MR Measurement of Intracranial CSF Volume in 41 Elderly Normal Volunteers

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A noninvasive nonplanimetric MR protocol was used to measure the total intracranial CSF volume in 41 normal subjects, aged 60–84 years, who were intensively screened to eliminate CNS disease. The protocol entailed application of MR imaging data acquired with a spin-echo sequence in a single thick slice encompassing the head. The results show a strong correlation between increased intracranial CSF volume and increasing age, and a weaker correlation between increased intracranial CSF volume and increasing total intracranial volume. The possibility of employing a CSF volume measurement as a reflection of brain atrophy to help diagnose dementia is discussed.

Ventricular volume changes and overall reduction in brain weight have been reported in patients with dementia of the Alzheimer type (AD) [1]. Efforts to recognize and quantify ventricular and/or sulcal expansion caused by parenchymal volume loss have been encouraging [2–4]. Additionally, recent investigations using volumetric measurements of CSF spaces in dementia suggest a correlation between increased volume and AD [5, 6].

We, and others, have developed a nonplanimetric technique for the noninvasive measurement of total intracranial CSF volume [7, 8]. The technique relies on data obtained from a single-slice MR head scan. In this article, we describe the use of this technique to measure intracranial CSF volumes in 41 volunteer subjects, aged 60–84, who were carefully screened to exclude any detectable CNS disease, particularly dementia.

Materials and Methods

Theory of Nonplanimetric Volume Measurement

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The nonplanimetric volume measurement relies on the fact that the MR signal from a fluid is proportional to the volume of that fluid. To use this proportionality to measure the CSF volume requires an MR head scan that only contains signal from the intracranial CSF. This CSF-only image is obtained by using a pulse sequence with a very long echo time (TE). Since the CSF has a T2 relaxation time that is much longer than the T2 for head and brain tissues, this long TE sequence will, therefore, result in an image that contains predominantly signal from the CSF. To obtain the CSF volume, a CSF sample of known volume can be placed next to the subject's head so that the sample appears as a distinct object in the resulting image. A simple proportion between the signal from the known volume of CSF and the signal from the intracranial CSF will then allow calculation of the latter volume:

$$\text{Intracranial CSF volume} = \frac{\text{Intracranial CSF signal}}{\text{Reference CSF signal}} \times (\text{Reference CSF volume})$$

CSF Samples and Universal CSF Standard

An important feature of the technique is that the MR signal from normal CSF shows little patient-to-patient variation. Therefore, in practice, it is not necessary to have an actual sample of the patient's CSF. Instead, the reference CSF volume is replaced by a reference vial of doped water, whose signal relative to a known volume of CSF is already known. In our protocol the fixed reference vial is 15 ml of 2 mmol/l copper sulphate solution.

To obtain the ratio of the signal of CSF to the signal of the copper sulphate reference vial we made use of patient CSF samples obtained during myelogram procedures. We used 2.5-ml samples from eight different patients who had no clinical evidence of any disease that would cause abnormal CSF. These eight samples, together with the 15-ml reference copper sulphate vial, were scanned using the same long-TE spin-echo (SE) sequence used to obtain the CSF-only head image. The ratio of the signal from the copper sulphate vial to the signal per ml from each 2.5-ml CSF sample was then calculated.

Subjects

The subjects used in this CSF volume study were part of a larger ongoing study of normal cognitive aging. As part of this protocol, subjects were imaged with multislice SE T1- and T2-weighted scanning sequences to evaluate the brain. The CSF volume measurement was taken after the T1- and T2-weighted scans. Subjects were recruited by advertisement and from spouses of demented patients seen clinically at our institution. Informed consent was obtained and the subjects were screened to exclude those with a history of neurologic or psychiatric disorders. The subjects were required to have a normal neurologic examination, normal neuropsychological test, and a normal electroencephalogram. A total of 71 volunteers were examined to obtain the 48 subjects who passed the above screening. T1- and T2-weighted and CSF volume scans were acquired in all 48 volunteers. Two subjects were excluded because of abnormal T1- and T2-weighted MR scans, and five were excluded because of technical difficulties with the CSF volume scan (e.g., misplaced reference vial or incorrectly selected echo times). The 41

remaining subjects used in the CSF volume study were composed of 28 women (mean age, 68 years; range, 60–79 years) and 13 men (mean age, 71 years; range, 65–84 years).

MR Imaging

All subjects were imaged on a 1.5-T system (Philips). Axial T2-weighted images were obtained from a half-Fourier SE sequence with imaging parameters of 3000/30,90 (TR/TE). Coronal T1-weighted images were obtained through the temporal lobes with an SE sequence of 700/20 and two acquisitions. The slice thickness on all studies was 4 mm.

The CSF volume study was performed after the T1- and T2-weighted imaging sequences. The technique for the volume study was as follows: a 15-ml copper sulphate reference vial was placed on the left side of the patient's head above the ear; a previously obtained sagittal scout image through an orbit was used to orient a single thick slice (approximately 140 mm) as shown in Figure 1A. This slice was angled approximately 45° to encompass the intracranial subarachnoid spaces but to exclude the orbits. The orbits were excluded since the vitreous humor contributes an MR signal even at long echo times.

An image was then obtained using an eight-echo multiecho SE pulse sequence having TR = 10 sec and eight echoes at TE = 100, 200, 300, 400, 500, 600, 700, and 800 msec, respectively. The field-of-view was 30 cm, with 64 phase-encoding steps. The sequence took approximately 11 min. The data for calculating the CSF volume were obtained from the eighth-echo image, an example of which is shown in Figure 1B. The irregular central bright region in Figure 1B is due to the signal from the intracranial CSF; the separate bright rectangular region to the right is the signal from the reference vial. Regions of interest (ROIs) were then drawn around each of these two areas; a summation of the pixels in each of these ROIs results in the intracranial CSF signal and the reference CSF signal used to calculate the intracranial CSF volume. Figure 1C is an example of the ROI used to obtain the intracranial CSF signal. The ROIs are positioned on the image by an operator using interactive manufacturer-
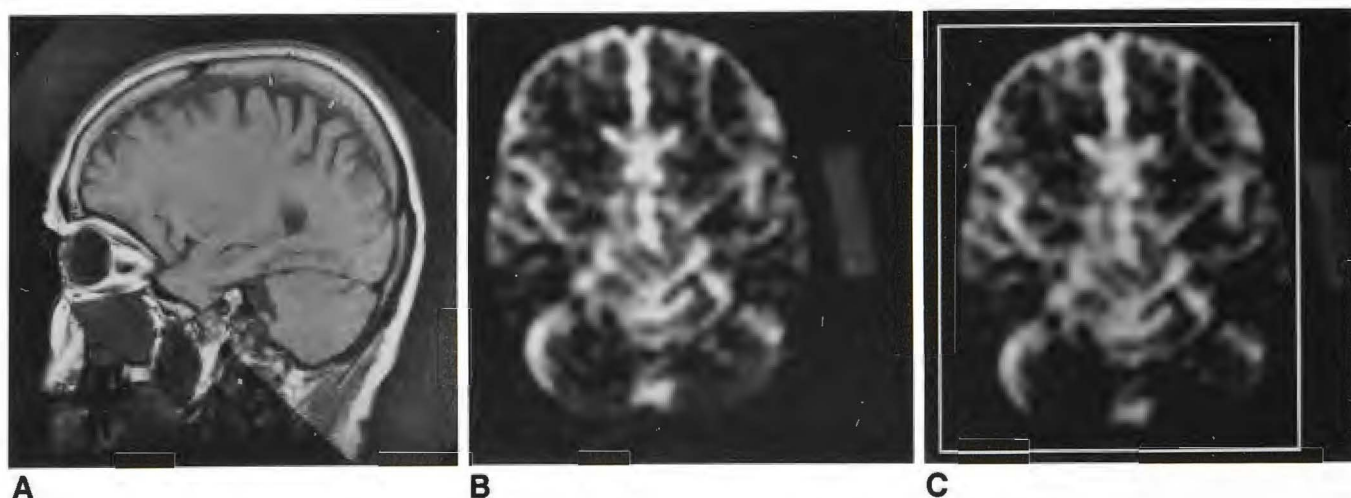

A   **B**   **C**

Fig. 1.—*A*, Sagittal scout image through the orbit, used to position a single-angled thick slice (highlighted area), which encompasses the intracranial subarachnoid spaces but excludes the orbits.

B, The image of the thick slice seen in *A*, obtained by using a spin-echo sequence with TR = 10 sec and TE = 800 msec. The large irregular bright area results from signal from the total intracranial CSF; the small rectangular area is signal from a reference vial of doped water placed adjacent to the subject's head.

C, The white rectangle is an example of an operator-drawn ROI that encloses the image of the total intracranial CSF.

supplied software; the software then automatically sums the image pixels within the defined ROI. If necessary, the ROI can have an irregular boundary traced by the operator.

Estimates and Use of Total Intracranial Volume

The measurement of total intracranial volume is not obtainable from the nonplanimetric CSF-volume protocol. However, advantage was taken of the multislice-T2-weighted sequence from the routine SE sequence to obtain an estimate of the intracranial volume. The area of each slice was obtained by tracing the borders of the subarachnoid space using the manufacturer-supplied software package for area calculation. The area of the slices, multiplied by the slice thickness, was then used as a measure of intracranial volume. These volumes were used to test for a correlation between intracranial CSF volume and total intracranial volume.

Results

Use of Standard Reference for CSF

The mean and standard deviation of the ratio of signal from each of the eight CSF samples to the copper sulphate sample was 4.65 ± 0.10. The small relative variation of these ratios ($0.1/4.65 = 2\%$) forms the justification for using a fixed copper sulphate reference standard for the CSF.

Intracranial CSF Volumes

A graph of the results for the calculated female intracranial CSF volumes versus age is shown in Figure 2 (solid circles). Also shown on this graph are data (open circles) on female intracranial CSF volumes for younger normal subjects obtained by other researchers who used a similar nonplanimetric technique and extracted by us from their published graphs [9]. Linear regression analysis of our data alone shows evidence of a correlation of intracranial CSF volume with age ($r = .45$ for $n = 28$). The straight line in Figure 2 is the result of a least-squares fit to the total ($n = 67$) graphed data points
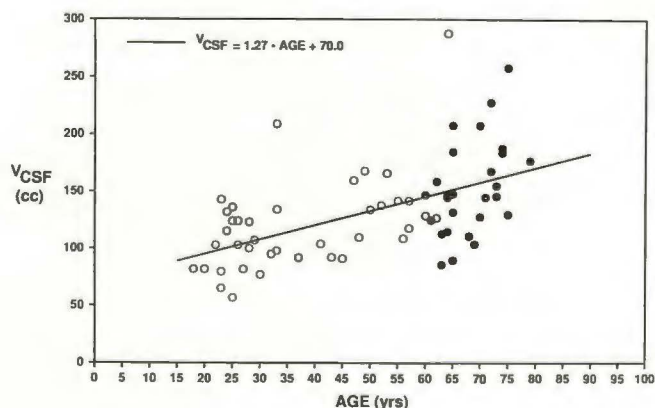

Fig. 2.—Graph of calculated intracranial CSF volume versus age for the 28 women in this study (*closed circles*); also shown are the data for 39 women taken from a previously published study [9] (*open circles*). The *straight line* is the result of a linear least-squares fit to all the data points (*closed* and *open circles*).

TABLE 1: Comparison of Intracranial Volumes in Men vs Women

Sex	Age (years)	No. of Subjects	Intracranial CSF Volume (ml)	Total Intracranial Volume (ml)
F	65–70	9	146 ± 44	1363 ± 109
M	65–70	7	189 ± 51	1619 ± 125

(open and closed circles) assuming the simple linear form:

$$\text{Intracranial CSF volume} = A \times \text{age} + B$$

where A and B are constants. This fit yields the following values: ($A = 1.27 \pm 0.24$; $B = 70.0 \pm 12.9$; $r = .55$). Owing to the limited sample size we have not made a similar fit to the male data.

There is some evidence of a correlation between the intracranial CSF volume and the total intracranial volume: for women ($r = .23$ for $n = 28$); for men ($r = .43$ for $n = 13$). Since the mean total intracranial volume for men (1581 ± 113 ml) was greater than that for women (1380 ± 100 ml), we chose not to combine the male data with the female data in Figure 2.

A comparison of the male and female intracranial CSF volumes is shown in Table 1, for the age range 65 to 70 years; this range was selected to maximize the limited sample size for the men.

Discussion and Conclusions

The observed increase of intracranial CSF volume with age is consistent with the accepted notion that normal brain volume decreases with age. Our data are also in agreement with the previously published data for younger volunteers [9]. A least-squares fit to a linear form for these data only (open circles in Fig. 2) yields $A = 1.49 \pm 0.42$, $B = 64.6 \pm 16.7$, $SD = 36$, which is consistent with the previously quoted fit to all the data.

The difference between the intracranial CSF volumes for men and women, as shown in Table 1, is statistically significant ($p < .06$ for two-tailed t test). However, this difference may be due to the difference in mean total intracranial volumes between the men and women (see last column of Table 1). There is not enough data to compare men and women with the same approximate intracranial volume for this age range.

To use CSF volume measurements as a reflection of brain atrophy to help diagnose dementia would require a comparison of the CSF volume measurement obtained from a patient with the results for mean CSF volumes obtained from a relevant normal data sample. The comparisons would involve statistical tests, the usefulness of which would depend on the inherent spread in the normal CSF data.

The relative spread in our data (SD/mean) is approximately 25%; this is approximately the same as that found by other investigators for younger normal subjects [9]. From six repeated measurements of the same subject we estimate that the inherent measurement error (SD/mean) is approximately 12%. This is higher than the approximate 3% measurement error we obtained when using simple fluid-filled phantoms

[8]. Possible causes of this increased measurement error are the effects of pulsatile CSF flow and nonuniformities in the clinical head coil.

The CSF-volume protocol used in this study was designed to be merged into the standard clinical scanning protocols, and as such was made to use the standard clinical head coil and the available manufacturer-supplied pulse sequences. The large CSF to parenchymal signal ratio was obtained with a standard clinical multiecho SE sequence and the unusual values TR = 10 sec and TE = 80 × 100 msec. With this sequence we estimated a parenchyma-to-CSF signal ratio of approximately 350 at TE = 800 msec, obtained by assuming a CSF-volume to brain-volume ratio of 0.1; and spin density, T2 values of 1.0, 1500 msec for CSF and 0.75, 95 msec for brain parenchyma.

In our previous phantom study [8], imaging was done with a standard body coil, which had better uniformity but less signal/noise than the clinical head coil used in the present study. In the present study we were constrained to use the head coil because of the need for high-quality multislice images in the T1- and T2-weighted scans. By performing comparison measurements on the same subject using the head coil and body coil, we conclude that the effect of the head coil is to introduce an approximate 10% change in volume measurement. In future studies, when possible, the CSF-volume measurement will be done with the body coil.

Flow-related effects from pulsating CSF can introduce artifacts into the image [10] and increase the measurement error. It is also known that the MR signal from flowing fluid is sensitive to TE [11]. To get an estimate of these effects, we made use of a phantom composed of a length of fluid-filled rubber tubing (¼-in. ID; fluid volume = 94 ml), which was wrapped into a tangled ball (5-in. diameter) and imaged using the CSF-volume protocol. The fluid-filled tubing of the phantom was connected to a straight length of fluid-filled rubber tubing that ran to the outside of the magnet and ended in a hemodialysis blood pump. A pulsatile fluid displacement was set up in the phantom by using the pump to periodically beat on the closed outside end of the straight rubber tubing. A fluid displacement rate of 0.1 ml/beat/sec was obtained in the phantom; this rate is similar to that expected for CSF [10]. The percent decrease between the volume calculated with the fluid pulsing and stationary was 8%. We also used the multiecho data from a representative sample of subjects to calculate the change in intracranial CSF volume obtained from the TE = 500 and TE = 800 data, since the effects of flow should increase with TE. The mean decrease in the calculated intracranial CSF volume, between TE = 500 and 800, relative to the TE = 800 value, was 12%. At least half of this change can be attributed to the increased signal from non-CSF tissues at the TE = 500 value. We conclude that these flow effects introduce an effect of no more than 10%. In future studies we plan to try other pulse sequences that may have different flow sensitivities, and to investigate the effects of gating and the use of flow-compensation gradients.

Finally, it has been reported [12] that brain atrophy associated with dementia is preferentially located in the medial temporal lobe. This would suggest that the kinds of CSF volume measurements discussed here may be more diagnostic if confined to this limited brain region as opposed to the total intracranial region.

ACKNOWLEDGMENTS

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