Cerebral Blood Flow in Normal Pressure Hydrocephalus

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A xenon-133 method was used to measure cerebral blood flow (CBF) before and after cerebrospinal fluid (CSF) removal in patients with normal pressure hydrocephalus (NPH). Preliminary results suggested that shunting should be performed on patients whose CBF increased after CSF removal. There was a significant increase in CBF in patients with NPH, which was confirmed by the favorable outcome of 88% of patients shunted. The majority of patients with senile and presenile dementia showed a decrease or no change in CBF after CSF removal. It is suggested that although changes in CBF and clinical symptoms of NPH may have the same cause, i.e., changes in the cerebral intraparenchymal pressure, there is no simple direct relation between these two events. The mechanism underlying the loss of autoregulation observed in NPH is also discussed. (Stroke 1987;18:1074–1080)

The combination of the typical syndrome defined by Hakim and Adams with dilatation of the whole ventricular system appears sometimes insufficient to distinguish between normal pressure hydrocephalus (NPH) and cerebral atrophy. Despite the use of tests such as computed tomography (CT) scan, pneumoencephalography, isotope cisternography, and the cerebrospinal fluid (CSF) infusion test, it has not been possible to determine which patients are the best candidates for shunting of CSF. In different series the number of patients improved after the surgical procedure varied from 40 to 70%, Greitz et al12 demonstrated that those patients showing clinical improvement had markedly increased cerebral blood flow (CBF). Since then, these results have been confirmed by other authors.13-15 Removal of CSF from patients with NPH resulted in increased CBF but had no effect on or decreased CBF in patients with an identical clinical picture due to cerebral atrophy. Greitz et al11,12 demonstrated that those patients showing clinical improvement had markedly increased cerebral blood flow (CBF). Since then, these results have been confirmed by other authors.13-15 Removal of CSF from patients with NPH resulted in increased CBF but had no effect on or decreased CBF in patients with an identical clinical picture due to cerebral atrophy.14-16 Grubb et al17 and Kushner et al18 did not confirm these observations. The accurate diagnosis of NPH is important because complications arising from CSF shunts (hemorrhage, infection) may be fatal in old and fragile patients. The aim of the present work is to contribute to the resolution of apparent disparities in the published reports by the use of a noninvasive xenon-133 method for CBF measurement in patients in whom NPH has been confirmed by clinical improvement after shunting. The possible correlation between CBF and the pathophysiology of NPH is also discussed.

Subjects and Methods

Patients and Protocol

Patients with NPH. We studied 25 patients aged 38–83 years (mean 65 years), 16 men and 9 women. Their symptoms consisted of either the triad of progressive dementia, gait disturbance, and urinary incontinence (14 cases, of which 2 had extrapyramidal signs), or an incomplete triad (11 cases) distributed as follows: 6 cases with dementia and gait disturbance (1 of which had extrapyramidal signs), 1 case with incontinence and ataxia, 3 with ataxia only, and 1 with dementia alone.

The etiology was known in 7 cases. Two had suffered subarachnoid hemorrhage and 2 had recovered from bacterial meningitis. Three had had neurologic surgeries, 1 for neurinoma of the eighth cranial nerve, 1 for sphenoidal meningioma, and 1 for frontal epidermoid tumor. In the 18 others the cause was uncertain although the symptoms appeared in 1 case (Case 12) after minor cranial trauma and in another (Case 10) after an unrelated operation. The first symptoms of NPH occurred between 6 weeks and 6 years before our examinations.

Patients also met the following criteria: 1) CT evidence of dilatation of the whole ventricular system with no sign of intraventricular obstruction of CSF circulation, 2) CSF pressure <20 cm H2O measured by lumbar puncture in the lateral recumbent posture, and 3) measurement of regional cerebral blood flow (rCBF) before and 3 hours after removal of 20–35 ml CSF, which lowered CSF pressure to 0 immediately after removal. rCBF showed a significant increase in cerebral perfusion in both hemispheres.

In 22 cases, the CSF shunting procedure used a medium-pressure valve (18 with Hakim valves, 2 with Pudenz valves, and 2 with Holter valves), and in 3 cases a low-pressure valve (Raimondi valves). In 15 cases shunts were ventriculo-atrial and in 10 cases ventriculo-peritoneal. The patients in our study were all investigated by skull x-rays, CT, electroenceph-
alography, and, in 21 cases, \(^{133} \text{In} \)diethylene triaminopentaoctate (DTPA) Ca iso tope cisternography (8 by lumbar puncture, 13 by suboccipital puncture). In 14 cases rCBF was measured 1 week to 4 months after shunting.

All patients had clinical preoperative and postoperative examinations by two independent neurologists. The examinations included memory deficit, intellectual impairment, behavior disturbance, gait abnormality, pyramidal and extrapyramidal signs, and sphincter incontinence. Discussions were held with the patients’ families. Every symptom was analyzed and categorized as Grades I–IV using the classification of Stein and Langfitt: I, slight deficit but able to function independently at home; II, some supervision required at home; III, custodial care required in spite of considerable independent function; or IV, no practical capacity for independent function. Postoperative results were evaluated according to the protocol of Black et al using a modified Stein and Langfitt’s grading classification and general categorization as excellent, resumed preillness activity without impairment; good, resumed preillness activity with moderate impairment; fair, improved but no return to previous work; or poor, no change or worsening. The general category “improved” included patients with excellent, good, and fair results. Only patients with moderate cognitive dysfunction were studied by the Wechsler Adult Intelligence Scale, the Benton test, and the Wechsler Memory Scale.

Control group. This group consisted of 20 patients aged 58–86 years (mean 70 years) who had been diagnosed as having senile or presenile dementia based on their history, data from clinical examination, and CT scan. CBF of these patients was measured before and after CSF removal under the same conditions employed for the NPH patients.

**rCBF Measurement**

rCBF measurements and computations have been described in detail.\(^{19-22}\) The intravenous route was preferred over inhalation for the administration of \(^{133} \text{Xe} \). Clearance curves were obtained by recording the activity of 26 head detectors equipped with 3/4-in. diam NaI crystals and 1-in. long cylindrical collimators. The doses of isotope (15–20 mCi) assured satisfactory counting statistics (800–1000 cps at the peak of the clearance curves) with a sampling time of 6 seconds so that statistical fluctuations were much smaller than the physiologically induced changes in repeated measurements. Clearance curves were analyzed with a bicompartmental model; the first compartment of fast flow was gray matter, and the second, parallel compartment of slower flow was both white matter and extracerebral tissues (bone, scalp, meninges). The input function, i.e., the variation with time of the tracer concentration in arterial blood entering the brain, was estimated by measuring the end-tidal tracer concentration. Blood flow per unit mass of gray matter was calculated using a least-squares method\(^{19} \) on the data derived from the clearance curves and the arterial concentration curve.

Perturbations at the end of the clearance curve caused by slow clearance of extracerebral tissues were eliminated by an end fit time of 11 minutes. Similarly, perturbations at the beginning of the clearance curve due to scattered radiation emitted from the airways and to the random time lag between the respiratory air curve and the cerebral clearance curves were minimized by a delayed-start fit time dependent on the mean hemispheric flow rate. Under these conditions, the gray matter flow measurements are similar to those after intracerebral injections (CV = ± 10%).\(^{20} \) SD of repeated measurements in the same patient was about 9 ml/100 g/min for the hemispheric mean flow and 11 ml/100 g/min for the regional flow values, similar to those of Blauenstein et al\(^{27} \) for the inhalation method.

CBF studies were performed in a quiet room that was separate from the data analysis area. A saline perfusion in the brachial vein was set up, and the head detectors were positioned symmetrically over both hemispheres perpendicular to the skull. The end-tidal CO\(_2\) concentration from which the alveolar P\(_{\text{co}_2}\) and P\(_{\text{aco}_2}\) were calculated was recorded by capnograph during the examination before and after CSF removal. P\(_{\text{aco}_2}\) was steady in all cases. Arterial blood pressure was measured just before and just after rCBF determination.

**Results**

**Clinical Results and rCBF**

*Clinical results.* Table 1 shows that in the 25 patients studied, the clinical results of shunting were graded excellent in 6, good in 9, fair in 7, and poor in 3 cases; 88% of cases were in the general category improved. One of the 3 cases with poor outcome (Case 23) showed a transitory improvement before a fatal cerebral infarct occurred. Among the 6 patients with excellent results, the evolution of one (Case 5) was particularly instructive. Immediately after the shunting procedure, there was a dramatic clinical improvement, but 3 months later a progressive deterioration set in, and he returned to his preoperative condition. Measuring rCBF before and after CSF withdrawal, we again observed a sharp increase similar to that found before shunting. When the shunt was found to be obstructed, the valve was changed and his condition again improved.

*rCBF results.* Analysis of rCBF in the 22 patients who improved clinically revealed the following:

1. The mean hemispheric rCBF in both hemispheres was lower than normal before CSF removal. The reduction was symmetrical (within 5%) in 16 cases and asymmetrical in 6 cases. There was no significant correlation between reduction in the mean hemispheric flow and clinical results observed after shunting.

2. The difference between CBF before and after CSF removal was not related to the clinical improvement seen after CSF shunting.

3. rCBF in the frontal regions (before CSF removal) was not relatively more reduced than rCBF in the other cortical regions. CSF removal did not induce a...
greater increase in rCBF of the frontal regions than of the other areas, however marked the dementia or its improvement after shunting.

4. When there was significant hemispheric asymmetry (>10%) of CBF, the absolute increase in CBF after CSF removal was significantly higher \((p < 0.05)\) on the side with the lower CBF.

5. The duration of NPH symptoms before shunting was not related to either the increase in CBF after CSF removal or to the clinical improvement after shunting. However, 1 patient had had symptoms for about 6 years, and CBF increased within a week after CSF withdrawal.

6. In the 16 patients graded good or fair, CBF some weeks or months after shunting was significantly less \((p < 0.05)\) than that immediately after CSF removal or soon after shunting. This fall in CBF was much less marked in the 6 patients graded excellent.

7. CBF increased after CSF removal or soon after shunting, and any subsequent clinical improvements were not a function of etiology, whether idiopathic or known.

8. The increase in CBF after CSF withdrawal was usually accompanied by equalization of the rCBF rates of cerebral perfusion, even if the rise was moderate.

CBF was measured under conditions of controlled \(P_{aco_2}\) and arterial pressure. There was no variation in \(P_{aco_2}\) before and after CSF removal. Similarly, there was no significant change in arterial pressure before and after CBF determination.
Comparison With Control Patients
In the control group, with presenile and senile dementia, CBF before CSF removal was reduced (mean ± SD, 43 ± 10.1 ml/100 g/min) compared with normal subjects of the same age range (50.1 ± 5.3 ml/100 g/min). This reduction in CBF was significantly smaller than that seen in the NPH patients (mean ± SD, 38.8 ± 10.3 ml/100 g/min). CBF after CSF removal in these control patients was not changed (6 cases) or, more frequently (14 cases), was significantly decreased (mean ± SD, 38.7 ± 5.9 ml/100 g/min).

Comparison With Other Examinations
CBF and CT scan. Hydrocephalus is defined as a marked enlargement of the entire ventricular system with a ratio of >0.30 (ratio = width of frontal horns measured behind the Monro foramen/maximum internal skull width). Slight enlargements have a ratio between 0.30 and 0.35, moderate enlargements between 0.35 and 0.40, and extreme enlargements >0.40. According to this criterion, dilatation of the frontal horns was not correlated with mean rCBF of the frontal regions or of the ipsilateral hemisphere or with the increase in rCBF after CSF removal.

rCBF and isotope cisternography. The results of [111mIn]DTPA cisternography in 21 patients were classed as typical, with isotope entry into the ventricles, long (>48 hours) retention of isotope, and failure of convexity resorption at 48 hours (Grade III); normal, with no ventricular entry and full convexity ascent (Grade I); or intermediate, with any other pattern (Grade II). In 5 cases classed intermediate (Grade II), the patients improved after shunting (4 good, 1 fair) in agreement with the CBF results. In 14 cases classed typical (Grade III), results were in agreement with clinical improvement and CBF measurement. In the 2 patients who did not improve after shunting, both cisternography and rCBF seemed to favor NPH (false-positive results).

Relation Between CBF and Cerebral Atrophy
In 5 patients who improved after CSF shunting, ventricular dilatation was accompanied by moderate but definite cortical atrophy, whereas CSF removal was followed by a significant increase in CBF. However, in 1 case with unfavorable outcome, there were also distinct signs of atrophy; another patient with cortical atrophy improved temporarily before dying of cerebral ischemia.

Before discussing the results of this study, it is necessary to explain the reasons for the restrictive criteria used in the selection of patients. We studied only patients who had CSF shunting and among them, we selected only those patients with increased CBF after removal of CSF. The main restrictive criterion was adopted to avoid introducing error into the study; only shunted patients were studied because the clinical picture and results of conventional investigations appear to be insufficient for an accurate diagnosis of NPH. Such a diagnosis can be certain only if there is a total or partial reversal of symptoms after CSF shunting. The second restrictive criterion, selection of patients with increased CBF after CSF removal, was a practical one. The very positive results obtained with the test in the first few cases and the negative outcome in 3 patients whose CBF did not increase after CSF removal indicated that the shunt should be used only in those cases showing a rise in CBF after CSF removal. While the lack of a systematic comparison may detract from the scientific rigor of this study, we do not believe it radically alters the deductions presented in this discussion.

Discussion
Comparison With Previous Work
Our data differ from those of Mathew et al13 in several respects: we did not observe any proportional- ity between initial CBF and the degree of improvement after shunting, we did not detect any significant relation- tion between the increase in CBF brought about by CSF removal and the improvement after shunting, and we did not find a greater deficit in the frontal than the other regions, whatever the degree of dementia. How- ever, we agree with Mathew et al15 that duration of the symptoms has no effect on the degree of improvement.

Grubb et al17 and Kushner et al18 found no value in measuring CBF before and after CSF withdrawal. They found no differences in patients with dilated ventricles because of cerebral atrophy and in those with NPH. The results of Grubb et al17 may be explained by the measurement of CBF immediately after CSF removal, by the small size of their series (5 patients, 1 of whom died after the operation), and by the criteria used to select patients.

The work of Kushner et al18 should be interpreted more cautiously; the paraclinical examinations were rather incomplete and not systematically performed, the mode of selection of NPH patients was somewhat suspect, and the measurement of CBF only 1 hour after CSF removal can be a source of error as our experience has shown. In certain cases of NPH, the CBF rises only several hours or even several days after CSF has been withdrawn.

With respect to the results obtained in the control group, composed of patients with presenile and senile dementia, there was no change or, most often, a reduc- tion in CBF after CSF removal. This is in agreement with the majority of studies on this problem, which have generally used other techniques for measuring CBF.14-16

Relation Between CBF and Normal Pressure Hydrocephalus
Mechanism of reduced CBF in normal pressure hy- drocephalus. We concur with the opinion of most au- thors that the reduction in CBF in patients with NPH is a result of increased intraparenchyma pressure in the brain. Greitz14 attributed the low CBF in patients with NPH to compression of small-caliber vessels by pressure in brain parenchyma, presumed to be caused by malfunction of the valve system of the Pacchionian granulations, which normally allows the CSF around
the cerebral hemispheres to be reabsorbed. Hakim et al.28 developed a theory of the genesis of NPH and the mechanism of the decrease in CBF based on a mechanical model. According to their theory, the brain is a hollow sphere with viscoelastic properties, which consists of the ventricles inside and the subdural cavities outside, with the pressure of both compartments at equilibrium under physiologic conditions. Thus, the brain is compared with a viscoelastic sponge, the cavities of which correspond to the venous network and, to a lesser extent, the extracellular space. On the basis of this theoretical model, Hakim et al.28 proposed the following explanation of NPH. After several hypertensive periods, the CSF reaches a new equilibrium with the brain, characterized by normalization of the CSF pressure, ventricular dilatation, and a corresponding reduction in the cerebral tissue volume. This loss of tissue volume affects various compartments to different degrees. The greatest and most rapid effect occurs in the venous compartment, which constitutes the only "open" system in direct communication with the rest of the organism, in contrast to the ventricular system, which may be considered "closed." The liquid compartment of the tissue, i.e., the extracellular liquid, and the cellular compartment are affected only after a certain latency. Reduction of the venous compartment is responsible for the reduction in rCBF by increasing the vascular resistance. Only Ingvar and Schwartz29 considered the fall in CBF, particularly in the frontal regions, to be a secondary phenomenon resulting from a decrease in cerebral metabolism caused by the decrease in volume of brain tissue. Perhaps this pathophysiologic mechanism can explain the CBF reduction in patients with NPH, but it seems not to be the main factor. Indeed, our results show no correlation between CBF in NPH and the clinical picture.

Mechanism of increased CBF after removal of CSF.

The observation of a rise in CBF after CSF removal in cases of NPH is the fundamental finding of this study. Simply observing reduced CBF before CSF removal is not sufficient to identify NPH in a patient with dilated ventricles because reduction is also observed when cerebral metabolism is decreased, as in senile or presenile dementia. Moreover, in those studies in which CBF was measured before and after CSF removal in cases of cerebral atrophy,14-16 there was either no change or a decrease in flow. These clinical observations seem clear-cut, but the pathophysiologic mechanism appears to be complex. In fact, it has been shown in both animals30,31 and normal people31 that under normal circumstances CBF remains constant when CSF is removed because of autoregulation. Consequently, the increase in CBF in patients with NPH implies loss of the autoregulatory properties of the cerebral circulation with respect to variations in CSF pressure.15 Although the mechanism is unknown, several explanations appear possible. For example, the increase in tissue pressure in the periventricular structures and brainstem in patients with NPH might affect the neurogenic mechanisms of CBF regulation, inducing loss of autoregulation. It is, however, difficult to imagine why the rise in tissue pressure should affect only the pathways of CBF control without affecting other autonomic mechanisms. A more plausible explanation is that the transmural pressure of cerebral vessels is abnormal in NPH. Because of the high pressure occurring in brain tissue as NPH becomes established, with unchanged cerebral perfusion pressure the vascular transmural pressure is much decreased and tension in the vessel walls is diminished. In this new steady state, even small changes in transmural pressure would induce a large variation of the vessel diameter because the wall is in a relaxed state.32 Thus, if CSF is withdrawn the transmural pressure increases, resulting in a sustained passive increase in vascular diameter; in a normal subject, the increase in pressure is compensated for by an active decrease in the diameter (Bayliss effect).

Role of reduced CBF in pathophysiology of clinical symptoms.

Some authors12,15,33 have affirmed a causal relation between low CBF and NPH symptoms.14 For example, stretching of the anterior cerebral arteries over the corpus callosum caused by hydrocephalus could induce a reduction in rCBF in the frontal regions, and this local ischemia could cause the clinical signs. Although the clinical picture of NPH and the reduction in CBF are produced by the same phenomenon, i.e., straining of the brain parenchyma, we do not believe that there is any direct relation between them. However, the substantial decrease in brain metabolism could be responsible to some degree for the diminished CBF. There are several reasons why there is probably no direct relation between reduction in CBF and NPH symptoms. The severity of symptoms bears no relation to the amount of CBF reduction, absolute CBF values in hydrocephalus patients are often equal to those of asymptomatic subjects over age 50, the amount of CBF increase following CSF removal is not related to clinical improvement (in contrast to the results of Mathew et al.15), and measurement of CBF after shunting shows that it tends to fall again after an initial rise although clinical improvement does not decline; this was particularly observed in cases graded good or fair, and less obvious in those graded excellent (Table 1). This different evolution of CBF is probably due to cerebral metabolism increasing more in the excellent cases than in the others so that the CBF increase resulting from this more active metabolism masks the CBF decrease that is normally seen when the metabolic demand is lower, as in the good or fair cases. We believe, therefore, that the rise in CBF is a mechanical phenomenon, originating through a decrease in CSF pressure, which produces a decrease in the intraparenchymal pressure. It seems likely that the clinical improvement stems from a metabolic improvement, resulting from a decrease in the cellular lesions, which also originates from a reduction in the tissue pressure.

Relation between increased CBF after CSF removal and clinical improvement after shunting.

There is no direct relation between the clinical symptoms of NPH and a reduction in CBF. It is possible that CBF may
increase after intraparenchymal decompression without a parallel change in neuronal activity because the damage may not be reversible in all neurons.

Practical Considerations

One major question is whether, as some authors\textsuperscript{13,15} suggest, the measurement of CBF before and after shunting is useful in the diagnosis of NPH. This study does not provide the evidence required to make such a decision because the neurosurgeons involved shunted only those patients who showed an increase in CBF after CSF removal. We cannot exclude the possibility that some patients who showed no change in CBF after CSF removal would also have benefited from shunting. Only a study that takes this parameter into account may provide a qualified answer to this question. It is noteworthy that the condition of 88% of the patients who showed an increase in CBF was improved by shunting while only 40–70% of those patients shunted on the basis of positive conventional examinations improved.\textsuperscript{3–10}

Another practical consideration is the delay of about 3 hours between CSF removal and CBF measurement. Our experience has shown that this delay is the most suitable in which to see an increase in CBF. However, in some cases in which this increase was not significant but where other criteria strongly favored the NPH diagnosis, we believed it useful to repeat the measurement of CBF 24 or 48 hours after removal of CSF. In such patients the rise in CBF may be delayed for several days after CSF withdrawal (Case 5).

Signs of cerebral atrophy on CT scan cannot be considered formal evidence against the diagnosis of NPH.\textsuperscript{34} In 5 of our cases, ventricular dilatation was associated with cortical atrophy, but there was a distinct rise in CBF after CSF removal and clinical improvement after shunting. On the other hand, we observed that in 3 cases with poor results, 2 had cortical atrophy. Our opinion is that cortical atrophy and NPH can coexist, but in such cases the result of CSF shunting is perhaps less predictable.

Finally, while our results provide a number of discussion points on the mechanism of NPH, a wider, less selective study would appear to be required to reach a firmer conclusion on the diagnostic value of CBF measurement before and after removal of CSF.

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