Regional Cerebral Blood Flow and Oxygen Metabolism in Normal Pressure Hydrocephalus after Subarachnoid Hemorrhage

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Abstract

To clarify the pathophysiology of normal pressure hydrocephalus (NPH) after subarachnoid hemorrhage, the authors measured cerebral blood flow (CBF), cerebral oxygen metabolic rates (CMRO2), the cerebral oxygen extraction fraction (OEF), and cerebral blood volume (CBV) in eight normal volunteers, six SAH patients with NPH, and seven patients without NPH by 15O-labeled gas and positron emission tomography (PET). In the NPH group, PET revealed a decrease in CBF in the lower regions of the cerebral cortex and a diffuse decrease in CMRO2. The decrease in CBF in the lower frontal, temporal, and occipital cortices was significantly greater in the NPH than in the non-NPH group. Reduction of CMRO2 was also more extensive in the NPH group, and both CBF and CMRO2 were more markedly decreased in the lower frontal region. OEF was increased in all areas in both of the patient groups, but the increase was not significant in most areas. CBF, CMRO2 and OEF did not significantly differ between the non-NPH group and the normal volunteers. There was no significant difference in CBV among the three groups. These results indicate that NPH involves impairment of cerebral oxygen metabolism in the lower regions of the cerebral cortex, particularly in the lower frontal region.

Key words: normal pressure hydrocephalus, subarachnoid hemorrhage, cerebral blood flow, cerebral oxygen metabolism, positron emission tomography, misery perfusion

Introduction

Normal pressure hydrocephalus (NPH), which is most often caused by subarachnoid hemorrhage (SAH), produces a surgically treatable dementia. Although NPH has been investigated from various perspectives, including cerebrospinal fluid (CSF) circulation, cerebral blood flow (CBF), and intracranial pressure, its pathophysiology is still unclear. Cerebral oxygen metabolism is closely related to brain neural function and, owing to recent developments in positron emission tomography (PET), can now be studied in vivo in humans. PET has been used to examine cerebral oxygen metabolism in many disorders, including cerebral ischemia, dementia, epilepsy, and brain tumors. In an attempt to clarify the pathophysiology of NPH, we used 15O-labeled gas and PET scanning to measure regional CBF and oxygen metabolism in patients with NPH consequent to SAH.

Patients and Methods

Six patients who developed NPH after SAH and seven SAH patients without subsequent NPH (non-NPH) were studied. All patients with NPH exhibited the classic triad of signs (dementia, gait disturbance, and urinary incontinence) and computed...
tomographic (CT) scans showed little or no cortical low density. CSF shunting was effective in all the NPH patients. Eight healthy volunteers were also studied as a control population. Informed consent was obtained from the subject or the next of kin prior to PET scanning.

Regional CBF and cerebral oxygen metabolic rate (CMRO₂) were studied by the method of continuous inhalation of ¹⁵O-labeled CO₂ and O₂ gases with a "Positologica III" PET scanner. This scanner provides images of seven slices at 16-mm intervals in one scan with an axial resolution of 12 mm full width at half maximum and a planar spatial resolution of 7.6 mm at the center of the field. The subjects were placed in the supine position and a polyethylene catheter was inserted into the left radial artery. The lowest slice was set at 8 mm above the orbitomeatal line, and the scan was made parallel to this line. After transmission scanning for attenuation correction, the brain tissue concentration of the tracer was measured for 5 minutes to obtain the steady-state value. The unextracted intravascular activity was corrected by separate measurement of the cerebral blood volume (CBV) after ¹⁵O-labeled CO gas inhalation. Duplicate arterial blood samples were drawn for measurement of the ¹⁵O concentrations in whole blood and plasma. After correction for attenuation, images of CBF, CMRO₂, the oxygen extraction fraction (OEF), and CBV were obtained.

For quantitative assessment, the regions of interest (ROIs) shown in Fig. 1 were selected. The cerebral cortical mantle was divided into three equal areas bilaterally and the mean values for corresponding areas were calculated for each slice. The slices that included the base of the skull were excluded from the analysis. To minimize interindividual variations in cerebral anatomy, relatively large ROIs were delineated to combine four slices into two (upper and lower slices). The mean values for CBF, CMRO₂, OEF, and CBV were calculated for the upper and lower slices in each of the three areas. Thus, six large cortical ROIs (A through F in Fig. 1) were created, encompassing almost the entirety of the cerebral hemispheres, for study of each parameter.

The mean values of all three groups were compared by one-way analysis of variance, and the Bonferroni method was used for comparisons between two groups. Student’s t-test and the Wilcoxon U test were applied in simpler two-group comparisons. The criterion for significance was p < 0.05.

Results

Table 1 lists the mean values and standard deviations for various physiological and clinical parameters, including the Hunt and Kosnik grade of clinical severity on admission, Fisher’s classification of subarachnoid blood as demonstrated by CT, the interval between SAH and ischemic symptoms, and the

![Image of regions of interest](image_url)

**Fig. 1 Illustration of regions of interest.** The cortex in each slice was divided into three equal areas and the mean values of each parameter were calculated for the bilateral corresponding thirds. In addition, the mean values of each third in the lower slices (slices 1 and 2) and upper slices (3 and 4) were calculated. Thus, mean values in six cortical areas (A through F) were obtained for each parameter.

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Glasgow Coma Scale score. Ischemic symptoms were classified into four grades: 0, no symptoms; 1, mild; 2, moderate; and 3, severe.

No significant differences were noted between the NPH and non-NPH groups with respect to the Hunt and Kosnik grade, Fisher's grade, the interval after SAH, ischemic symptoms, or cortical low-density areas. However, significant differences were registered in the Glasgow Coma Scale score, the incidence of hydrocephalus, and the incidence of periventricular lucency, which are parameters that characteristically differentiate NPH patients from those with an uneventful post-SAHI course. The mean age was higher in the NPH group, but the difference was not statistically significant. Comparison of physiological data obtained by PET study revealed significant differences in all parameters except PaCO2 and mean blood pressure. Postoperative anemia may have been responsible for the low hemoglobin and hematocrit values in both the NPH and the non-NPH group. The low PaO2 values in the NPH group were probably due to slight respiratory depression associated with mild disturbance of consciousness.

CBF, CMRO2, and OEF were quite similar among the control group (Fig. 2A). In the non-NPH group, CBF and CMRO2 were slightly decreased while OEF was slightly increased over a wide area (Fig. 2B). In the NPH group, the reductions in CBF and CMRO2 were more marked and extensive, especially in the lower frontal region (Fig. 2C). A diffuse increase in OEF was also noted. No changes were observed in CBV.

Six cortical ROIs were compared among the three groups in terms of CBF, CMRO2, OEF, and CBV (Fig. 3). One-way analysis of variance revealed a significant decrease in CBF in the NPH group in areas A, B, and C, which correspond to the lower regions of the cerebral cortex. The reduction in the NPH group was significant relative to both the control and non-NPH values and was most marked in area A, which corresponds to the lower frontal cortex. CMRO2 in NPH patients was significantly reduced in all areas except area E, in comparison with controls. It was significantly low only in areas A, B, and C compared to the non-NPH group. In contrast to CBF and CMRO2, OEF was increased in all areas in the NPH patients, but one-way analysis of variance revealed the increase to be significant only in area B, which corresponds to the lower temporal cortex. If Student's t-test was applied without Bonferroni's correction, OEF was significantly increased in all areas in the NPH group compared to that in the control group. No significant differences in CBF, CMRO2, or OEF were observed between the non-NPH and control groups. No significant difference in CBV was noted among the three groups, although it was higher in area A in the NPH group.

Discussion

Recent progress in PET with 15O-labeled gas inhalation allows investigation of the regional flow-metabolism relationship in the living human brain, providing quantitative information concerning regional CBF, CMRO2, OEF, and CBV by means of tomographic images. However, the results may be difficult to interpret because there are many problems in terms of physics, biomathematics, quality control, neuroanatomy, and computer science. One confounding factor is the great interindividual variability in cerebral anatomy. To minimize errors from this, we used large ROIs. Also, since the spatial resolution of PET is not adequate to differentiate the white matter from the lateral ventricle, no ROI was assigned in the white matter. Finally, to avoid errors due to partial volume effect, the ROIs did not include the periventricular gray matter.

In the present study, statistical analysis was carried out so as to distinguish the NPH group from both the control and non-NPH groups. The three groups were age-matched, although the mean age of the NPH patients was slightly higher. The patients' physiological parameters at the time of the PET study varied, but the PaCO2 and mean blood pressure were not significantly different.

In the NPH group in this study, CBF showed the greatest decrease in the lower regions of the cerebral cortex, especially in the lower frontal region. Since it was first reported by Greitz et al., the mean hemispheric CBF has been known to be decreased in NPH. As for regional differences in CBF, Hartmann and Alberti, using the 133Xe inhalation method, found a marked decrease in the frontal, central, and parietal regions in chronic communicating hydrocephalus. Tamaki et al., using the same method, also observed a marked decrease in the frontal region in NPH. Using xenon-contrast CT, Meyer et al. found a reduction in CBF and the partition coefficients throughout the frontal and temporal lobes, basal ganglia, and thalamus. On the other hand, using 133Xe inhalation with single photon emission tomography, Vorstrup et al. observed no focal decrease in CBF specific to NPH. Although there have been discrepancies in the reported regional differences in CBF in NPH, frontal hypoperfusion in addition to a general reduction in CBF has been observed by many investigators.

In NPH, CT often shows periventricular lucency...
around the frontal horn. This white matter lesion may contribute to a decrease in CBF in the frontal cortex. SAH is the commonest cause of NPH, and its frequent occurrence in the anterior part of the basal cisterns may explain the frontal hypoperfusion, although in our study there were no differences in the Hunt and Kosnik or Fisher’s grades between the NPH and non-NPH groups. High pressure hydrocephalus can cause a decrease in CBF, but the regional differences in CBF between normal and high pressure hydrocephalus are not clear.

In comparison with the other groups, CMRO₂ was also decreased to a greater extent in the NPH group, especially in the lower regions of the cerebral cortex. In contrast, an increase in OEF was noted over a wide area, although one-way analysis of variance
showed this difference to be nonsignificant in most areas. The relationship among CBF, CMR\(_{O_2}\), and OEF is summarized by the equation

\[
\text{CMR}_{O_2} = \text{CBF} \times \text{OEF} \times O_{2ct}
\]

where \(O_{2ct}\) is the \(O_2\) content of the blood. This implies that CMR\(_{O_2}\) is stable until the decrease in CBF is greater than can be compensated for by an increase in OEF when there is no difference in the \(O_{2ct}\). In the present study, \(O_{2ct}\) was almost the same in the NPH and the non-NPH groups. Baron et al.\(^1\) reported an increase in OEF in chronic ischemia, which was reversed by bypass surgery. This uncoupling of flow-metabolism was termed "misery perfusion," and much attention has been paid to the reversibility of cerebral ischemia. Our results suggest that NPH corresponds to "misery perfusion" and that the decrease in CMR\(_{O_2}\) is greater than can be compensated for by an OEF increase. In contrast, there was only a minimal decrease in CMR\(_{O_2}\) in the non-NPH group. Thus, the cerebral oxygen metabolism in NPH is considered to be impaired. Using PET, Gibbs et al.\(^4\) found an increase in CBV on the affected side in patients with unilateral carotid artery occlusion. This autoregulatory response to diminishing perfusion pressure may operate in NPH, but we were unable to demonstrate a significant increase in CBV in any areas.

Few reports are available concerning CMR\(_{O_2}\) in NPH. Grubb et al.\(^6\) noted a decrease in CBF and
CMRO₂ in NPH patients following intracarotid injection of ¹⁵O-labeled oxyhemoglobin and H₂¹⁵O. The data reported were hemispheric means; there was no information about regional differences. Lying-Tunell et al.⁹ also found decreases in mean hemispheric CBF and CMRO₂ in NPH patients. Using PET, Powell et al.¹² measured decreases in CBF and CMRO₂ with no increase in OEF, in chronic hydrocephalus. They did not mention any regional differences in these parameters. Their findings somewhat contradict ours, in that OEF was diffusely increased in our NPH patients, although no significant difference was found by one-way analysis of variance. This discrepancy may be due to patient selection, because Powell and coworkers included cases in which CSF shunting was ineffective.

PET is a useful tool in the evaluation of regional flow and metabolism in various kinds of dementia. In Alzheimer’s disease, for example, blood flow and metabolism are decreased in both temporoparietal cortices.³ Although our findings are not conclusive, NPH that developed after SAH exhibited a unique pattern of disturbance in both CBF and CMRO₂: that is, both showed the greatest decrease in the lower regions of the cerebral cortex, particularly in the lower frontal region. Additional studies are necessary to further elucidate the alterations in CBF and CMRO₂ in NPH after CSF shunting and also the differences in CBF and CMRO₂ between normal and high pressure hydrocephalus.

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References


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