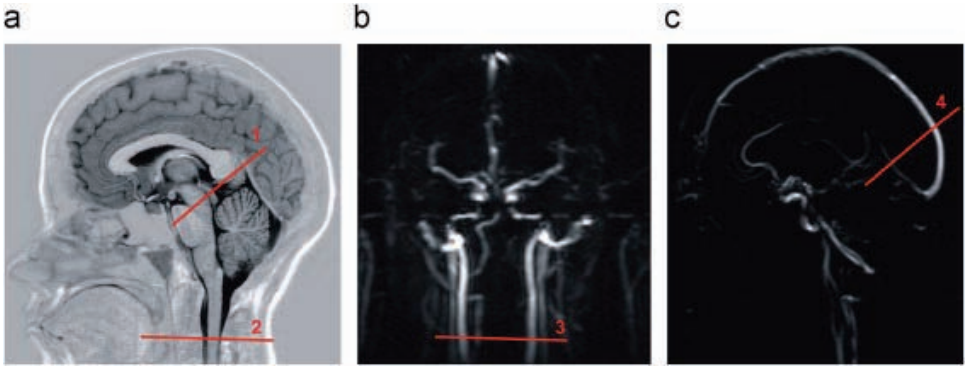

Figure 1 Locators for the four acquisitions of PC-MRI. a) Sagittal slice of a T1 weighted turbo inversion recovery sequence used to determine flow acquisition level for the cerebral aqueduct (1) and C2-C3 space (2). b) Fast coronal angiography used to determine the acquisition level for the internal 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[16] 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 mm^2 for the aqueduct of Sylvius, 12 ± 2 mm^2 for the carotids, 107 ± 22 mm^2 for the C2-C3 perimedullary space, 7 ± 2 mm^2 for the straight sinus and 26 ± 7 mm^2 for the superior sagittal sinus.

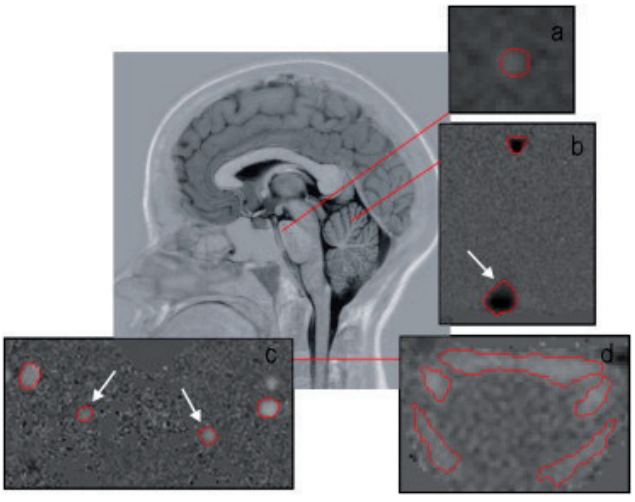

Figure 2 Regions of interest defined in the examined regions of a volunteer: a) aqueduct of Sylvius; b) superior sagittal sinus (arrow) and straight sinus; c) vertebral arteries (arrows) and internal carotid arteries, and d) C2-C3 intervertebral disc.

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 biomarcadores 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).[3,17,18] 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.[14] 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

Table 1 Amplitude Parameters Values Obtained from 15 Healthy Volunteers

Parameters	Arterial Input	Aqueduct of Sylvius	Space C2-C3	Straight Sinus	Superior Sagittal Sinus
Systolic volume (μl/cycle)	1.300 ± 196	34 ± 18	544 ± 122	58 ± 18	247 ± 76
Mean flow (ml/min)	660 ± 104	5 ± 2	75 ± 12	90 ± 10	320 ± 90
Pulsatility Index	1.03 ± 0.15	0.35 ± 0.26	1.42 ± 0.33	0.33 ± 0.04	0.39 ± 0.10
Compliance Index	Reference Value	35 ± 10	1.10 ± 0.45	—	—
Amplitude pressure gradient (mm Hg/cm)	0.31 ± 0.08	0.07 ± 0.03	0.07 ± 0.02	0.11 ± 0.03	0.09 ± 0.03

[a]The results are expressed as mean ± standard deviations.
[b]The arterial flow is the sum of the flow measured in the internal carotid arteries and vertebral arteries.

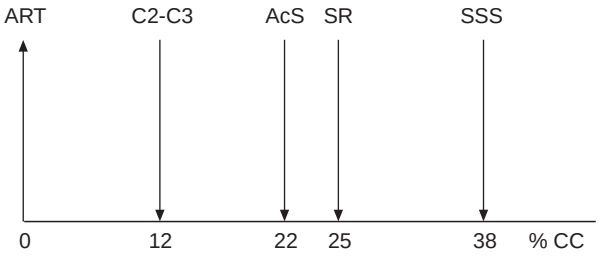

Figure 3 Temporal distribution of intracranial fluids. AcS: aqueduct of Sylvius; ART: arterial input; SR: straight sinus; SSS: superior sagittal sinus, and C2-C3 intervertebral disc.

affectation, it is imperative to know the mean values and their dispersion in a series of subjects with neither illness nor degeneration.

The intracranial dynamic is defined as the interaction between the cerebral tissue, the CSF and the blood flow within the central nervous system. The mean flow in the internal carotid arteries and the vertebrae gives an estimate of the total volume of arterial entry into the interior of the cranium. The CSF in the aqueduct of Sylvius and in the perimedullary space at level C2-C3, joined with the venous outflow through the straight sinus and the superior sagittal sinus, reflect the compensation of volume that occurs as a consequence of the expansion of the arterial vascularisation. Given that the bone cavity of the cranium is fixed, the intracranial volume ought to be constant and the relationship between the distinct components that contribute to the total volume stable in normal conditions. Therefore, the entry of blood volume to the interior of the cranium ought to be equal to the sum of the output of the venous fluid volumes and of CSF in the C2-C3 perimedullary space. In this investigation, the input of arterial volume did not equal the 2 evaluated outputs, primarily due to the fact that the total venous flow is also achieved through other avenues, which were not included in their entirety. We studied the large venous structures, such as the straight sinus and the superior sagittal sinus, instead of smaller structures like the jugular veins and anastomotic drainages, which are less rigid and more difficult to identify and quantify.[19] As an internal control, the obtained values in this study in the aqueduct of Sylvius did not present relevant differences compared to the flow parameters previously obtained in a different own series of normal subjects with the mean flow (5 ± 2 vs. 6 ± 3 ml/min, 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 biases associated with the differences in age, hourly stripe of acquisition of the studies and magnetic field intensity of the equipment utilised.[20]

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 distensibility 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.[15] 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 multiple effects of field strength intensity (at a lower intensity decreased flow measures).[21] The 30% increase in volume of CSF measured by Bateman et al.[15] agrees with the aging of his population and the loss of arterial absorption.[22] 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 theCI 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,[23] 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.[10] 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 transparenchymal production and absorption of CSF. Greitz et al.[24] have confirmed the absorption of liquid through the perivascular spaces and brain capillaries, suggesting that this mechanism occurs through the Starling principle[25] 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.

Financing

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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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