Pattern of white matter regional cerebral blood flow and autoregulation in normal pressure hydrocephalus

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Summary
The mean cerebral blood flow (CBF) has generally been demonstrated to be lower in normal pressure hydrocephalus (NPH) than in normal controls. We investigated the distribution of the regional peri- and paraventricular white matter CBF (WM CBF) in NPH at baseline and during a controlled rise in intracranial pressure (ICP). Twelve patients with idiopathic NPH (mean age 69 years) underwent a CSF infusion study. CBF was measured by H215O PET at baseline and then during the steady-state plateau of raised ICP. The PET images were co-registered and resliced to 3D structural T1-weighted MRIs. Ten healthy normal volunteers served as control subjects for baseline CBF determination only. Profiles of the regional distribution of the baseline WM CBF and of the percentage change in WM CBF as a function of distance from the ventricles were plotted. The global mean baseline CBF in patients (28.4 ± 5.2 ml/100 ml/min) was lower than in the control subjects (33 ± 5.4 ml/100 ml/min) (P < 0.005). In patients, the profile of the regional WM CBF at baseline showed an increase with distance from the ventricles (P < 0.0001), with a maximal reduction adjacent to the ventricles and progressive normalization with distance, whereas in controls no relationship was apparent (P = 0.0748). In 10 patients, the rise in ICP during the infusion produced a fall in cerebral perfusion pressure (CPP) and a significant decrease of the global mean CBF from 27.6 ± 3.1 to 24.5 ± 2.9 ml/100 ml/min (P < 0.0001). The profile of the percentage changes in regional WM CBF in patients showed a U-shaped relationship with distance from the ventricles (P = 0.0007), with a maximal decrease skewed on the side of the lateral ventricles at around a mean distance of 9 mm. The WM CBF is reduced in NPH, with an abnormal gradient from the lateral ventricles towards the subcortical WM. An excessive decrease in CBF is brought about by reductions in CPP and appears to be maximal in the paraventricular watershed region. These results are discussed in the light of previous hypotheses concerning the aetiology of periventricular CBF reduction in NPH.

Keywords: normal pressure hydrocephalus; cerebral blood flow; autoregulation; white matter

Abbreviations: ABP = arterial blood pressure; CBF = cerebral blood flow; CPP = cerebral perfusion pressure; ICP = intracranial pressure; MCA = middle cerebral artery; NPH = normal pressure hydrocephalus; rCBF = regional CBF; SRAR = static rate of autoregulation; WM = white matter


Introduction
In normal pressure hydrocephalus (NPH), the physiological alterations related to the ventricular dilatation that lead to the Hakim and Adams clinical syndrome remain unclear, notably because the physiological abnormalities that have been noted so far are inconsistent and inconclusive (Mori and Mima, 1998). This is particularly the case for the underlying mechanisms and the significance of the changes of cerebral blood flow (CBF) occurring in NPH, in which the global mean CBF has generally been demonstrated to be lower than in normal controls and where a postoperative increase of CBF...
has often been demonstrated after successful shunting (Owler and Pickard, 2001). A CBF increase has also often been revealed after CSF withdrawal by lumbar puncture in patients ultimately responding to shunting (Owler and Pickard, 2001; Mori et al., 2002; Hertel et al., 2003).

The reduction in baseline CBF is often more pronounced in the frontal region and appears to predominate in the white matter (WM) (Owler and Pickard, 2001). In some cases, although the mean global CBF was within the normal range, the regional CBF (rCBF) pattern was abnormal compared with normal controls, with a slightly reduced rCBF in the central WM (centrum semiovale) and with an enlargement of the area of the region of subcortical periventricular low CBF (Waldemar et al., 1993). Therefore, a possible primary dysfunction of the axons in the WM rather than a primary dysfunction of the grey matter might have a dominating role in the generation of the clinical syndrome.

However, both the relationship between the reduction in baseline CBF and the initial clinical impairment and the relationship between the magnitude of the postoperative CBF increase and the degree of clinical improvement are controversial. Therefore the correlation between the clinical syndrome and global/regional CBF is not established. The question whether the CBF reduction is the cause or the consequence of the neuronal dysfunction remains unresolved.

The present study was designed to assess the distribution of the regional periventricular WM CBF using H$^{15}$O PET co-registered on MRI anatomy. The relationship between the WM CBF response to a controlled rise in intracranial pressure (ICP) [and hence a fall in cerebral perfusion pressure (CPP)] induced by an infusion of CSF was also studied.

**Material and methods**

**Patient population and controls**

Twelve patients (eight women and four men) ranging in age from 46 to 76 years (mean age 69 years) were prospectively included in the present study. These patients were diagnosed as suffering from normal pressure hydrocephalus according to the following criteria. All patients presented with a Hakim and Adams clinical triad of urinary symptoms (0 = nil, 1 = present) was used to characterize and modify Stein–Langfitt score was 2.3 (median 2, range 2–4). The course of symptoms was relatively short, with a mean duration of 11 months (range 6–18 months) and progressive, with no stepwise deterioration suggestive of cerebrovascular disease. Their brain MRI scan showed communicating hydrocephalus with a bicaudate ratio greater than 0.25. The ICP, measured in the ventricles through an Ommaya reservoir at the time of the infusion study (see below), was normal (mean 11.1, median 12.4, standard deviation 2.5, range 6.2–13 mmHg). In addition, on the T2-weighted MRI scans, nine of the patients had contiguous periventricular rims of hyperintensity. Three patients had limited foci of paraventricular subcortical white matter T2 hyperintensity suggestive of minor associated ischaemic changes (deep WM lesions). No cause for the hydrocephalus was defined in these patients, hence the diagnosis of idiopathic NPH. Five patients had a history of treated arterial hypertension, with a blood pressure consistently in the normal range. Their only antihypertensive medication was a thiazide diuretic.

According to the standard clinical practice established in our unit, patients presenting with NPH undergo a CSF infusion study so that we can determine the CSF circulatory and compensatory parameters (Czosnyka et al., 1996) and hence decide whether a shunt is appropriate. For this, a right-frontal ventricular catheter connected to an Ommaya reservoir is surgically placed and the infusion study is carried out a least 1 week after the procedure. In our patient group this test was performed on average 24 days (range 7–82 days) after the operation.

Ten healthy volunteers (eight men and two women) ranging in age from 30 to 60 years (mean age 45 years), without a history of neurological or cardiovascular disease, served as control subjects for CBF.

The present study was approved by the Local Research Ethics Committee of the Cambridge Health Authority. Informed written consent was obtained from the patients or their families, and from the control subjects, according to the Declaration of Helsinki.

**CSF infusion study**

For the infusion study, the patients were lying supine in the gantry of the PET scanner and two needles (gauge 25) were inserted into the Ommaya reservoir. One needle was connected to a pressure transducer via a stiff saline-filled tube and the other to an infusion pump. CSF pressure was monitored and recorded on a laptop personal computer. After a minimum of 30 min of baseline measurement, an infusion of normal saline at a constant rate of 1.0 or 1.5 ml/min was started and continued until a steady-state ICP plateau was reached, which usually occurred within approximately 10 min. This ICP plateau was then maintained for 20 min by continuing the infusion. CSF circulatory and compensatory parameters were then calculated using computer-supported methods based on physiological models of the CSF circulation (Czosnyka et al., 1996).

**PET and MRI scans**

PET studies were undertaken with a General Electric Advance scanner (GE Medical Systems, Milwaukee, USA) (Owler et al., 2003). A 10 min transmission scan using two rotating $^{68}$Ge/$^{68}$Ga rod sources was first performed in all patients and used to correct subsequent emission scans for photon attenuation. Emission data were acquired during a 20 min steady-state intravenous infusion of 800 MBq of H$^{15}$O, first at the baseline ICP and then once the
steady-state plateau of ICP had been reached. The PET scan room was silent and the patients had their eyes closed during the scanning.

Images were reconstructed using the PROMIS 3D filtered back-projection algorithm (Kinahan and Rogers, 1989). Emission images were coregistered using Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK) onto 3D structural T1-weighted MRIs obtained just before the PET scan on a Bruker MedSpec S300 scanner (Bruker, Ettlingen, Germany) operating at 3 T. The voxel size of this 3D MRI acquisition was 1 × 1 × 1 mm and the co-registered PET images were resliced to this resolution. Parametric maps of CBF were calculated by inputting simultaneous PET and arterial tracer activity measurements into standard models (Frackowiak et al., 1980).

The MRI scan also included the acquisition of T2-weighted images, which were used to judge whether the patients had contiguous periventricular rims and/or deep WM lesions.

The arterial catheter placed in each patient’s left radial artery for the collection of arterial blood samples for arterial tracer activity determination was also connected via a stiff saline-filled tube to a pressure transducer. The arterial blood pressure (ABP) was monitored and recorded continuously during the infusion study and the PET scan session. The arterial partial pressure of oxygen (PaO2), the arterial partial pressure of carbon dioxide (PaCO2), pH and haematocrit were measured at the baseline and during the infusion.

In the control subjects, image acquisition and reconstruction were accomplished in the same manner, except that only a baseline CBF determination was performed.

Analysis of global CBF and of its change
The global mean CBF (mCBF) at baseline and during the infusion was calculated from the PET parametric maps. For this, individual structural MRIs were segmented to extract a template that identified the brain tissue excluding the extracerebral tissue (scalp, skull, major blood vessels) and CSF. This brain template was then applied to the brain tissue excluding the extracerebral tissue (scalp, skull, major blood vessels) and CSF. This brain template was then applied to the structural MRIs to identify the white matter. Only the WM on the external aspect of the lateral ventricles was retained. A binary map of this WM was generated (Fig. 1). The ventricles were also segmented on these slices and a binary map of their walls was created. For the regional analysis of the changes of CBF, as we did not have control data and as the aim was to study a possible influence of ventricular dilatation on the distribution of the CBF changes, we retained only the slices where the ventricular enlargement was maximal, i.e. at the level of the septum pellucidum.

A program written in-house (by S.M.) in MATLAB (MathWorks, Natick, MD, USA) was then used to calculate the shortest distance in millimetres between each WM voxel and the ventricular wall, along with the baseline CBF and the percentage change in CBF at that voxel. For each patient, the WM voxels were binned according to their distance from the ventricular wall. The mean baseline CBF and the mean percentage change in CBF at each millimetre increment in distance were calculated. As the largest thickness of WM was different across the patients, depending on the ventricular enlargement, the distance from the ventricular surface was normalized for each patient by dividing it by the largest thickness of WM in that particular patient. This yielded distances ranging from 0 (WM adjacent to the ventricles) to 1 (outermost subcortical WM), which were binned in increments of 0.1. A profile of the regional distribution of the baseline WM CBF and of the percentage change in WM CBF as a function of distance from the ventricles could then be plotted.

Analysis of regional CBF and its change as a function of distance from the ventricles
The periventricular and paraventricular subcortical WM at the level of the lateral ventricles, above the caudate nucleus, was chosen because of the extensive range of distances from the ventricles to the cortex without intervening grey matter. In patients, the axial slices meeting these criteria ranged from the level of the corona radiata down to the level of the septum pellucidum, whereas in controls the slices spanned from the level of the corona radiata down to the level of the corpus callosum only (the slices at the level of the septum were excluded as they included portions of the caudate). The axial T1-weighted MRI slices meeting these criteria were retained and the WM was segmented on these slices to exclude the cortical grey

Fig. 1 Image processing steps. (A) A patient’s typical T1-weighted axial MRI slice at the level of the lateral ventricles and above the caudate nucleus. (B) Binary map of the ventricular walls. (C) Binary map of the segmented white matter. (D) Binary map of the white matter on the external aspect of the lateral ventricles, which was retained for the regional analysis.
In control subjects, the analysis was performed as described above, except that only the profile of the regional distribution of the baseline WM CBF was available.

**Statistical analysis**

Data are presented as mean ± SD. The paired Student’s t-test was used for testing the changes in ICP, ABP, CPP and global mean CBF. The relationship between changes in CPP and changes in global mean CBF was tested and quantified by linear regression analysis. The relationships between the distance from the ventricles and the baseline WM CBF as well as the percentage change in WM CBF were analysed using the Kruskal–Wallis test. The threshold for significance was \( P < 0.05 \).

**Results**

The mean baseline ICP of the 12 patients was 11.1 ± 2.5 mmHg and the ICP increased significantly during the infusion in all patients to a mean of 28.4 ± 8 mmHg (\( P < 0.0001 \)), the mean difference being a rise of 17.3 mmHg. A significant rise in ABP was also measured in all patients, from 89.9 ± 14.8 to 97.9 ± 15.7 mmHg (\( P < 0.001 \)), the mean difference being a rise of 8 mmHg. CPP decreased in 10 patients, whereas in two the ABP rise outweighed the ICP rise, resulting in an increase in CPP. The mean CPP reduction in the 10 patients was 13.1 mmHg, from 79.6 ± 15 to 66.5 ± 14.7 mmHg (\( P < 0.0001 \)).

The resistance to CSF outflow was 17.6 ± 8 mmHg/ml/min in the whole group of 12 patients and 19.4 ± 7.6 mmHg/ml/min in the subgroup of 10.

The global mean baseline CBF in the 12 patients was 28.4 ± 5.2 ml/100 ml/min, whereas it was 33 ± 5.4 ml/100 ml/min in the control subjects. This difference was significant (\( P < 0.005 \), unpaired Student’s t-test). In the 10 patients whose CPP fell, the global mean CBF significantly decreased during the infusion, from 27.6 ± 3.1 to 24.5 ± 2.9 ml/100 ml/min (\( P < 0.0001 \)), whereas it increased in the two patients whose CPP rose. In the 12 patients, there was a linear correlation between the changes in CPP and the changes in CBF (\( r = 0.96, P < 0.0001 \)) (Fig. 2). This relationship remained valid when we analysed only the 10 patients whose CPP and CBF fell (\( r = 0.95, P < 0.0001 \)).

The static rate of autoregulation calculated from the global mean CBF indicated on average poor autoregulation in the patients (37 ± 12%).

The relationship between the distance from the ventricles and the mean regional WM CBF at that distance showed a logarithmic profile in all patients (\( P < 0.0001 \)), whereas in controls no relationship was apparent (\( P = 0.0748 \)) (Fig. 3). In the patients, WM CBF was maximally reduced adjacent to the ventricles and progressively normalized with distance, whereas in controls it remained constant and in the normal range through the entire thickness of WM.

In the subgroup of 10 patients whose CBF fell, the profile of the mean percentage change in regional WM CBF as a function of distance from the ventricles showed a polynomial relationship (\( P = 0.0007 \)), with a regional CBF reduction increasing from the ventricles to a maximum at 0.3 of normalized distance, followed by a progressive decline.
clinical improvement (Kimura et al., 1992; Tanaka et al., 1997). In more acute hydrocephalus, CBF is reduced in the areas of periventricular lucency, notably in the frontal WM, and increases after successful shunting (Matsuda et al., 1990; Kimura et al., 1992; Nakano et al., 1996; Pena et al., 1999).

Furthermore, it has recently been shown in an animal model of chronic adult hydrocephalus that the only statistically significant regional CBF reduction persisting in the late stage of hydrocephalus was located in the periventricular WM (Klinge et al., 2003), which is consistent with our study.

Various authors have advanced the following hypotheses, which are not mutually exclusive, to explain the reduction in periventricular CBF in NPH.

### Tissue distortion

It has been hypothesized that distortion and stretching of the periventricular tissue, including vessels, lead to an increase in local cerebrovascular resistance and predispose to ischaemia (Greitz, 1969; Hakim et al., 1976; Meyer et al., 1984; Akai et al., 1987; Del Bigio and Bruni, 1988). Hakim further proposed that, in the early stages of development of NPH, the mechanical strain on the brain parenchyma (and hence the interstitial tissue pressure) would be more pronounced centrally in the periventricular region, with a decreasing gradient from there. Later, as the periventricular tissue yields, the brain parenchyma shrinks and CSF pressure returns to normal (i.e. when the state of NPH is reached), the gradient of stress distribution would be inverted, with more pronounced strain at the periphery of the brain (Hakim et al., 1976). Therefore, at this stage of the condition, CBF is expected to be predominantly reduced at the periphery of the cerebral mantle or, if some degree of added periventricular vessel stretching and distortion is also admitted, evenly reduced throughout the cerebral mantle and its WM.

### Watershed ischaemia

Watershed ischaemia within the corona radiata might occur in the boundary zone between middle cerebral artery perforators and the medullary branches from the pial arteries, compounded by a disturbance of cerebrovascular autoregulation within the WM (Mathew et al., 1975; Meyer et al., 1984). Such a watershed phenomenon is consistent with the profile of the regional change of WM CBF brought about by a decrease in CPP, showing a polynomial U-shaped curve from the lateral ventricles to the subcortex. The maximal CBF decrease occurred at 0.3 of the normalized distance, which corresponded to a mean distance of 9 mm. Infarction in these watershed zones is generally presumed to be due to decreased cerebral perfusion (Bladin and Chambers, 1993). Our findings are consistent with vulnerability of the corona radiata to reductions in CPP within the conventionally defined autoregulatory range when accompanied by exhaustion or impairment of CBF pressure autoregulation. There is little normative data available on regional autoregulation, notably
in the vascular border zones, following changes in ICP equivalent to the global studies of Johnston and colleagues (Johnston et al., 1972). The poor global autoregulation found in our group of patients is probably the average of mediocre autoregulation close to the ventricles, notably in the watershed territories, and relatively normal autoregulation close to the cortex. This is consistent with our previous study using transcranial Doppler ultrasonography with insonation of the distal middle cerebral artery (MCA), supplying the cortex and the superficial subcortical WM, where autoregulation was relatively preserved in patients with raised CSF outflow resistance (Czosnyka et al., 2002). There are remarkably few studies of CBF pressure autoregulation in NPH (Schmidt et al., 1990), where it has never been tested during a reduction of CPP brought about by an increase in ICP. Cerebral blood flow pressure autoregulation to reductions of CBF pressure has been considered by some authors to be impaired in NPH (Mathew et al., 1975; Mamo et al., 1987). Moreover, another form of cerebrovascular responsiveness, cerebrovascular reactivity to acetazolamide or CO₂, has been demonstrated in some studies to be reduced in NPH compared with normal controls (Meyer et al., 1984; Lee et al., 1998; Chang et al., 2000).

**Vasoactive metabolites**

In NPH the CSF may suffuse from the ventricles into the parenchyma and the flow of interstitial fluid may be reversed, which can bring about interstitial/extracellular oedema, predominantly in the periventricular tissue (Tamaki et al., 1990). Such oedema does not cause ischaemia, but inappropriate vasoactive metabolites may stagnate in this oedema and, if the ISF/ECF (interstitial/extracellular fluid) contains vasoactive compounds, local cerebrovascular reactivity may be reduced (Marmarou et al., 1980; Whittle et al., 1992). These compounds could have deleterious effects by interfering with intrinsic mechanisms (such as nitric oxide) subserving cerebrovascular reactivity. Moreover, the accumulation of amyloid-β protein by failure of drainage may damage various tissue components, including vessels (Silverberg et al., 2003). Such pathological processes could lead to failure of autoregulation in NPH. Our study showed heterogeneity of regional autoregulation, with deeper regions more and shallower regions less affected, which could be related to the predominance of the interstitial/extracellular oedema in the periventricular tissue.

**Vascular disease**

Changes in the material properties of the brain may predispose to ventricular enlargement and hence to stretching and distortion of the periventricular WM and its blood supply. In some idiopathic NPH cases, cerebral small vessel disease, notably due to hypertension, might be the initial pathological process leading to hydrocephalus, by multiple small deep cerebral infarctions in the periventricular WM and basal ganglia. It has been suggested that such multiple areas of infarction reduce the elasticity of the periventricular tissue, leading to enlargement of the ventricles provoked by intraventricular CSF pressure pulsations, which are also increased in case of systemic hypertension (Earnest et al., 1974; Koto et al., 1977). Arterial hypertension has been found to be more prevalent among idiopathic NPH patients than among age-matched demented Alzheimer’s disease patients (Graff-Radford and Godersky, 1987) and healthy age-matched controls (Casmiro et al., 1989; Krauss et al., 1996a). However, the direction of the association between idiopathic NPH and hypertension is still not clear, as Miller Fisher, who noted the association between NPH and lacunes, alternatively suggested that the compressive effect of NPH may predispose to lacunar white matter infarction (Fisher, 1982). Deep WM lesions on MRI suggestive of concomitant vascular encephalopathy do not exclude NPH patients from improving with a shunt, but the degree of improvement is negatively correlated with the extent of these lesions (Krauss et al., 1996b).

**Interstitial fluid pressure increase**

The suffusion of CSF into the periventricular tissue and the reversal of interstitial fluid flow might be supposed to compress local vessels, particularly underneath the ventricular wall and tapering off peripherally (Shulman et al., 1975; Tamaki et al., 1990; Kimura et al., 1992). The distribution of interstitial parenchymal pressure in NPH has recently been modelled using finite-element analysis based on Biot’s theory of deformation of a poroelastic medium (Pena et al., 2002). Pena and colleagues have proposed the hypothesis that the chronic ventricular dilatation of communicating hydrocephalus can be explained by a combination of reversal of interstitial fluid flow into the parenchyma and reduced tissue elasticity. In the presence of significant CSF suffusion into the brain parenchyma, the profile of the interstitial parenchymal pressure in the cerebral mantle would have a U curve from the ventricular surface to the cortical surface, with a minimum at the middle of the cerebral mantle. If the magnitude of CSF suffusion from the ventricles is larger than that from the subarachnoid CSF spaces, the distribution of the interstitial parenchymal pressure would have a skewed U shape, with a minimum located much closer to the brain convexity, possibly at the boundary between the WM and the cortical grey matter. The distribution of the interstitial pressure in the WM would appear as an exponential decrease from the ventricles through the WM. It is thus conceivable that the logarithmic profile of WM CBF found in the present study mirrors and results from such an exponential distribution of interstitial tissue pressure. However, the ICP essentially remains in the normal range in NPH, and hence it could be argued that any gradient of interstitial tissue pressure would be too low to compress the capillaries. We would suggest that failure of autoregulation and of drainage of vasoactive/toxic substances (see above) would provide the
additional links in the chain of causation of border-zone ischaemia and tissue damage. It is not possible to say whether the reduced WM CBF observed in our study is sufficiently low to be categorized as ischaemic without measurements of cerebral oxygen extraction ratio by $^{15}$O$_2$ PET. However, we suggest that the impairment of autoregulation and the reduction in WM CBF closer to the ischaemic threshold render the WM vulnerable to periods of modest systemic hypotension or rises in CSF pressure; for example, during REM sleep. Pantoni et al. (1996) have suggested that WM is more vulnerable to ischaemia than previously thought. Three of our 12 NPH patients had deep WM ischaemic changes on the T2 MRIs. Repeated falls of CBF below the ischaemic threshold could also produce delayed ischaemic neuronal damage in the ischaemia-vulnerable hippocampus (Klinge et al., 2003).

In our study the control subjects were younger than the patients. However, Meltzer et al. (2000) have shown that, if account is taken in H$_2^{15}$O PET CBF studies of the partial volume effect created by age-related cerebral atrophy, CBF does not decline with age in healthy individuals. Moreover, an intra-group analysis showed no relationship between CBF and age in our control population ($r^2 = 0.217, P = 0.127$). Our younger control group can therefore be considered as legitimate.

Conclusions
The WM CBF is reduced in NPH, with an abnormal gradient from the lateral ventricles to the outermost subcortical WM. Furthermore, CBF pressure autoregulation to reductions in CPP produced by CSF infusion is impaired, with particular vulnerability of the paraventricular watershed region of the corona radiata between the deep and superficial territories of the MCA. These findings are consistent with a contribution from various processes, including tissue distortion, reversal of CSF and interstitial fluid flow and hence failure of drainage of vasoactive and toxic substances from the parenchyma, watershed ischaemia compounded by failure of WM CBF autoregulation and, finally, changes in the material properties of the brain provoked by cerebral small vessel disease. Such a combination of factors could explain the increased incidence of deep WM lesions in NPH and why a primary CSF disorder might promote cerebral watershed ischaemia. When assessing elderly patients, who often harbour a number of possible pathologies, it is important to look for a remediable hydrocephalic component that might respond to a shunt.

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