Neuroradiology (1994) 36: 210–215

Neuro radiology

Cerebrospinal fluid flow and production in patients with normal pressure hydrocephalus studied by MRI

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Abstract. An interleaved velocity-sensitised fast low-angle shot pulse sequence was used to study cerebrospinal fluid (CSF) flow in the cerebral aqueduct, and supratentorial CSF production in 9 patients with normal pressure hydrocephalus (NPH) and 9 healthy volunteers. The peak aqueduct CSF flow, both caudal and rostral, was significantly increased in patients with NPH. No significant difference in the supratentorial CSF production rate was found between patients (mean 0.60 + / – 0.59 ml/min) and healthy volunteers (mean 0.68 + / – 0.31 ml/min). Our method may be useful for investigation and monitoring of patients with NPH before and after ventriculoperitoneal shunt operations.

Key words: Cerebrospinal fluid flow – Cerebrospinal fluid production – Magnetic resonance imaging – Normal pressure hydrocephalus

In 1964 Hakim first described the syndrome of normal pressure hydrocephalus (NPH) [1–3], characterised by hydrocephalus and normal or slightly increased intracranial pressure. The symptoms consist of the triad: progressive dementia, gait disturbance, and urinary incontinence [1–7]; one or more of these may predominate. The causal relationship between hydrocephalus and these symptoms is substantiated by the documented improvement or resolution of the symptoms following shunting [4–8]. The mechanism by which the distended ventricles cause the effects on gait, bladder function, and mentation is unclear, but it is related to the distention and pressure on the fibres to and from the frontal cortical and subcortical areas [6–8].

Cerebrospinal fluid (CSF) is produced predominantly by the choroid plexus in the ventricular system, and from the supratentorial ventricular system it flows via the cerebral aqueduct and the fourth ventricle into the cranial and spinal subarachnoid spaces, whence it is absorbed through the arachnoid villi into the superior sagittal sinus. In the spinal subarachnoid space CSF is also absorbed along the spinal nerve roots. Pulsatile movement, here after called 'flow' of CSF in the cerebral aqueduct [9, 10] has been described by several groups using the cerebral aqueduct flow void found on magnetic resonance imaging (MRI) [11–16]. More quantitative velocity methods have also been described [17, 18], as well as recent phase methods giving absolute velocity information [19–24]. Few studies have presented quantitative information about CSF volume flow in the aqueduct in patients with CSF hydrodynamic diseases [24].

A modified cardiac-gated interleaved MR phase method for quantification of supratentorial CSF production and flow through the cerebral aqueduct has been presented previously [20, 21]. Using this method a circadian variation in CSF production in normal humans has been found [25]. Very little is known, however, about the production rate in hydrocephalic states or in increased intracranial pressure.

Our aim was to measure the supratentorial CSF production and CSF flow in the cerebral aqueduct in patients with NPH and in healthy volunteers, using the above-mentioned cardiac-gated MR phase method.

Patients and methods

We studied 9 patients (age range 56–79 years, mean 68 years) with NPH: 5 men and 4 women. One patient was re-examined one year after a shunt operation. All patients fulfilled the following diagnostic criteria for NPH: a history of progressive dementia, gait disturbance, and/or urinary urgency or incontinence; hydrocephalus on CT and MRI; a mean intracranial pressure (ICP) below 15 mm Hg. The intracranial pressure was monitored for 24 h, using a precoronal cannula in the ventricular system connected to a pressure transducer, and B-wave activity [26, 27] was noted. The resistance to CSF outflow (R_{out}) (normal < 9.10 mm Hg/ml/min [28]) was measured by ventricular infusion as described by Gjerris and Børgesen [27], resistance to CSF outflow being the reciprocal value of conductance to CSF outflow [4].

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We also examined 9 healthy volunteers (age range 22–58 years, mean 33 years): 5 men and 4 women, none of whom had any prior history of neurological disease; none was taking medication, and all had a normal brain MRI.

A whole body MR imager operating at 1.5 Tesla was used. All patients and healthy volunteers were examined supine, with the head extended approximately 20° to position an 8 mm axial slice perpendicular to the cerebral aqueduct at the level of the inferior colliculi. All examinations were carried out within a 4 h period in the afternoon. Velocity information was obtained using a phase-mapping method, as described previously [20, 21]: two specially designed fast low-angle shot (FLASH) sequences, echo time (TE) 15 ms and flip angle 30°, were executed in an interleaved mode to give velocity sensitivity. In both sequences, three gradient lobes were used in the slice-select direction, which also was the flow-sensitive direction. The first sequence was velocity-compensated while the second was sensitive to slowly-flowing CSF. After subtraction of phase images obtained with the two sequences, a phase map, on which phase signal was proportional to velocity, was obtained; the velocity corresponding to a phase angle of π was 137 mm/s [21]. The field of view was 215 cm and matrix size was 256×256 after sinc interpolation, giving a pixel size of $0.84 \times 0.84 \times 8$ mm^3. To cover the full R-R interval each train of coded or noncoded pulse sequences was run for 100% of the R-R interval triggering on every second R wave. Thus the noncoded pulse sequence train was triggered on the first R wave covering the full R-R interval. The coded pulse sequence train was triggered on the third R wave also covering the full R-R interval. The repetition time (TR) was set at one tenth of the R-R interval, and the two basic sequences were executed in an interleaved mode, giving $10 + 10$ phase images covering the entire cardiac cycle in 2×256 heartbeats, or 6–12 min, depending upon heart rate [20]. After subtraction of corresponding phase images, 10 flow-phase maps equally distributed over the entire cardiac cycle were obtained. To calculate the average CSF velocity in the aqueduct, a circular region of interest (ROI) was placed over the cerebral aqueduct, the area which was 11–15 mm^3, corresponding to 16–21 pixels. Partial volume effects are unavoidable; the linear velocity will be underestimated if the ROI is larger than the cerebral aqueduct and overestimated if it is smaller, whereas estimation of volume flow is less sensitive, if the ROI is as larger or larger than the aqueduct. Volume flow was obtained by multiplying the average CSF velocity by the area of the aqueduct [19–21]. There is a cumulative error of 30% in the calculation of CSF production using this method [21], partly due to fluctuations in the length of the R-R interval caused by breathing. Additional circular regions of interest were placed on both sides of the aqueduct within the mesencephalon, to correct for phase offset [20]. Phase noise in our system was approximately $+/-2$ mm/s [21].

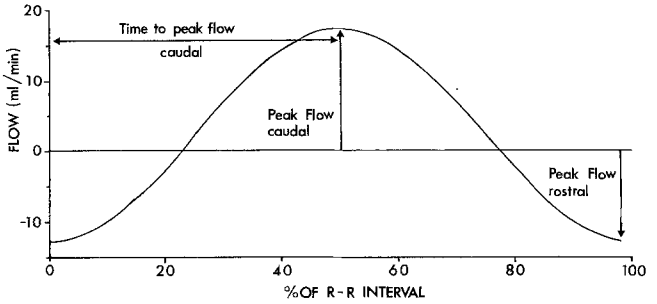

Fig. 1. Idealised CSF flow curve through the cerebral aqueduct within one cardiac cycle, illustrating the flow parameters examined: peak caudal flow; peak rostral flow; the time to peak caudal flow. Supratentorial CSF production was calculated by numerical integration of the CSF flow curve over the entire R-R interval. Fourier analysis of the CSF flow curve was also performed, expressed as the quotient between the amplitudes of the second and first curve harmonics [21]

The CSF flow parameters studied are shown in Fig. 1, which illustrates an idealised cycle of the CSF motion through the cerebral aqueduct. The parameters were: CSF peak flow in caudal and rostral directions through the aqueduct, and time to peak caudal flow as a percentage of the length of the cardiac cycle. From Fourier analysis of the CSF flow curve [21], the quotient between the amplitudes of the second and the first curve harmonics was also calculated. Finally, the supratentorial CSF production in ml/min was calculated by numerical integration of the flow curve over the whole cardiac cycle [19–21].

Ethics and Statistics:

The study was approved by the Ethics Committee for Copenhagen and Frederiksberg Municipalities, and informed consent was obtained in all cases. The Mann-Whitney rank sum test for unpaired samples was used to compare the results from the two different groups. The level of significance was set at $P < 0.05$.

Table 1. Flow parameters in nine healthy volunteers

	Volunteer									
	1	2	3	4	5	6	7	8	9	Mean (SD)
Sex/age (years)	M/25	F/22	M/30	M/24	F/58	M/36	F/22	F/39	M/40	32.9 (11.8)
Heart rate (beats/min)	70	70	60	60	80	55	70	80	80	69.4 (9.5)
Peak caudal velocity (mm/s)	11.3	8.4	14.2	24.7	9.9	3.8	10.2	7.9	11.4	11.3 (5.8)
Peak rostral velocity (mm/s)	4.8	6.5	8.5	18.3	5.1	2.2	4.6	6.5	7.3	7.1 (4.6)
Peak caudal flow (ml/min)	4.3	3.2	5.5	9.5	3.8	1.4	3.9	3.0	4.4	4.3 (2.2)
Peak rostral flow (ml/min)	1.8	2.5	3.3	7.0	1.9	0.8	1.8	2.5	2.8	2.7 (1.8)
CSF production (ml/min)	0.87	0.83	0.34	1.22	0.60	0.28	0.98	0.52	0.52	0.68 (0.31)
Time to peak caudal flow (%)	43	39	43	44	44	31	39	44	42	40.6 (4.4)
Harmonic analysis	0.33	0.39	0.43	0.17	0.23	0.39	0.66	0.11	0.28	0.33 (0.16)

Table 2. Flow parameters in patients with normal pressure hydrocephalus

	Patient										
	1	2	3	4	5	6	7	8	9	Mean (SD)	1:2[c]
Sex/age (years)	M/79	M/56	F/76	M/68	F/70	M/68	F/69	F/67	M/63	68.4 (6.7)	M/80
Heart rate (beats/min)	65	65	80	60	80	85	70	80	50	70.6 (11.6)	60
Mean ICP (mm Hg)[a]	12	8	12	13	8	13	8	14	5	10.3 (3.1)	–
R_{out} (mm Hg/ml/min)[b]	17	12	25	29	20	7	24	12	15	17.9 (7.2)	–
B-wave activity (%)	100	25	50	100	100	25	50	100	90	71.1 (33.2)	–
Peak caudal velocity (mm/s)	33.8	6.6	10.1	32.5	24.3	17.2	24.1	65.7	29.2	27.1 (17.3)	34.7
Peak rostral velocity (mm/s)	27.8	7.6	6.2	16.9	19.9	15.1	27.5	40.8	17.6	19.9 (10.8)	37.0
Peak caudal flow (ml/min)	13.0	2.6	3.9	15.7	11.8	6.6	11.7	37.6	11.2	12.7 (10.3)	16.8
Peak rostral flow (ml/min)	10.7	2.9	2.4	8.2	9.6	5.8	13.3	23.4	6.8	9.2 (6.4)	17.9
CSF production (ml/min)	0.85	0.00	0.33	0.63	−0.10	1.32	0.30	1.68	0.37	0.60 (0.59)	0.11
Time to peak caudal flow (%)	43	33	44	33	42	45	42	34	36	39.1 (5.0)	45
Harmonic analysis	0.17	0.41	0.40	0.52	0.26	0.19	0.29	0.29	0.18	0.30 (0.12)	0.14

[a] Normal < 15 mmHg; [b] Normal < 9.10 mm Hg/ml/min; [c] Patient 1 re-examined a year after surgery
ICP, intracranial pressure; R_{out}, resistance to CSF outflow

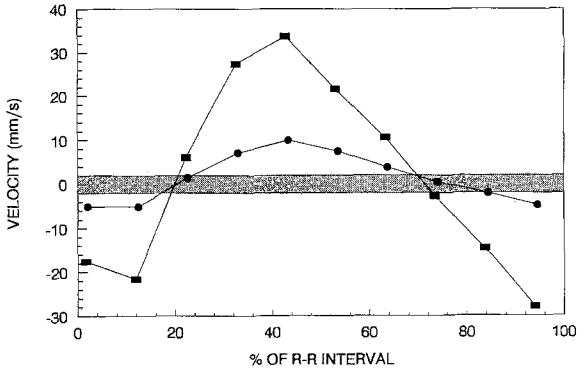

Fig. 2. Characteristic examples of in vivo CSF flow curves through one cardiac cycle, illustrating the differences in flow amplitude in the cerebral aqueduct between healthy volunteers and patients with NPH. The hatched area illustrates the level of detection [21]. • Volunteer; ■ patient

Results

The results obtained from the volunteers are shown in Table 1. There was no apparent difference in the peak aqueduct flow velocity, peak CSF volume flow or CSF production between male and female controls, nor was there any apparent correlation with age. The mean time to peak caudal flow was 40.6% of the cardiac cycle and the mean supratentorial CSF production rate was 0.68 ml/min. The flow curve was nearly sinosoidal, as is seen from the mean quotient of 0.33 between the amplitude of the second and first flow curve harmonics.

The results of the pressure measurements and the MR measurements obtained from the patients are shown in Table 2. The cause was unknown in six patients, while NPH developed after subarachnoid haemorrhage in two and after head trauma in one. All patients had normal mean intracranial pressure with abnormal B-wave activity, and eight patients had increased R_{out}. The peak caudal aqueduct volume flow was significantly higher in patients than in volunteers ($P < 0.02$), and the peak rostral volume flow was also significantly higher ($P < 0.01$). The mean supratentorial CSF production rate in patients was 0.60 ml/min, and this did not differ significantly from that in volunteers. There was no significant difference in the time to peak flow within the cardiac cycle between patients and volunteers. The CSF flow curve form in the patients was basically sinosoidal and not significantly different from that in normals. One patient was re-examined one year after a ventriculoperitoneal shunt operation (patient no. 1:2) because of clinical suspicion of shunt obstruction due to lack of clinical improvement. No differences were found in the CSF flow parameters compared to the first examination.

Characteristic CSF flow curves, through the cardiac cycle, illustrating the differences found in the CSF flow velocity amplitude in the cerebral aqueduct in patients and volunteers are shown in Fig. 2. The phase maps obtained from the same subjects are shown in Fig. 3. The differences in the peak to peak CSF flow velocities are shown in Fig. 4.

Discussion

We showed the peak caudal and rostral flow in the aqueduct to be significantly increased in patients with NPH, compared to healthy volunteers. This has been suggested

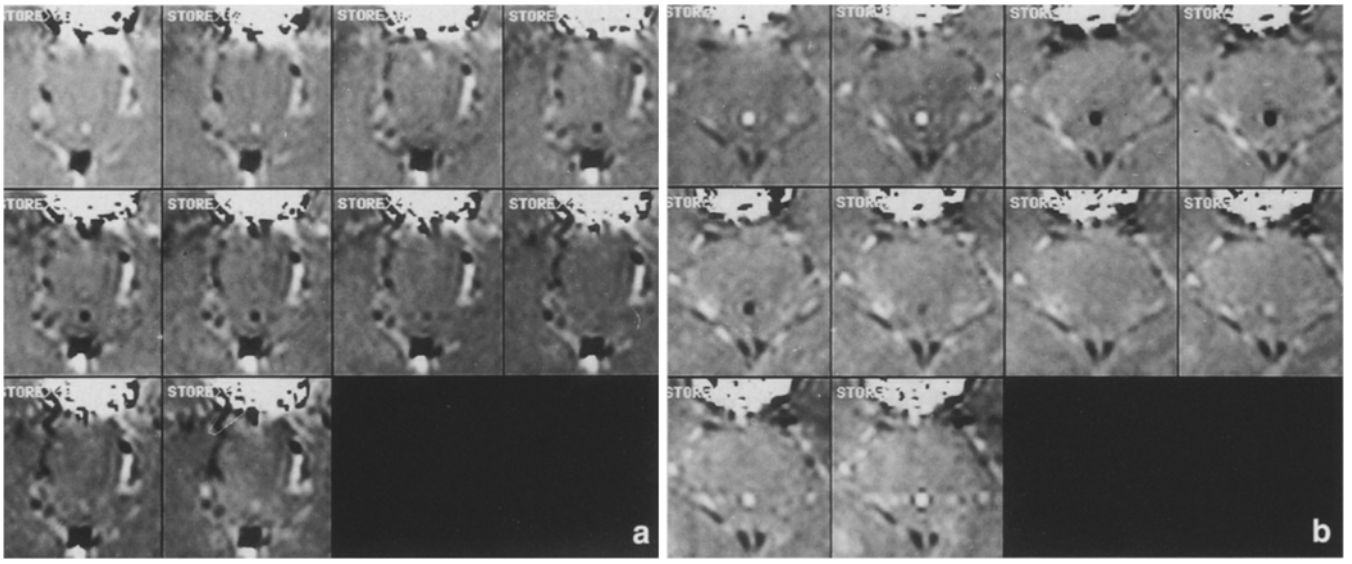

Fig. 3 a, b. Subtracted phase maps from the subjects shown in Fig. 2. **a** Volunteer; **b** patient

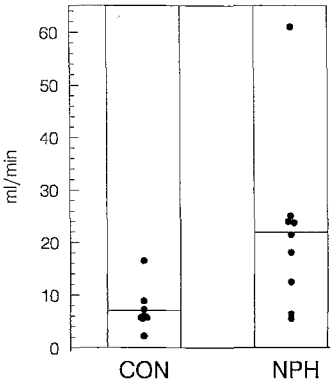

Fig. 4. Peak-to-peak CSF volume flow in volunteers (CON), and patients (NPH). Horizontal bars denote mean values

in previous studies using the flow void [11, 29] and velocity-sensitive phase methods [24, 30–32]. Barkhof et al. [30] found increased CSF velocity and volume flow in the cerebral aqueduct of patients with communicating hydrocephalus, but the diagnostic criteria for hydrocephalus were not specified. Using a phase-contrast method, with retrospective cardiac gating Nitz et al. [24] found a tendency towards higher flow velocities and volumetric flow rates in NPH.

In the group of healthy volunteers, substantial interindividual variations in CSF flow velocity and supratentorial CSF production were found, as in previous studies [21, 23, 25, 32, 33]. Enzmann et al. [23] found a mean caudal CSF peak velocity of 11.8 mm/s, and Quencer et al. [32] values ranging between 3.7–7.6 mm/s. Our results are in good agreement with these findings.

The mean age of our patients was considerably higher than that of the volunteers. However, no apparent difference was found with respect ot age or sex within the group of volunteers, as was also the case in a previous study using a similar phase method, which did not reveal significant changes in aqueduct CSF flow with increasing age [33]. In two of our patients (patients 2 and 3) the results clearly fall within the normal range, while the remaining 7 patients exhibited increased amplitudes of the CSF flow curves. No apparent difference in mean ICP, R_{out} or B-wave activity was found between these two patients and the remaining seven. The normal aqueduct CSF flow velocity and volumetric flow rate in these two patients suggests that the enlarged ventricular system is not in itself responsible for the increase in these parameters found in the others. In a recent study Bradley et al. [29] suggested that the finding of normal aqueduct CSF dynamics in patients suspected of having NPH probably indicates that they have central atrophy rather than NPH, and should not be shunted. A follow-up study of these patients after shunting is necessary, to assess whether an increase in CSF flow velocity and volumetric flow rates could be used to predict a good response to shunting. In patient 6 R_{out} was normal but the CSF flow was slightly increased. Shunt operation is normally performed if R_{out} is over 12 mm Hg/ml/min [4]. Bradley et al. [29] found a correlation between a marked CSF flow void in the aqueduct and a good response to a shunt operation. The flow void seen on conventional MRI is caused by signal loss due to a combination of time-of-flight losses, turbulence, and dephasing [11, 29] and while degree reflects CSF velocity, it is also strongly dependent on the MRI technique. However, Bradley et al. [29] suggested that aqueduct CSF flow in NPH is at a higher velocity than in healthy subjects or in other hydrocephalic states [11, 29]. Even though a few studies have quantified CSF flow within shunts using phase methods [34, 35], no quantitative studies of flow in the aqueduct before and after shunt operations using velocity-sensitive phase methods have been reported. In our single observation no changes in aqueduct CSF flow were seen after operation, which may support the clinical suspicion of shunt malfunction.

The time to peak caudal flow within the R-R interval of 40.6 % is in the same order of magnitude as that reported by Ciraolo et al. [22]. We found no significant difference in the time to peak flow between patients and volunteers. The CSF flow curve form seems to be the same in patients

and in volunteers, judging by the Fourier analysis [21], as in a preliminary study of patients with pseudotumour cerebri [36].

The mean supratentorial CSF production in the volunteers was 0.68 ml/min, or approximately 1000 ml/24 h. This is somewhat higher than the rates of 0.2–0.5 ml/min reported previously using invasive methods [37–39], but of the same order of magnitude as in previous MR studies [19–21]. In a preliminary study we also found normal CSF production rates in patients with pseudotumour cerebri [36]. The CSF production rates we measured naturally reflect only CSF production within the lateral and third ventricles, which may account for only 60–70 % of the total production [8, 40], thus underestimating the total production rate. The mean supratentorial production rate in the patients did not differ significantly from that in young, healthy volunteers. As mentioned previously, there is a cumulative error of approximately 30 % in the calculation of the CSF production rate using our method [21], which may explain the single negative production rate observed in one patient. It is important for studies of CSF production and flow in patients with hydrocephalus or other pathological conditions to take into account the circadian variation in CSF production, which is minimal around noon and reaches a maximum just after midnight [25]. The measurements in the present study were all performed during the afternoon and hence probably reflect an intermediate level of production.

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