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The pathophysiology of the aqueduct stroke volume in normal pressure hydrocephalus: can co-morbidity with other forms of dementia be excluded?

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Abstract Variable results are obtained from the treatment of normal pressure hydrocephalus (NPH) by shunt insertion. There is a high correlation between NPH and the pathology of Alzheimer's disease (AD) on brain biopsy. There is an overlap between AD and vascular dementia (VaD), suggesting that a correlation exists between NPH and other forms of dementia. This study seeks to (1) understand the physiological factors behind, and (2) define the ability of, the aqueduct stroke volume to exclude dementia co-morbidity. Twenty-four patients from a dementia clinic were classified as having either early AD or VaD on the basis of clinical features, Hachinski score and neuropsychological testing. They were compared with 16 subjects with classical clinical findings of NPH and 12 aged-matched non-cognitively impaired subjects. MRI flow quantification was used to measure aqueduct stroke volume and arterial pulse volume. An arterio-cerebral compliance ratio was calculated from the two volumes in each patient. The aqueduct stroke volume was elevated in all three forms of dementia, with no significant difference noted between the groups. The arterial pulse volume was elevated by 24% in VaD and reduced by 35% in NPH, compared to normal ($P = 0.05$ and $P = 0.002$, respectively), and was normal in AD. There was a spectrum of relative compliance with normal compliance in VaD and reduced compliance in AD and NPH. The aqueduct stroke volume depends on the arterial pulse volume and the relative compliance between the arterial tree and brain. The aqueduct stroke volume cannot exclude significant co-morbidity in NPH.

Keywords Normal pressure hydrocephalus · Vascular dementia · Alzheimer's disease · Aqueduct stroke volume · Compliance

Introduction

Normal pressure hydrocephalus (NPH) is unusual among the causes of dementia in that it is treatable by shunt tube insertion. This elevates NPH in importance, despite the fact that it is rare compared with the other major forms of dementia. Careful preoperative selection of patients is crucial, as the postoperative improvement following shunting has been shown to range from 10% to 90% in various series [1]. In NPH the risk of treatment is significant; therefore, there is the need for a predictor of response to treatment [2]. Aqueduct stroke volume has been described as a diagnostic test for NPH [3], but aqueduct stroke volume in other forms of cognitive impairment has received only limited study. The exact physiology behind the volume of CSF expelled by the ventricular system has not been widely examined, in spite of the extensive use made of this variable in the

diagnosis of NPH. Greitz has popularized a hydrodynamic theory as the cause of the elevated aqueduct stroke volume in NPH [4]. This theory has been given support from the work of Egnor et al., who have modelled the cerebral hydrodynamic system using electrical circuit theory [5]. Essentially, this theory predicts that a reduction in the compliance of the arterial tree should increase the pulse pressure of the arterial flow within the brain parenchyma, thus increasing brain pulsation at the expense of a reduction in arterial pulsation within the subarachnoid space.

It is noted that there is difficulty in clinically differentiating between NPH and Alzheimer's disease (AD), and, at brain biopsy, there is a high correlation between NPH and the pathology of AD [6]. There is also a correlation between NPH and leukoaraiosis [7, 8], leukoaraiosis being a major radiological feature of vascular dementia. It is widely believed that a continuum exists between the classically described dementias of AD and vascular dementia (VaD), with approximately 40% of patients studied that meet the clinical criteria for VaD having concurrent AD pathological deposits involving senile plaques and fibrillary tangles [9]. Therefore, there would appear to be a significant risk of co-morbidity between NPH and other non-treatable forms of dementia, perhaps accounting for the variable response to treatment. The risk factors for AD and VaD are predominantly vascular risk factors [9] and, as these risk factors tend to promote atherosclerosis and atheroma, it would be expected that some reduction in arterial compliance should accompany AD and VaD. If the hydrodynamic theory of NPH is correct, then a reduction in compliance in the arterial tree in all three forms of dementia may account for the difficulties noted in differentiating between these diseases.

We aim to test the hypothesis that, through a better understanding of the physiology of the aqueduct stroke volume, we may be able to quantify the ability of the aqueduct stroke volume to differentiate between NPH and other dementia co-morbidity.

Methods

Subjects

The NPH patients were selected on the basis of a classical clinical syndrome of early dementia plus either ataxia or incontinence and a significant clinical improvement following CSF shunt diversion. The NPH group consisted of 16 patients, 12 male and four female, of mean age 76 ± 9 (SD) years. Twenty-four patients were recruited from neurovascular and memory clinics in a tertiary referral hospital setting. Cognitively impaired patients were classified as having either probable AD or probable VaD on the basis of clinical features, CT and/or MR brain imaging, Hachinski score and bedside neuropsychological testing. Dementia or cognitive impairment was confirmed with formal neuropsychological testing using NINDS–DSM IV criteria. Finally, by consensus and blind to the MR flow data, a neurologist skilled in cerebro-vascular disease (C.L.), a neurologist skilled in memory disorders (P.S.) and a neuro-psychologist (E.L.) designated patients as having early vascular dementia/cognitive impairment or early Alzheimer's disease/cognitive impairment. In order to obtain informed consent we excluded patients with a mini-mental state examination score of less than 17. The Alzheimer's patient group consisted of eight women and four men, mean age 76 ± 4 (SD) years. The AD group contained ten patients with confirmed early dementia and two with significant cognitive impairment. The VaD patient group consisted of five women and seven men, mean age 70 ± 11 (SD) years. Eight of these patients had confirmed early dementia, and four had significant cognitive impairment. The control group was selected from the non-demented spouses of patients enrolled in the study and healthy volunteers, with each patient undergoing mini-mental state examination and then formal neuropsychological testing. The control group consisted of six women and six men of mean age 70 ± 5 years. Informed consent was obtained from all patients, and the hospital ethics committee approved the study protocol.

MRI and analysis

All patients were imaged on a 1.5-T superconducting magnet scanner (Magnetom Vision, Seimens, Erlangen, Germany), with the reporting radiologist blind to the clinical details. The NPH patients were scanned preoperatively but were included in the study on the basis of the postoperative clinical response. A retrospectively cardiac gated phase contrast flow quantification sequence was used, with a TR of 29 ms, TE 7 ms, flip angle 30°, slice thickness of 6 mm, matrix 192×512 pixels, FOV 200 cm^2 and a single nex. This is a standard sequence available on this scanner. The velocity encoding (venc) values of 20 cm/s and 75 cm/s were used. The lower venc value was selected to maximize the measurement of the aqueduct, with the higher one being used to maximize the arterial measurement. The plane of section was selected to intersect the basilar artery and the cavernous portion of the internal carotid arteries, as per the literature [10]. Regions of interest were placed around the carotid arteries and basilar artery in each patient as well as the aqueduct. Care was taken to exclude aliasing by retrospectively manipulating the base lines of each resultant graph to give an effective arterial flow limit of 150 cm/s.

The arterial pulse volume represents the degree to which the arterial tree and brain expand in systole and is calculated from the graphs obtained from each carotid and basilar artery. The mean blood flow velocity for each artery for the entire heartbeat was subtracted from the mean blood flow velocity for the period of systole for the same artery, to give the mean increase in flow velocity over systole for that vessel. This value, when multiplied by the time taken for systole to occur and by the cross-sectional area of the vessel (region of interest), gives the volume of expansion of that vessel in systole. This method is similar to one previously published [10]. An example of this process is given in Fig. 1. The addition of the value of vessel expansion obtained for both carotids and the basilar arteries gave the arterial pulse volume. The aqueduct stroke volume was obtained for each patient by a process similar to that for the arterial pulse volume. By obtaining the mean flow velocity directed inferiorly (negative flow below the base line in Fig. 2) and multiplying this result by the time taken for the negative flow and by the cross-sectional area of the aqueduct we obtained the stroke volume. The relative compliance index measures the degree to which the arterial pulse volume is dissipated by the structures outside the brain (principally the arterial tree) compared to compression of the ventricular system and is discussed in Fig. 3. It was obtained by the subtraction of the aqueduct stroke volume from the arterial pulse to obtain the volume of fluid to be dissipated through the subarachnoid space excluding the brain compression of the ventricles; the aqueduct stroke volume was then divided into this.

The degree of ventricular dilatation was measured with the frontal ventricle/cerebral index, which was obtained as the ratio of maximal width of both anterior horns of the ventricles to the diameter of the inner table of skull along the line of measurement of the anterior horn transverse dimension expressed as a percentage. The degree of leukoaraiosis was estimated in each patient by a four-part scale (no white matter disease, grade 0; mild disease with less than 25% of the white matter affected, grade 1; moderate disease with between 25% and 50% affected, grade 2; and severe disease with greater than 50% affected, grade 3). Mean and standard deviations were obtained for each group of patients. Differences between the groups were tested by a non-paired *t*-test.

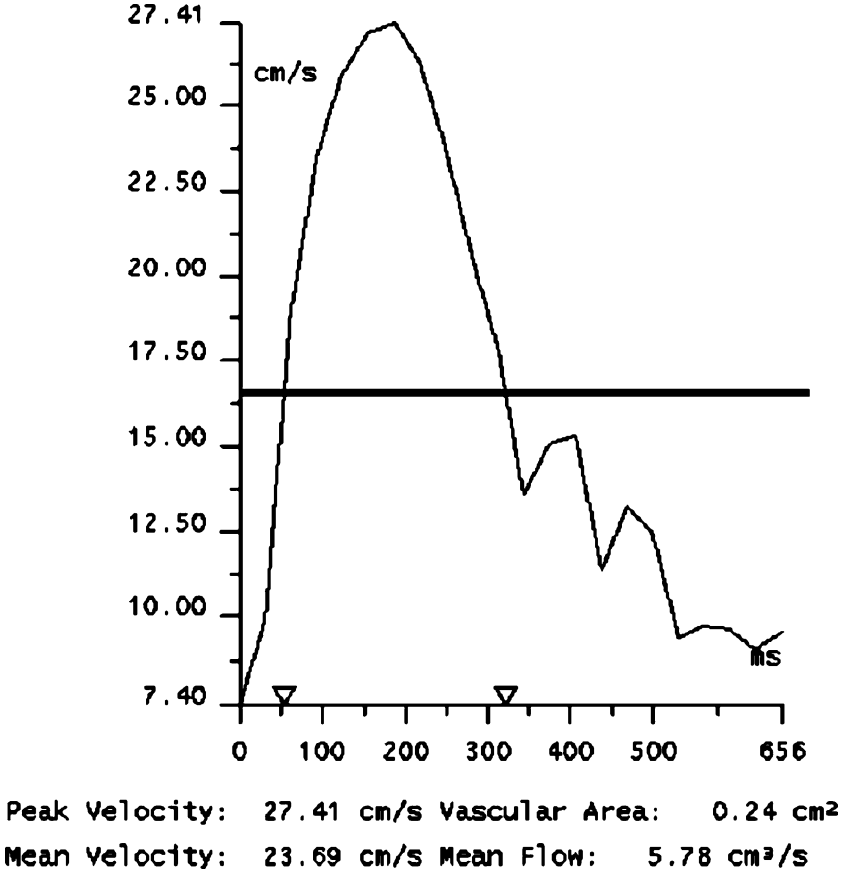

Fig. 1 A right carotid flow graph from a control patient. *The horizontal line* represents the mean blood flow velocity across the entire heartbeat (16.6 cm/s). *The area between the horizontal line and the arterial flow above it* is the arterial pulse volume for this vessel. *The two small triangles* indicate that only the systolic portion of the graph is currently being calculated (where the arterial flow and horizontal line intersect). Thus, the mean increase in velocity over systole is 23.69−16.6 = 7.09 cm/s. Multiplication of this number by the arterial cross-sectional area (0.24 cm^2) and the time for systole (270 ms) gives the arterial pulse volume for this vessel of 460 µl

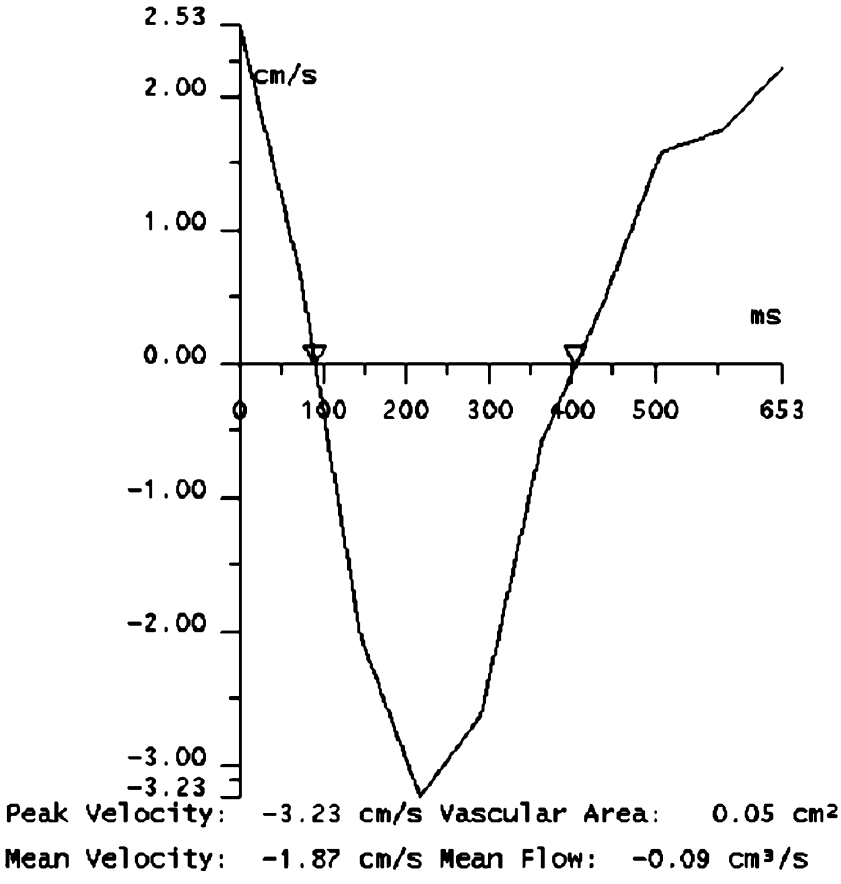

Fig. 2 An aqueduct flow graph from a control patient. *The area of the graph between the base line and the negative portion of the graph* represents the aqueduct stroke volume. This area of the graph is indicated between *the two small triangles*. The mean velocity is 1.87 cm/s, the aqueduct area is 0.05 cm^2 and the length of systole 310 ms, giving a stroke volume of 29 µl

Results

The imaging findings are summarized in Table 1. The moderate reductions in mental state seen in the dementia groups were a requirement for informed consent. The average mini-mental state examination result for the control group was $29/30 \pm 2$, the AD group $23/30 \pm 4$, the VaD group $26/30 \pm 2$ and the NPH group $23/30 \pm 6$. The arterial pulse volume was elevated by 24% in VaD compared to normal ($P = 0.05$) and reduced by 35% in NPH ($P = 0.002$). The arterial pulse volume in AD was not significantly different from that in the controls. There was no significant difference in the aqueduct stroke volume between any of the groups. The control group had an average frontal ventricle/cerebral index that was not significantly different from that of the VaD patients (ventricles 33% of frontal lobe cross-section), but the AD patients showed some mild volume loss at $38 \pm 4\%$ ($P = 0.05$), and the NPH patients ventricles were significantly dilated at $47 \pm 6\%$ ($P < 0.001$). There was little white matter disease in the control group, with an average leukoaraiosis score of 0.5; the AD, VaD and NPH patients had significantly more leukoaraiosis than the healthy patients but were not dissimilar to each other, with average scores of 1.3, 1.4 and 1.3, respectively.

Discussion

The use of MR to measure the arterial pulse volume has previously been described in the literature [10]. The arterial pulse volume is a measure of the degree to which the blood flow into the arterial tree increases in systole above the mean blood flow. The pressure of the vascular supply to the brain varies with time, and this pulse pressure induces pulsatile flow in the arterial tree. The larger the capacitance and therefore the compliance of the arterial tree, the greater the dampening of the pulse pressure of the blood delivered to the brain parenchyma. Dampening occurs because blood is stored in the arterial capacitor in systole and can be delivered to the capillary bed in diastole, thus reducing the downstream pulsation. Brain parenchymal pulsation directly compresses the ventricles, and the volume of CSF ejected through the aqueduct should correlate with the brain parenchymal pulsation. The relative ability of the arterial tree to dampen the pulse pressure before it reaches the brain

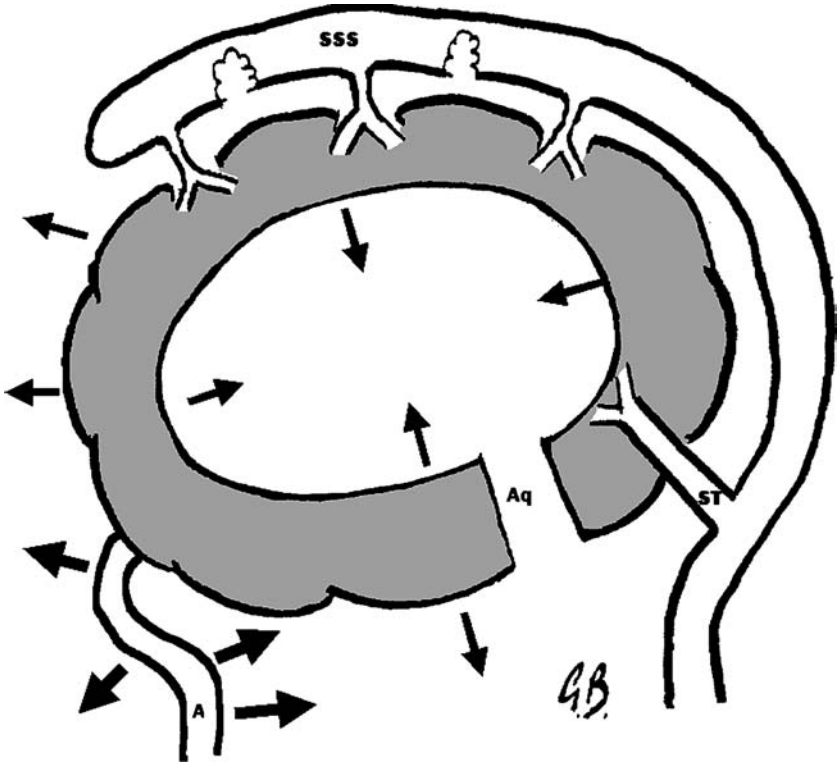

Fig. 3 An illustration indicating that during systole there is some expansion of the arterial tree and brain, which occurs both toward the ventricles and toward the subarachnoid space. The brain expansion toward the ventricles causes aqueduct CSF flow, and the expansion outwards causes a shift of CSF, out of the skull, and compression of the venous structures. The degree of inward/outward displacement depends on the relative compliance between the arterial walls and the brain. *A* artery, *Aq* aqueduct, *SSS* superior sagittal sinus, *ST* straight sinus

should be related to the ratio of the arterial pulse volume and the aqueduct stroke volume that this induces, i.e. a compliant arterial tree will generate a large arterial pulsation with significant dampening of the pulse pressure and lead to a lower aqueduct stroke volume and vise versa. If the hydrodynamic theory of NPH is correct, then the arterial pulse volume should be lower, and the aqueduct stroke volume higher, than normal. The ratio of these two is the arterio-cerebral compliance ratio, and this should be reduced in NPH compared to normal.

The treatment of NPH remains controversial, owing to the variable results obtained following treatment with ventriculo-peritoneal shunting [1]. Bradley et al. have shown that, when they used cine-phase contrast MR flow quantification, measuring aqueductal CSF stroke volume and using a cutoff of 42 μl, 12 of 18 patients improved with shunting, whereas three of six patients with normal values improved [3]. This suggested to the authors that the hyperdynamic CSF flow through the aqueduct could be used to discriminate which patients should be offered surgery. Dixon et al. have questioned the sensitivity of this test to detect NPH, finding in their series of 14 patients with normal MR CSF flow that ten patients (71%) had improvement in gait after shunting [11]. It was concluded that a normal aqueductal CSF flow measurement should not affect the decision to proceed to shunt in patients who are believed to have NPH on clinical grounds [11]. This finding indicated that the sensitivity of the test was probably in doubt. Bradley stated that low aqueduct flow should exclude patients from treatment because low flow indicates atrophy [12]. Mase et al. found that the CSF aqueduct flow was significantly larger in NPH than in a group with asymptomatic ventricular dilatation or brain atrophy [13], thus supporting exclusion on the grounds of low flow. On the other hand, Barkhof et al. found no consistent correlation between CSF flow and ventricular size or cortical atrophy [14], and Stollman et al. found a higher prevalence of hyperdynamic CSF flow in patients with

Table 1 Vascular pulsation, ventricular size and compliance (*VSI* ventricular size index)

Patient group	Age (years)	Arterial pulse (μl)	Aqueduct pulse (μl)	VSI (%)	Compliance ratio
Healthy elderly $n = 12$ (SD)	70 (5)	1,330 (370)	48 (29)	34 (2)	32 (15)
Vascular $n = 12$ (SD)	70 (11)	1,650 (380)	48 (27)	33 (4)	46 (27)
Alzheimer $n = 12$ (SD)	76 (4)	1,150 (380)	53 (24)	38 (4)	23 (10)
NPH $n = 16$ (SD)	76 (9)	860 (200)	70 (50)	47 (6)	17 (12)

atrophy rather than active hydrocephalus [15]. Krauss et al. found that aqueduct flow correlates directly with ventricular size, irrespective of aetiology [1]. We believe that the confusion about the usefulness of this test, either to include or to exclude patients for treatment, derives from the lack of information regarding what initiates the hyperdynamic flow and how other diseases may affect this flow. We agree with Turner and Goodman that "the ability to more accurately identify those patients who will respond to a shunt lies with quantification of the contribution of the coexisting disease to the patient's syndrome" [16]. If AD or VaD also affect arterial compliance in a similar way to NPH then the aqueduct stroke volume will not be useful to discriminate between them.

Most authors state that the movement of CSF in the intracranial cavity depends on the Monroe–Kellie doctrine, which indicates that, because water is non-compressible and the skull rigid, the increased arterial volume of blood that enters the skull in systole must be exactly compensated for by a reduction in the volume of CSF and/or venous blood [17]. It has been shown that the primary force generator of CSF movement within the ventricular system is the whole arterial tree and not just the choroid plexus alone [18]. With the brain and its arterial supply increasing in volume in systole, the degree of CSF displaced from the ventricles and subarachnoid spaces through the foramen magnum, plus the degree of compression of the cortical veins and sinuses, must be equivalent to the size of the original pulsation. Thus, the arterial pulse volume would be expected to correlate with the amount of CSF displaced through the aqueduct. As Fig. 3 indicates, there are two possibilities: the brain and its arteries can expand outward away from the ventricles or expand inwards and compress them [19]. In the first instance there would be no effect on CSF aqueduct flow, and in the second there would be an increase in CSF aqueduct flow. Clearly, both inward and outward expansion occur in life with the relative sizes of the arterial/brain expansion away from the ventricles and the residual aqueduct flow, depending on the relative compliance between the ventricles and inner portion of the brain compared with the compliance of the outer portion of the brain and arterial tree [1, 20, 21]. Greitz has popularized a hydrodynamic theory, which predicts that a reduction in arterial tree compliance in NPH will lead to a reduction in conversion of the pulse pressure within the arterial tree to pulsatile flow [4]. Essentially, this reduces the ability of the arterial tree to dampen the pulse pressure and results in a greater brain parenchymal pulsation, which causes hyperdynamic compression of the ventricles and a water hammer effect. This water hammer effect both dilates the ventricles and elevates the aqueduct stroke volume.

This study has attempted to quantify the relative effects of the total arterial pulsation, the size of the ventricles and the relative compliance of the arterial tree and brain on the aqueduct stroke volume for both NPH and the two most common dementia syndromes that are likely to cause significant co-morbidity, i.e. AD and VaD. The findings suggest that ventricular size may be related to aqueduct stroke volume (see Table 1), similar to the findings in the literature previously discussed [1]. It is uncertain, however, whether this is cause or effect. It is to be noted that the hydrodynamic hypothesis postulates that the aqueduct stroke volume is causal in the degree of ventricular dilatation. Both arterial pulse volume and relative compliance between the arterial tree and brain are important in the magnitude of the aqueduct stroke volume. Note the smallest arterial expansion found was in NPH, but this group had the largest aqueduct stroke volume, indicating that, in NPH, relative compliance was more important than the arterial pulse volume in determining aqueduct flow (Table 1). These findings support the hydrodynamic theory. Luetmer et al. compared CSF flow in healthy elderly patients with mild cognitive impairment/AD and idiopathic NPH, using a slightly different technique [22]. They found an aqueduct stroke volume of 53.8 μl in the healthy elderly and between 48 μl and 56 μl in Alzheimer/cognitive impairment patients [22], which corresponds well with our findings. Their NPH group had a higher aqueduct stroke volume, at 176 μl, than our findings (70 μl) but may represent a more highly selected group.

The results in the three forms of cognitive impairment confirm a varying relationship between arterial pulse strength and compliance in each disease. The aqueduct stroke volumes do not vary significantly between them. However, there is a spectrum of pulsation strength and, therefore, relative compliance. The variation of arterial pulse and compliance must be in balance in each disease because the aqueduct flow in the three diseases is not significantly different. Therefore, in VaD, there is an elevated arterial pulsation but a normal-to-high compliance; in AD there is normal pulsation but reduced compliance, and in NPH a low pulsation and very low compliance. The literature supports the findings that there is reduced compliance in the subarachnoid space in NPH [23, 24]. Any reduction in subarachnoid space compliance will also limit arterial compliance. It is the compliance of the subarachnoid space that provides the volume into which the arterial tree expands. CSF is incompressible, so, if there is no available space for the arterial tree to expand into, then it does not expand. The available compliance in NPH has been shown to be related to larger than normal pulse pressure (not flow) waves interacting within a craniospinal cavity of significantly reduced compliance [10]. A reduction in compliance in AD is also supported by the literature. Uftring et al. state, "normal aging patients and Alzheimer's patients have a tendency for vascular pulsations to cause

increased spinal cord oscillations and reduced CSF oscillations compared to young adults with the data suggesting that the AD patients' changes are of larger amplitude than normal aged patients''[25]. However, the site of the reduced compliance may be different in AD than in NPH. The risk of AD is related to atheroma, atherosclerosis and hypertension [7]. All these risk factors will increase the intrinsic stiffness of the walls of the arteries supplying the brain and thus cause failure of the dampening of the arterial pulse pressure. Whether the reduction in compliance is in the subarachnoid space and secondarily affects the arteries or is a primary arterial wall pathology may affect the clinical presentation. However, alternatively, AD may be a low-grade form of chronic hydrocephalus.

Thus, the findings in this paper are that the mean aqueduct stroke volume and relative compliance in AD falls between normal and NPH, with significant overlap. The aqueduct stroke volume as a marker of NPH appears to fail on two grounds: (1) The predictive value of a negative test is not able to exclude patients on the basis of low aqueduct flow (<42 µl); in this series five of 16 patients (31%) with a good response to shunting would have been excluded and (2) the predictive value of a positive test is in doubt; in this series seven of 12 patients (58%) in both the VaD and AD groups had hyperdynamic flow (>42 µl). Although asymptomatic atrophy and ventricular dilatation have been shown to have a low aqueduct flow [13], asymptomatic patients are not a surrogate for early active AD or VaD. Therefore, if a patient with coexistent, long-standing, benign, ventricular dilatation were to develop AD it is possible that hyperdynamic flow might also develop. The confusion lies in patients who have an active dementia process and not asymptomatic atrophy; therefore, the comparison of NPH with asymptomatic atrophy is unhelpful. If any one patient has 40% of their symptoms attributable to NPH but 60% attributable to AD (currently this distinction is not possible without autopsy) it would appear most unlikely that aqueduct flow, arterial pulsation or relative compliance would be able to quantify this degree of co-morbidity because of the overlap noted at the NPH/AD end of the spectrum. Thus, there seems little utility in measuring aqueduct flow in NPH. Whether or not the parameters outlined have some utility in differentiating between VaD and AD, or are related in some way to the underlying causation of these diseases, is beyond the scope of this paper and will require further study. Interested readers are directed to a paper discussing what further hypotheses may be drawn from these results [26].

Conclusion

The size of the aqueduct stroke volume depends on the arterial pulse volume and the relative compliance of the arterial tree and the brain. The aqueduct stroke volume is not significantly different between early AD, VaD and NPH and, therefore, cannot exclude significant co-morbidity in NPH. There may be a spectrum of compliance and arterial pulse volume in the diseases studied.

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