Eur Radiol (2003) 13:1019–1024
DOI 10.1007/s00330-002-1697-3

Tosiaki Miyati
Mitsuhito Mase
Tatsuo Banno
Toshio Kasuga
Kazuo Yamada
Hiroshi Fujita
Kichiro Koshida
Shigeru Sanada
Masahisa Onoguchi

Frequency analyses of CSF flow on cine MRI in normal pressure hydrocephalus

Received: 19 March 2002
Revised: 2 August 2002
Accepted: 19 August 2002
Published online: 31 October 2002

T. Miyati (✉) · T. Kasuga · K. Koshida
S. Sanada · M. Onoguchi
Department of Radiological Technology,
School of Health Sciences,
Faculty of Medicine, Kanazawa University,
5–11–80, Kodatsuno, Kanazawa,
Ishikawa 920–0942, Japan
e-mail: ramiyati@mhs.mp.kanazawa-u.ac.jp
Tel.: +81-76-2652540
Fax: +81-76-2344366

H. Fujita
Department of Information Science,
Faculty of Engineering, Gifu University,
Yanagido 1–1, Gifu 501–1193, Japan

T. Banno
Department of Central Radiology,
Nagoya City University Hospital,
1 Kawasumi, Mizuho-cho, Mizuho-ku,
Nagoya, Aichi 467–8602, Japan

M. Mase · K. Yamada
Department of Neurosurgery,
Nagoya City University Medical School,
1 Kawasumi, Mizuho-cho, Mizuho-ku,
Nagoya, Aichi 467–8602, Japan

Abstract Our objective was to clarify intracranial cerebrospinal fluid (CSF) flow dynamics in normal-pressure hydrocephalus (NPH). Frequency analyses of CSF flow measured with phase-contrast cine MRI were performed. The CSF flow spectra in the aqueduct were determined in patients (n=51) with NPH, brain atrophy or asymptomatic ventricular dilation (VD), and in healthy volunteers (control group; n=25). The changes in CSF flow spectra were also analyzed after intravenous injection of acetazolamide. Moreover, a phase transfer function (PTF) calculated from the spectra of the driving vascular pulsation and CSF flow in the aqueduct were assessed. These values were compared with the pressure volume response (PVR). The amplitude in the NPH group was significantly larger than that in the VD or control group because of a decrease in compliance. The phase in the NPH group was significantly different from that in either the VD or the control group, but no difference was found between the VD and control groups. The amplitude increased in all groups after acetazolamide injection. The PTF in the NPH group was significantly larger than in the control group, and a positive correlation was noted between PTF and PVR. Frequency analyses of CSF flow measured by cine MRI make it possible to noninvasively obtain a more detailed picture of the pathophysiology of NPH.

Keywords Magnetic resonance imaging · Cine · Cerebrospinal fluid · Hydrocephalus · Normal pressure

Introduction

The aim of this study was to investigate the usefulness of a Fourier analysis of cerebrospinal fluid (CSF) flow wave and a spectral phase transfer function (PTF) analysis in normal-pressure hydrocephalus (NPH) measured by cine MRI [1, 2]. Concerning the Fourier analysis, Thomsen et al. [3] investigated amplitude and phase in 5 healthy volunteers, whereas Gideon et al. [4] measured the ratio of the first to second harmonic in patients with NPH after subarachnoid hemorrhage (SAH–NPH). Neither of these authors provided valid grounds for the use of Fourier analysis in the evaluation of changes in intracranial conditions in NPH and other diseases, nor did they substantiate it. On the other hand, the PTF analysis was applied as a means to measure the characteristic intracranial response function that is independent of hemodynamics, based on the model of Alperin et al. (linear

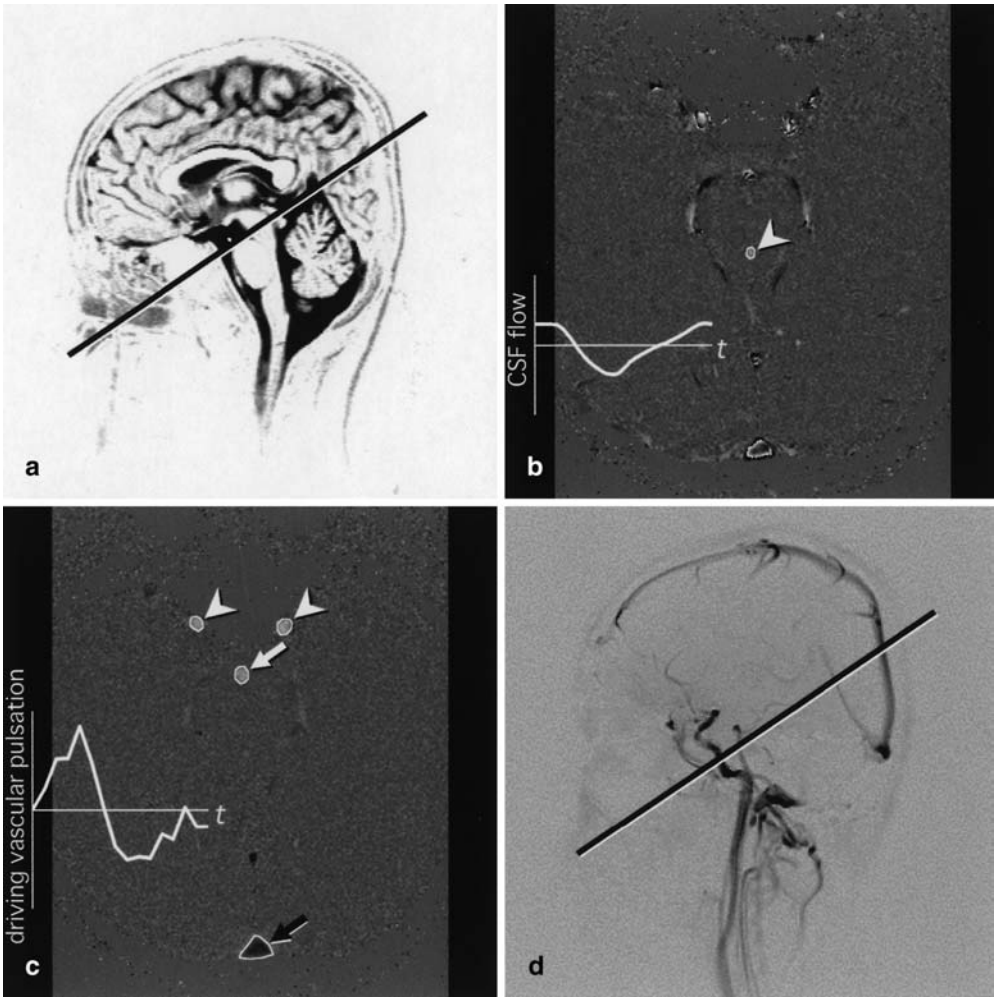

Fig. 1 **a** Location of the slice plane. Velocity-mapped phase-contrast cine MRIs for assessing **b** the cerebrospinal fluid (CSF) flow (*arrowhead*) and **c** blood flow (internal carotid arteries *arrowheads*, basilar artery *open arrow*, and superior sagittal sinus *closed arrow*). **d** Phase-contrast MR angiography for measuring angles between the slice plane and blood vessels. Graphs in **b** and **c** show cardiac phase (t) – CSF flow and cardiac phase (t) – driving vascular pulsation curves, respectively

and shift invariant system) [5, 6]. Moreover, these values were evaluated after an intravenous injection of acetazolamide, and were compared with the compliance of the craniospinal cavity.

Materials and methods

Fourier analysis of CSF flow wave

The CSF wave is not a simple trigonometric function of one cycle in the cardiac cycle. It has distortions that include multiple frequency components, and it is affected by the blood flow waves for inflow and outflow to the brain as well as the pulsation response.

We first set the vertical slice plane against a midpoint on the long axis of the aqueduct (Fig. 1a) [7], and obtained a phase image with velocity mapping (Fig. 1b). Next, we set the region of interest (ROI) in the aqueduct and measured the flow velocity in the cardiac phase (Fig. 1b). At this time, we corrected the baseline offset due to eddy currents by a subtraction process [3, 5]. Next, we multiplied the cross-sectional area of the aqueduct by the velocity to obtain the CSF flow wave. The measured flow is positive in the cranial direction, and negative in the caudal direction. A Fourier transform was conducted for the CSF flow wave, and the amplitude and phase for each frequency was assessed. In some cases, we measured CSF flow spectra before and after intravenous injection of acetazolamide (15 mg/kg).

Measurements of phase transfer function

As intracranial conditions change, such as in NPH, the time for transmission of driving vascular pulsation to CSF pulsation is thought to change in accordance with the degree of pressure damping. This delayed response corresponds to the phase transfer property in the frequency domain, so an investigation was made by calculating phase transfer function [$PTF(f)$]. The difference in each cardiac phase between arterial inflow [$A(t)$] and venous outflow [$V(t)$] in the brain changes the volume of brain tissue, thereby producing CSF pulsations and changes in the CSF flow. Then, taking $A(t)$-$V(t)$ as the input function (driving force or driving vascular pulsation [5]) (Fig. 1c), and the flow wave arising from CSF pulsation in the aqueduct as the output function [$C(t)$] (Fig. 1b), the impulse response [$G(t)$] which is related to the intracranial dynamical properties is expressed by the following equation [5]:

$$[A(t) - V(t)] * G(t) = C(t), \ * : \text{convolution} \quad (1)$$

where, contrary to arterial flow (cranial direction is positive), the flow in the opposite direction is taken as positive for the ve-

nous and CSF flows (caudal direction is positive). The frequency response function $G(f)$ is obtained from the Fourier transform $[A(f)\text{-}V(f), C(f)]$ of each function in Eq. (2):

$$G(f) = C(f)/[A(f) - V(f)] \quad (2)$$

where, taking $R(f)$ and $I(f)$ as the real and the imaginary part of $G(f)$, $PTF(f)$ is obtained from

$$PTF(f) = \tan^{-1}\left[I(f)/R(f)\right] \quad (3)$$

In practice, the blood flow waves were measured in the same slice plane as for the CSF flow described above, but the velocity encoding alone was changed (Fig. 1c). Then ROIs were set in both internal carotid arteries, basilar artery, and superior sagittal sinus. After measuring flow velocity, the baseline was corrected by a subtraction process. Next, from sagittal phase-contrast (PC) MR angiography (imaging time 20 s; Fig. 1d), the angles of intersection in the slice plane and each blood vessel were measured, and the real flow velocities and cross-sectional areas were calculated from the geometrical relationships. Next, the sum of the flow waves obtained for both the internal carotid arteries and the basilar artery was taken as the arterial flow wave $[A(t)]$ for the intracranial inflow. Then, to match the difference in inflow and outflow capacity to the cranium in a cardiac cycle, the flow wave of the superior sagittal sinus was scaled down [5, 8], and the PTF from vascular pulsation to CSF pulsation was calculated using Eqs. (1), (2), and (3). Here, when measuring incoming and outgoing brain blood vessels, the time phase difference from setting the slice plane at the aqueduct level was ignored because the temporal resolution of the cardiac phase on cine MRI is exceeded due to the extremely fast propagation velocity of the pulse wave (approximately ten and several meters per second) [9]. Moreover, since the input function was obtained using only the major blood vessels that could be measured on the slice plane, it may contain some errors, but this is presumed to have little effect on PTF.

Study subjects

Fourier analysis was performed in patients with SAH–NPH (n=26, 6 of whom underwent acetazolamide loading), idiopathic NPH (I-NPH; n=4, 3 of whom underwent acetazolamide loading), asymptomatic ventricular dilation or brain atrophy (VD; n=21, 14 of whom underwent acetazolamide loading), and in healthy volunteers (control group; n=25, 6 of whom underwent acetazolamide loading). The PTFs were determined in the SAH–NPH group (n=5), SAH–NPH post-shunt operation group (n=4), and control group (n=4). The PTF was also measured 5 min after acetazolamide injection. The Mann-Whitney U test was used as the test of significance between the groups, and the Wilcoxon signed-rank test as the test of significance for changes before and after acetazolamide injection. The purpose and procedures of all investigations were sufficiently explained to all patients, and studies were performed after obtaining consent from each patient.

Relation with compliance

During the shunt operations, ICP and the pulse pressure (PP) of the ICP pulse wave in the lateral ventricle were recorded in the SAH–NPH group. Pressure–volume response [PVR; ICP changes after a bolus injection of saline (1–5 ml) to the lateral ventricle] was also obtained as an index of the intracranial compliance. $PaCO_2$ was kept within a normal range during the measurement (38.2±3.6 mmHg). The relation between the obtained values and the results of frequency analyses on cine MRI [amplitude and phase (n=9), PTF (n=5)] was investigated.

Imaging conditions

Measurements were done using retrospective cardiac-gated PC cine MRI on a 1.5 T MR system (Gyroscan ACS II, Philips Medical Systems, Best, The Netherlands), and 16 or 32 phase images were obtained in a cardiac cycle. A gradient-echo pulse sequence (T1-FFE) was used with parameters of 12–15 ms echo time (shortest), 20° flip angle, 3-mm slice thickness, two signals averaged, 150×120 mm rectangular field of view, and 256×256 or 256×128 acquisition matrix. The raw data matrix was zero padded to 512×512. Prior to imaging, first-order flow compensation gradients were applied to the three axes. Velocity was encoded along the cranio-caudal axis. The velocity-encoding value for the CSF flow measurement was ±25 cm/s in patients suspected of having NPH, and ±10 cm/s in all others. The velocity encoding when measuring blood flow was ±80 cm/s. In cases of acetazolamide loading, measurement was done with each velocity-encoding value taken at approximately 1.3 fold.

Results and discussion

Fourier analysis of CSF wave

Amplitude and phase

We show the results of the zero to third harmonic (Fig. 2) and discuss these herein, because the wave becomes distorted as frequency components are added until the third harmonic, but from the fourth harmonic on there is almost no change in the wave even with the addition of frequency components in each group. In fact, no differences were seen between the groups in the fourth and higher harmonic components.

The amplitude at the first harmonic of the CSF flow wave was significantly greater in the SAH–NPH and I-NPH groups (Fig. 2a) than in the control and VD groups, which is thought to be due to the large difference between intraspinal and intracranial compliance in the NPH group (structurally the pressure in the spinal cavity makes dumping easier), and the lower compliance of the craniospinal cavity in the NPH group. This is supported by the strong positive correlation between the amplitude of the first harmonic and the PVR (Fig. 2c). Moreover, the significant difference between the SAH–NPH group and control group, and the correlation with PVR when assessing the amplitude at the first harmonic, exceeds those of the conventional assessment of maximum flow velocity [7], indicating the utility of the Fourier analysis.

In the phase of the CSF flow wave, there was a significant lag in the SAH–NPH group compared with the control group (first harmonic and second harmonic), and VD group (first harmonic; Fig. 2b). The cause of this is difficult to identify because there are numerous uncertainty factors. We suspect that SAH–NPH may induce changes in the nature of intracranial components, including brain tissue, resulting in changes of pulsation movement of the brain and its transmission.

On the other hand, there was no significant difference in either amplitude or phase between the VD group and

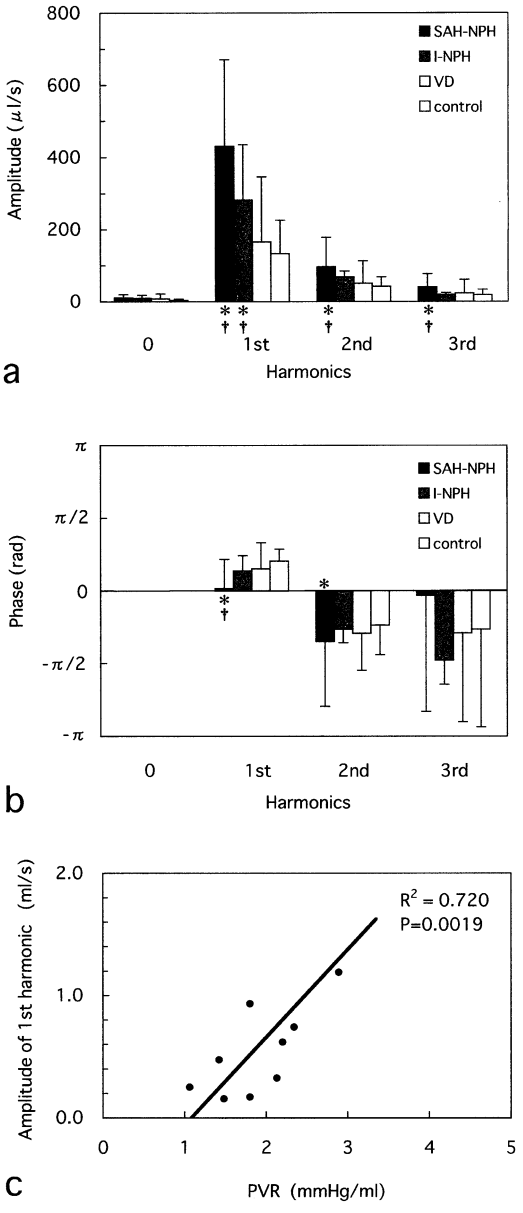

Fig. 2 **a** Amplitude and **b** phase in the CSF flow spectra of the aqueduct in each group. The *asterisks* and *crosses* show that values are significantly different from those in the control and brain atrophy or asymptomatic ventricular dilation (*VD*) groups, respectively ($P<0.05$). Data are shown as mean±SD. **c** The relationship between pressure volume response (PVR) and the amplitude of the first harmonic phase of the CSF flow spectrum in the aqueduct ($n=9$). *SAH* subarachnoid hemorrhage; *NPH* normal-pressure hydrocephalus; *I-NPH* idiopathic normal-pressure hydrocephalus

control group, but there were significant differences between the VD group and the NPH group. At times when it is difficult to differentiate VD from NPH on ordinary MRI or X-ray CT, the Fourier analysis will likely be useful.

In addition, the control group was divided by age into three groups of ≤39 years ($n=12$), 40–59 years ($n=6$), and ≥60 years ($n=7$), and matched for age. No significant difference was found in either amplitude or phase.

Acetazolamide loading

The amplitude for the zero to third harmonics at 5 min after acetazolamide injection was significantly greater than before the injection in all groups (Fig. 3). This is thought to be because acetazolamide caused cerebrovascular dilatation, resulting in the increase of cerebral blood volume, which entails increased intracranial elastance. The rate of change at the zero harmonic from 5 to 15 min after acetazolamide injection increased in the NPH group, but decreased in the control group, demonstrating a significant difference between the groups (Fig. 3). This was thought to be due to the difference in outflow resistance between the two groups; in other words, the difference in the compensatory faculty of ICP. This fact suggests that new information can be obtained by observing the CSF flow wave following acetazolamide injection.

Phase transfer function

The result of the PTF measurement (Fig. 4a) means that in the control group, at a delay of approximately one-fourth the cycle after input, the first harmonic component of the CSF flow starts the pulsation in the caudal direction. In the SAH–NPH group the pulsation starts earlier. This and the strong positive correlation between PTF at the first harmonic and PVR (Fig. 4b) indicate less pressure damping in the SAH–NPH in which compliance is small (intracranial elasticity is high). Moreover, the fact that the PTF of the SAH–NPH post-shunt operation group at the first and second harmonics tends to be closer to that of the control group than that of the SAH–NPH group can be explained by the increased compliance resulting from the shunt operation (Fig. 4a).

There was no significant change in PTF in each group after acetazolamide injection, even though the phase of the first harmonic of the CSF flow wave changed significantly. Alperin et al. demonstrated that the impulse response and modulation transfer functions, which reflect the mechanical properties of intracranial tissues, were independent of the wave of the hemodynamic pulsation [5]. Our results suggest that the PTF was also independent of blood dynamics; however, this hypothesis may not hold true when compliance is very small, with a lack of a compensatory faculty in ICP, because CSF would no longer move freely. Moreover, when blood flow cannot be measured because of metal artifacts due to a cerebral aneurysm clip, it is impossible to calculate the PTF. Naturally, this method measures only PTF for the CSF flow in the aqueduct alone; how-

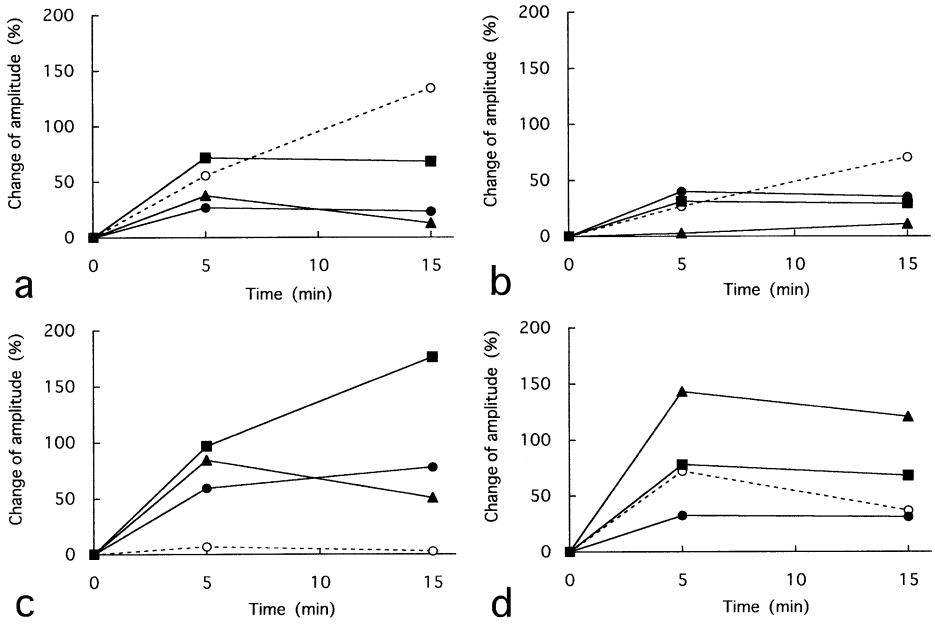

Fig. 3 The changing rate of amplitude of each of the zero (*open circles with dashed lines*), first (*closed circles with solid lines*), second (*squares with solid lines*), and third (*triangles with solid lines*) harmonics after acetazolamide injection in **a** SAH–NPH, **b** I-NPH, **c** VD, and **d** control groups. The rate (R) of change in CSF amplitude or phase following the acetazolamide injection was calculated by:

$$R(\%)=100(S_t-S_o)/S_o,$$

where S_o and S_t indicate the amplitude or phase before and 5 or 15 min after acetazolamide injection, respectively

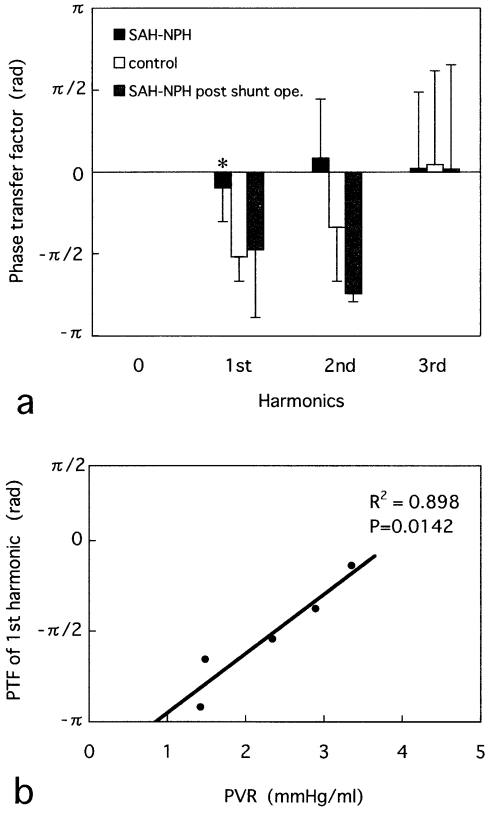

Fig. 4 a Phase transfer functions (*PTF*) in the SAH–NPH, control, and SAH–NPH post-shunt operation groups calculated from spectra of the driving vascular pulsation and CSF flow in the aqueduct. Note that PTF of the first harmonic in the SAH–NPH group is significantly larger than in the control group (* $P<0.05$). **b** The relationship between PVR and PTF of the first harmonic ($n=5$)

ever, in diffuse pathogenesis, such as NPH or VD, the present method is thought to reflect intracranial conditions. In fact, because compliance of the cerebrospinal cavity clearly participates in PTF, the PTF may be considered an indicator of dynamical properties such as intracranial elasticity. In the calculation of PTF, the CSF flow wave data obtained from Fourier analysis in the aqueduct described above can be used without modification; a 3- to ~6-min pulse sequence in the same radiofrequency coil configuration and slice plane is added to CSF flow measurement only to determine blood flow; thus, there is less burden on the patient, making this method easy to apply clinically.

Conclusion

In this study, frequency analyses (amplitude, phase, and PTF) of CSF flow measured by cine MRI were investigated in NPH patients and compared with VD and healthy subjects. Frequency analyses of CSF flow provided, non-invasively, a detailed picture of the pathophysiology of NPH and the changes in intracranial conditions.

References

1. Ohara S, Nagai H, Matsumoto T, Banno T (1988) MR imaging of CSF pulsatory flow and its relation to intracranial pressure. J Neurosurg 69:675–682
2. Bradley WG, Scalzo D, Queralt J, Nitz WN, Atkinson DJ, Wong P (1996) Normal-pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging. Radiology 198:523–529
3. Thomsen C, Stahlberg F, Stubgaard M, Nordell B (1990) Fourier analysis of cerebrospinal fluid flow velocities: MR imaging study. Radiology 177:659–665
4. Gideon P, Stahlberg F, Thomsen C, Gjerris F, Sorensen PS, Henriksen O (1994) Cerebrospinal fluid flow and production in patients with normal pressure hydrocephalus studied by MRI. Neuroradiology 36:210–215
5. Alperin N, Vikingstad EM, Gomez-Anson B, Levin DN (1996) Hemodynamically independent analysis of cerebrospinal fluid and brain motion observed with dynamic phase contrast MRI. Magn Reson Med 35:741–754
6. Uftring SJ, Chu D, Alperin N, Levin DN (2000) The mechanical state of intracranial tissues in elderly subjects studied by imaging CSF and brain pulsations. Magn Reson Imaging 18:991–996
7. Mase M, Yamada K, Banno T, Miyati T, Ohhara S, Matsumoto T (1998) Quantitative analysis of CSF flow dynamics using MRI in normal pressure hydrocephalus. Acta Neurochir 71:350–353
8. Enzmann DR, Pelc NJ (1993) Cerebrospinal fluid flow measured by phase-contrast cine MR. Am J Neuroradiol 14:1301–1307
9. Giller CA, Aaslid R (1994) Estimates of pulse wave velocity and measurement of pulse transit time in the human cerebral circulation. Ultrasound Med Biol 20:101–105