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RESEARCH ARTICLE

Intracranial Cerebrospinal Fluid Volume Evaluation in Healthy People and Hydrocephalus Patients using SPACE Sequence

Xiaofeng Wu[1], Seidu A. Richard[2,4], Xu Xiangdong[1], Zhang Lirong[3] and Wu Min[1,2,*]

[1]*Department of Neurosurgery, Jiangyin Hospital, Southeast University, Jiangyin, 214400, Jiangsu province, P.R. China;* [2]*Department of Neurosurgery, The Affiliated Hospital of Jiangsu University, Zhenjiang, 212001, Jiangsu Province, P.R. China;* [3]*Department of Radiology, The Affiliated Hospital of Jiangsu University, Zhenjiang, 212001, Jiangsu Province, P.R. China;* [4]*Department of Medicine, Princefield University, P. O. Box MA 128, Ho, Ghana West-Africa.*

Abstract: ***Introduction*:** Cerebrospinal Fluid (CSF) is produced mainly by the choroid plexus but with a substantial influence by the ependymal lining of the ventricles in the brain. Hydrocephalus occurs as a result of discrepancy in the production as well as circulation of CSF as a result of congenital and acquired conditions. Nevertheless, studies on the differences between CSF dynamics according to age and gender are still insufficient. Thus, this study evaluated the volume of intracranial CSF in healthy people and hydrocephalus patients taking into account the differences between CSF dynamics according to age and gender using **S**ampling **P**erfection with **A**pplication optimised **C**ontrast using different flip-angle **E**volution (SPACE) sequence.

***Methods*:** 120 healthy volunteers and 60 patients with hydrocephalus were included in this study. SPACE sequence was used to evaluate intracranial CSF with a 3.0T magnetic resonance machine. The total volume of intracranial CSF and the amount of CSF in the ventricle were obtained using a software, and the volume ratio of CSF in the subarachnoid space, the ventricle and the subarachnoid space were calculated.

***Results*:** The mean volume of intracranial CSF, ventricular CSF, and subarachnoid CSF of male volunteers were (206.9±47.7) cm3, (33.0±10.7) cm3, (173.9±37.9) cm3 respectively. The average volume of intracranial CSF, ventricular CSF, and subarachnoid CSF of female volunteers were (199.7±44.9) cm3, (30.8±9.4) cm3, and (168.9±37.0) cm3, respectively. Thus, no significant statistically ($P>0.05$) difference between males and females was found. (3) The mean values of intracranial CSF, ventricle CSF and subarachnoid CSF, ventricle and subarachnoid CSF volume ratio in patients with hydrocephalus were significantly greater than health volunteers. Thus, the difference between the two groups was statistically significant ($P<0.05$).

***Conclusion*:** SPACE sequence can quantitatively determine the content of CSF. The change of CSF volume has nothing to do with gender but with age. It is feasible to use SPACE sequence to evaluate the spatial distribution and volume of intracranial CSF.

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1. INTRODUCTION

Cerebrospinal Fluid (CSF) is produced mainly by the choroid plexus but with a substantial influence by the ependymal lining of the ventricles in the brain [1, 2]. CSF is produced at a rate of approximately 500 mls/day (0.35 ml/min) and the entire cerebral as well as CSF volume is about 150mls in normal individuals [1]. Water passes down an osmotic gradient into the ventricle *via* a maintained energy dependent sodium pump across the epithelial cells of the choroid plexus [1]. CSF is transported into the subarachnoid space through the foramina of Luschka as well as Magendie of the fourth ventricle [1, 2]. Finally, CSF is absorbed into the venous system through the arachnoid villi as well as granulations into the superior sagittal sinus [1, 2].

Hydrocephalus occurs when the ventricular system enlarges due to excessive accumulation of CSF, leading to distortion of the brain as well as increased Intracranial Pressure(ICP) [1, 3, 4]. In most cases, this occurs as a result of discrepancy in the production as well as circulation of CSF as a result of congenital as well as acquired conditions [1, 2]. Based on the site of CSF obstruction, hydrocephalus is classified into non-communicating (obstruction within the ventricular system) or communicating (obstruction outside ventricular system) [1, 2, 5]. The symptomatology of hydrocephalus varies according to age as well as will the underlying etiology [1, 4]. Management of hydrocephalus is often based on the underlying etiology [1-3].

*Address correspondence to this author at the Department of Neurosurgery, Jiangyin Hospital, Southeast University, Jiangyin, 214400, Jiangsu province, P.R. China; E-mail: wumin650822@sina.com

Magnetic Resonance iImaging (MRI) is the gold-standard technique for the evaluation of CSF dynamics [6, 7]. Most often, T1 or T2-weighted sequences have been utilized to evaluate intracranial CSF volume during magnetic Resonance (MR) procedures [8-10]. Sampling Perfection with Application optimised Contrast using different flip-angle Evolution (SPACE) a modified T2-weighted turbo spin echo sequence with variable flip angles along the echo train was recently discovered [6, 7, 11-15]. The refocusing pulse train of the SPACE sequence is made up of variable flip angle pulses, while the usual T2-weighted consists of turbo spin echo sequence with refocusing pulses of 180° [6, 11].

It was observed that, with lower flip angles radiofrequency energy deposition reduces, which permits longer echo trains, shorter echo spacing as well as higher turbo factors providing 3D thin sections in a time-effective manner [6, 11, 12, 14]. Studies on the differences between CSF dynamics according to age and gender are still insufficient. Thus, the main purpose of this study is the utilization of SPACE sequence to measure as well as evaluate the spatial distribution and volume of intracranial CSF in healthy volunteers as well as patients with hydrocephalus. Furthermore, we analyzed the differences between CSF dynamics according to age and gender.

2. MATERIALS AND METHODS

This study was approved by our institutional review board and written informed consent was obtained from all individuals included in the study before the MR examination. Patients with communicating and obstructive hydrocephalous admitted in our institution from January 2017 to February 2020 were included. Healthy volunteers were drawn from the general population.

2.1. Radiological Diagnostic Criteria for Hydrocephalus

Patients (adults) with unobvious ventricular enlargement have the following radiological diagnostic (MRI) criteria for hydrocephalus: (1) The distance between the tips of the frontal angles of the bilateral ventricles >45 mm; (2) The distance between the edges of the caudate nucleus on both sides >25 mm; (3) The width of the third ventricle >6 mm; (4) The width of the fourth ventricle >20 mm. Any one of the above criteria, except for primary brain atrophy, can be diagnosed as hydrocephalus.

2.2. Volunteers

A total of 120 healthy volunteers comprising 60 men and 60 women were included in the study. The selected volunteers had no neurological diseases such as Parkinson's disease, epilepsy and head trauma. No mental illness such as depression, alcohol dependence and drug dependence. Furthermore, Cerebral infarction, subarachnoid cysts, and intracranial space occupying lesions were excluded during initiation evaluations with conventional Three-Dimensional Turbo Spin Echo (TSE) sequence T2-weighted images (T2WI).

2.3. Patients

All 60 patients admitted with both communication and obstructive hydrocephalus were included in the study. A total of 30 patients with communicating hydrocephalus comprising 15 males and 15 females were included. Also, 30 patients with obstructive hydrocephalus comprising 15 males and 15 females were included. Hydrocephalus in all patient categories were clinical and radiologically established before the MR investigation. Clinical parament used in establishing hydrocephalus included headache, vomiting, blurred vision, and unstable gait. The imaging findings in both patients categories were that the whole ventricle system was expanded, the brain parenchyma was compressed and thinned, and there was no obvious abnormality in the pituitary and brain parenchyma as per the radiological diagnostic criteria for hydrocephalus above.

2.4. Image Acquisition

MRI was performed through 3.0T superconducting magnet (TrioTim, Siemens Systems, Erlangen, Germany) using a body phased array coil (TrioTim, Siemens Systems). All 120 volunteers and 30 x 2 patients underwent conventional TSE T2WI brain MR sequence and TSE sequence using the SPACE CSF imaging sequence scanning triggered by pulses with different flip angles.

T2WI was used for SPACE CSF imaging sequence scanning and positioning. SPACE sequence check is performed only when the above listed lesions were negative or absent. The scanning parameters are as follows: 3D SPACE sequence TR = 2000 ms, TE = 758 ms, inversion angle 170 degrees, matrix 384 × 384, field-of-view (FOV) = 220 mm × 220mm, layer thickness of 1.5 mm per 96 layers, the average number of acquisitions was times one (x1). Scanning location was based on the connection of the anterior and posterior segments of the corpus callosum on the central level of the sagittal position of the conventional T2. The whole brain (above the occipital foramen) was scanned, and the positions were mainly cross-sectional.

2.5. Image Analysis and Post-processing

Heavy T2WI obtained *via* SPACE CSF imaging sequence was used to distinguish CSF from the surrounding tissues in both communicating and obstructive hydrocephalous patients. The collected images are post-processed using OsiriX software. Two- or three-dimensional (2D/3D) sectional function and threshold segmentation (lower/upper bound) algorithm was used to develop the images. We first selected a lower limit of the overall signal threshold. At this point, we selected the level of the two ventricle bodies connection by clicking on the areas in the image. The OsiriX software was used to construct 3D images in the sequence. The OsiriX software automatically calculated the sum of all levels, and based on it, obtained total volumes of 3D images of the volumes of CSF after clicking on initially constructed 2D images.

Specifically, the volumes of the ventricles were established by clicking on initial 2D constructed images to identi

fy the CSF in each layer of the ventricle, and then automatic calculation of the volume of the CSF in the ventricle to obtain a 3D image of the volume of the CSF of the ventricles. The volume of CSF in the subarachnoid space was obtained by subtracting the volume of the cerebral ventricle from the total volume of intracranial CSF, and the volume ratio of the CSF of the ventricle and the subarachnoid space was calculated. After many times of practice using 50, 55 and 60 thresholds, it was determined that the appropriate lower threshold for CSF measurement of all volunteers was 55. Thus, a threshold value of 55 was utilized for measurements in all healthy volunteers as well as hydrocephalus patients in the same approach to ensure reproductible parameters.

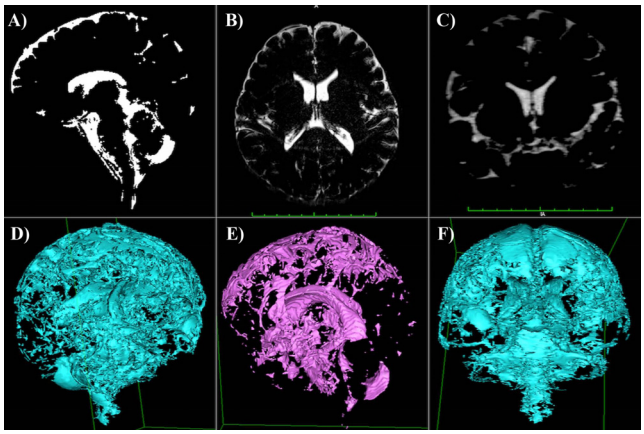

Fig. (1). CSF segmentation of one of the volunteers. Sagittal **(A)**, and axial (**B**) coronal (**C**) planes. **D-E** are 3D images of the intracranial CSF volumes. This heavily T2-weighted sequence shows convincing differentiation between the CSF and the surrounding tissues. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2.6. Statistical Analysis

Using SPSS 16.0 statistical software, all measured data were collected and analyzed for variance, Student t-test was used and P <0.05 was considered statistically significant.

3. RESULTS

3.1. Volunteers and Patients' Characteristics

In volunteers, the ages of the males were arranged from 20-85 years old with a mean age of 49.97±17.39. The ages of females also ranged from 20-85 years old with a mean age of 50.01±18.34. In both sexes, they were no statistical differences (t=0.015, p=0.987). The ages of the patients (males and females) with communicating hydrocephalus ranged from 57-85 years old with a mean age of 71.00±7.51. Also, the ages of patients (males and females) with obstructive hydrocephalus ranged from 39-81 years with a mean age of 59.80 ±11.93.

3.2. Intracranial CSF Dynamics

The axial position and 3D volume reproduction imaging of intracranial CSF in healthy volunteers and patients with hydrocephalus were established. Intracranial CSF of healthy volunteers is shown in Fig. (**1A-B**), while patients with hydrocephalus are shown in Fig. (**2A-B**). The amount of CSF in the ventricle and subarachnoid space, and the volume ratio of the volume of the CSF in the ventricle and subarachnoid space in healthy volunteers are shown in Table **1**. The average values of the total volume of intracranial CSF, the amount of CSF in the ventricle and subarachnoid space and the volume ratio of the CSF in the ventricle and subarachnoid space of healthy volunteers and patients with hydrocephalus are shown in Table **2**.

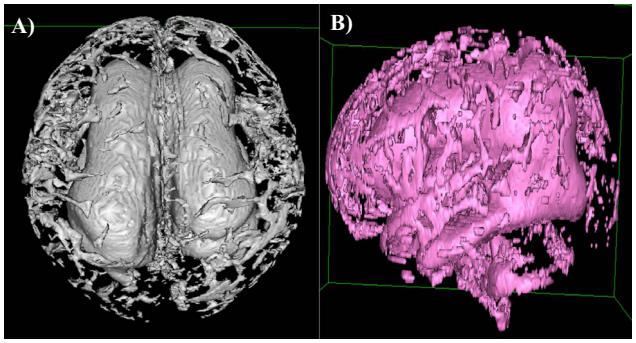

Fig. (2). SPACE sequence images (3D) of one of the hydrocephalus patients. Axial (**A)** and sagittal (**B**) planes showing expanded intracranial CSF volumes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

There were no statistically significant differences in the volume ratios of the total CSF, ventricular CSF, subarachnoid CSF, and volume ratio between the ventricle and the subarachnoid CSF in the male and female groups of healthy volunteers and patients with hydrocephalus (P value>0.05) as shown in Table **2**. In both groups, the average volume ratio of total CSF, ventricle CSF, subarachnoid CSF, and volume ratio of ventricle to subarachnoid CSF was slightly larger in males than that of females. In patients with hydrocephalus, the intracranial CSF, intraventricular CSF, subarachnoid CSF, and the volume ratio of ventricle and subarachnoid CSF volume were significantly greater than healthy volunteers, the difference between the two groups was statistically significant (P<0.05) as shown in Table **2**.

4. DISCUSSION

In adulthood, the weight and volume of the human brain gradually decrease, and the volume of CSF increases accordingly especially after 60 years of age [16-18]. This physiological brain atrophy is inevitable mainly due to long-standing chronic ischemia of cerebral blood vessels [16]. Also, the volume of the ventricular system, cistern, and sulcus in healthy people increases with age, mainly because they appear to expand relatively as the surrounding brain tissue shrinks [16, 17]. Physiological brain atrophy is manifested clinically as memory loss and the degree of unresponsiveness of the individual [16, 19]. Over the years, several neuroscientists and radiologists have attached importance to dynamics CSF volume and well as distribution in adults and

Table 1. The average amount of intracranial CSF, the amount of CSF in the ventricle and subarachnoid space, and the average volume ratio of the volume of the CSF in the ventricle and subarachnoid space between the male and female healthy volunteers.

Group	Total CSF Volume (cm^3)	Ventricular CSF Volume (cm^3)	Subarachnoid CSF (cm^3)	Cerebral Ventricle and Subarachnoid CSF Volume ratio (%)
Male	206.9±47.7	33.0±10.7	173.9±37.9	18.7±2.9
Female	199.7±44.9	30.8±9.4	168.9±37.0	18.1±2.8
P-value	0.39	0.23	0.46	0.26

Abbreviation: cerebrospinal fluid=CSF

Table 2. The average amount of intracranial CSF in healthy volunteers and patients with hydrocephalus, the amount of CSF in the ventricle and subarachnoid space, and the average volume ratio of the volume of CSF in the ventricle and subarachnoid space.

Group	Total CSF volume (cm^3)	Ventricular CSF volume (cm^3)	Subarachnoid CSF (cm^3)	Cerebral Ventricle and Subarachnoid CSF volume Ratio (%)
Healthy volunteers-A	203.3±46.3	31.9±10.1	171.4±37.4	18.4±2.9
Communicating hydrocephalus-B	577.6±112.3	213.0±53.0	364.6±88.5	60.6±16.6
Obstructive hydrocephalus -C	650.4±127.1	417.2±96.2	233.1±82.4	208.3±112.7
P-value 1(A, B)	t=28.3 p<0.01	t=35.3 p<0.01	t=19.6 p<0.01	t=26.5 p<0.01
P-value 2(A, C)	t=31.3 p<0.01	t=43.4 p<0.01	t=6.60 p<0.01	t=18.6 p<0.01
P-value 3(B, C)	t=2.35 p<0.05	t=10.18 p<0.01	t=5.96 p<0.01	t=7.10 p<0.01

Abbreviation: cerebrospinal fluid=CSF

children [2, 16, 20]. Radiological modalities like CT scan and MRI have been used to assess the dynamics of CSF by several researches but with varied findings [8-10, 21].

3D series of T1WI of MR technology was adopted to study CSF hydrodynamics [20, 22]. Nevertheless, many tissues such as fat, white matter and gray matter were included during imaging [22]. Also, bone and brain tissue are often not subtracted during imaging with T1WI MR technology [22]. Furthermore, stereotactic MR technology was used to measure the volume of CSF with the assistance of a combination automatic and manual segmentation during post-processing [23, 24]. Nevertheless, the signal of the CSF outside the brain was indistinguishable from the surrounding tissues mainly at the junction between the CSF and the tissues. Thus, manual segmentation method was often used [23]. This method was time-consuming and had a certain impact on the accuracy of the measurement [23].

Studies have demonstrated that, SPACE sequence was very feasible in the evaluation of the spatial distribution and volume of intracranial CSF [6, 7, 11-15]. SPACE sequence was capable of localizing only CSF [6, 7, 11-15]. Also, SPACE sequence was advantageous because, the 3D images of CSF were automatically generated without signals from the surrounding structures [6, 7, 11-15]. The volume of the subarachnoid space in most healthy volunteers was narrow, and only a few people had a uniform distribution of CSF volume in the subarachnoid space on 3D images [6, 11]. Studies have shown that the lateral fissure pool, subarachnoid space, ventricles, and sulcus gradually widen with increasing age [6, 11, 12, 14]. Nevertheless, in patients with hydrocephalus, the pressure from the ventricular system does not uniformly occur on the surface of the brain resulting in an uneven dilation of the sulcus [6, 11]. The combination of changes in the sulcus and the expansion of the ventricle often provides clues for the diagnosis of hydrocephalus [6, 11, 12, 14]. Thus, 3D volume imaging can provide more targeted subarachnoid CSF volume in comparison with axial or coronal imaging [6, 7, 11-15].

The volume of intracranial CSF in healthy male volunteers calculated in this study was 206.9±47.7 cm^3, and that for females was 199.7±44.9 cm^3, which is different from the previous studies [25, 26]. The variation in our study could due to the fact that previous researchers used different research methods and thus obtained varied results [20]. Also, the ages of volunteers in this study were different from that of initial studies because age has a greater impact on the volume of CSF. Furthermore, differences between different races and ethnic groups also have an impact on the results obtained by previous studies compared with those of study. Additionally, the visible old lacunar infarction or enlarged perivascular space was not included in the range of CSF in the subarachnoid space, because these spaces are filled with CSF. Thus, our study revealed that human brain starts aging at about 60 years. At this age, the volume of many parenchymal structures in the skull starts atrophying. Reduction of the volume of the brain parenchyma will inevitably lead to a significant increase in the volume of CSF in a relatively closed cranial cavity. Besides the difference above, there was no significant difference in the volume of CSF between males and females.

In this study, we found that the ratio between the CSF in the ventricle and the subarachnoid space was very different between healthy volunteers and patients, indicating that the ratio could aid in distinguishing patients with hydrocephalus from normal people. The management of hydrocephalus generally involves the passing of lateral ventricle-abdominal drainage shunt [1-3]. Previously, only the size of the lateral

ventricle or the film phase contrast method were used to evaluate the dynamics of CSF before and after surgery [27-29]. These methods only qualitatively assess the degree of hydrocephalus without a quantitative basis [27-29]. Also, these assessment modalities often ignore the changes in the amount of CSF in the subarachnoid space [10, 27-29]. Furthermore, even if the amount of CSF in the subarachnoid space had changed significantly, the degree of change was unquantifiable [27-29]. Thus, the SPACE sequence is characterized by rapid data collection, without interference from the surrounding tissues around the CSF, and directly obtains 3D images of the CSF. Comparing the volume of CSF before and after hydrocephalus patients undergoing ventricular-abdominal drainage shunt, SPACE sequence maybe capable of evaluating the surgical effect and better assist in clinical diagnosis and treatment [30].

Studies have demonstrated that the SPACE sequence can be a game changer as it significantly improves the diagnosis of central nervous system degenerative diseases [6, 7, 11-15, 31]. It was capable of detecting brain atrophy in different regions of the brain in patients with dementia [6, 7, 11-15, 31]. Thus, SPACE sequence was capable of determining increased levels of CSF as well as brain atrophy in patients with dementia. The SPACE sequence scanning method is non-invasive and is capable of excluding normal brain tissues, artifacts, bone, *etc.* during imaging. Furthermore, SPACE sequence can be repeated for the same sample during imaging, complete the follow-up study of the same sample, and determine the presence or absence of disease by measuring the content of CSF in the patient.

CONCLUSION

SPACE sequence can quantitatively determine the content of CSF. The change of CSF volume has nothing to do with gender but with age. In patients with hydrocephalus, the average volume ratio of intracranial CSF, ventricle CSF and subarachnoid CSF are quantifiable with SPACE sequence. Also, CSF of ventricle and subarachnoid space hydrocephalus patients was significantly greater than that of healthy volunteers. Furthermore, the greater the ratio of the volume of CSF between the ventricle and the subarachnoid space, the more accurate the diagnosis of hydrocephalus. Thus, it is feasible to use SPACE sequence to evaluate the spatial distribution and volume of intracranial CSF.

LIST OF ABBREVIATIONS

CSF = Cerebrospinal Fluid

ICP = Intracranial Pressure

MR = Magnetic Resonance

MRI = Magnetic Resonance Imaging

SPACE = Sampling Perfection with Application Optimised Contrast using Different Flip-angle Evolution

TSE = Turbo Spin Echo

T2WI = T2-weighted Images

2D/3D = Two- or Three-dimensional

AUTHOR'S CONTRIBUTIONS

All the authors contributed to conception, design, acquisition of data, analysis and interpretation of data. All authors approved the final version to be published and agreement to be accountable for all aspects of the work including accuracy and integrity of any part of the work. **Seidu A. Richard** wrote the paper.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by "The Affiliated Hospital of Jiangsu University" research ethical committee.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this study. All the human procedures were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

The patients as well as volunteers were dually informed about our intention to involve them in a study and they fully concerted to the use of their information. Written informed consent was signed by all the patients and volunteers.

AVAILABILITY OF DATA AND MATERIALS

Data is available on reasonable demand from the corresponding author.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

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