Cerebral Critical Closing Pressure During Infusion Tests

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Abstract We studied possible correlations between cerebral hemodynamic indices based on critical closing pressure (CrCP) and cerebrospinal fluid (CSF) compensatory dynamics, as assessed during lumbar infusion tests. Our data consisted of 34 patients with normal-pressure hydrocephalus who undertook an infusion test, in conjunction with simultaneous transcranial Doppler ultrasonography (TCD) monitoring of blood flow velocity (FV). CrCP was calculated from the monitored signals of ICP, arterial blood pressure (ABP), and FV, whereas vascular wall tension (WT) was estimated as CrCP − ICP. The closing margin (CM) expresses the difference between ABP and CrCP. ICP increased during infusion from 6.67 ± 4.61 to 24.98 ± 10.49 mmHg (mean ± SD; $p < 0.001$), resulting in CrCP rising by 22.93 % ($p < 0.001$), with WT decreasing by 11.33 % ($p = 0.005$) owing to vasodilatation. CM showed a tendency to decrease, albeit not significantly ($p = 0.070$), because of rising ABP (9.12 %; $p = 0.005$), and was significantly different from zero for the whole duration of the tests (52.78 ± 22.82 mmHg; $p < 0.001$). CM at baseline correlated inversely with brain elasticity ($R = -0.358$; $p = 0.038$). Neither CrCP nor WT correlated with CSF compensatory parameters. Overall, CrCP increases and WT decreases during infusion tests, whereas CM at baseline pressure may act as a characterizing indicator of the cerebrospinal compensatory reserve.

Keywords Critical closing pressure • Hydrocephalus • Infusion tests • Ischemia • Closing margin

Introduction

An external infusion of cerebrospinal fluid (CSF) into the cerebrospinal space, termed an infusion test, consists of a quick and accurate bedside assessment of CSF dynamics in patients diagnosed with hydrocephalus [3, 11]. During this procedure, the CSF, which is infused at a constant rate, presents an uncompensated volume process resulting in a loss of equilibrium between CSF volume and intracranial pressure (ICP) [6, 11]. The resistance to CSF outflow (Rcsf), as estimated during the test and based on a nonlinear analysis of the CSF system [13], has been identified as a predictor (class 2 evidence) of responses to the treatment of hydrocephalus with shunting [1] with a high positive and a very low negative predictive power. Consequently, with measured raised Rcsf, a decision may be reached to treat hydrocephalus via implantation of a shunt system to compensate for disturbed CSF circulation [1, 2]. However, this simple and historically well-documented statement has been recently contradicted by some studies, which challenge the association of Rcsf with outcome [19], or that present a lack of a relationship between Rcsf and ICP in normal-pressure hydrocephalus (NPH) [9].

There is evidence that disturbed CSF circulation interferes with cerebral blood flow (CBF). Our previous studies have demonstrated lower mean CBF, particularly close to the

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walls of the ventricles, in NPH than in normal controls [14]. Positron emission tomography–assessed cerebrovascular reactivity proved to be disturbed in patients suffering from hydrocephalus, with a noticeable augmentation after shunting associated with clinical improvement [12]. Autoregulation of CBF seems to correlate negatively with resistance to CSF outflow, probably consisting of an epiphenomenon of interplay between CSF circulatory problems and possible underlying cerebrovascular diseases in elderly patients [7].

In cases of spontaneous intracranial hypertension, increasing ICP has been shown to elevate critical closing pressure (CrCP) [17]. CrCP denotes a lower limit of arterial blood pressure (ABP), below which the small brain vessels are prone to collapse owing to a critically reduced transmural pressure, as first described by Burton [4]. Burton's model suggested CrCP to be equal to the sum of ICP and vascular wall tension (WT), with WT being a parameter of active vasomotor tone [4, 8]. In addition to the obvious clinical potential of being able to know a critical threshold of ABP, CrCP has also been able to provide a more thorough description of vascular tone in pathological states [16]. For this study we used our own, recently introduced impedance CrCP [16, 17], which is not susceptible to the nonphysiological negative values of pressure, as was the case for the earlier methods [15, 16].

The primary aim of this study is to assess the behavior of both CrCP and WT during the rise in ICP provoked by an increased CSF circulation rate, and to study their relationship to CSF compensatory parameters, such as the resistance to CSF outflow, the brain's elasticity, and the RAP index. A secondary aim was to apply a recently introduced mechanism for ischemia [17], called the closing margin (CM), and to measure its changes during infusion tests, investigating how it correlates with CSF compensatory parameters. A positive CM can be considered a pillow of safety for the small brain vessels, whereas a zero or negative CM would then indicate their collapse [17].

Materials and Methods

We retrospectively analyzed data collected during the period 1992–2000 from 34 nonshunted patients who were diagnosed with NPH by consultants (neurologists or neurosurgeons), on the basis of imaging and clinical symptoms, and who undertook an infusion test to investigate the extent of the disturbance of CSF compensation. Infusion tests consisted of a routine clinical investigation in the Hydrocephalus Clinic, Addenbrooke's Hospital, Cambridge; in this context, no separate approval from the local ethics committee was required [7]. Data were analyzed anonymously as a part of a clinical audit. The median age of the patients was 58 years (interquartile range [IQR]: 35.50–67.00 years), with 53 % of them being male ($n = 18$). All of the patients were diagnosed with ventricular dilation indicated by the bicaudate index (mean 0.28; IQR: 0.19–0.34), with the mean width of the third ventricle being 13.06 mm (IQR: 9.98–16.65 mm). Seven patients demonstrated evidence of ischemia (presence of infarcts and deep white matter lesions) on cranial imaging, as assessed by independent neuroradiologists on blinded data. Cases in which TCD-assessed FV was very high (>200 cm/s) were not included in the analysis, as they may indicate the presence of vasospasm, thus not serving the actual purposes of this study.

Data Acquisition and Analysis

The ICP measurements were made with the patient in a supine position, at which all the CSF spaces were leveled, with the foramen of Monro as the zero level of reference. TCD ultrasonography (Neuroguard; Medasonics, Fremont, CA, USA) was also used for the monitoring of blood flow velocity (FV) in the middle cerebral artery, through a 2-MHz probe fixed on the cranium by using a commercially available fixation system. ABP was recorded noninvasively by using a Finapress finger cuff (Ohmeda, Englewood, CO, USA) positioned at the level of the heart. The recorded signals were analyzed using our own software for clinical data processing (ICM+; http://www.neurosurg.cam.ac.uk/icmplus). An example of a full array of monitored signals during the infusion test is demonstrated in Fig. 1.

Cerebrospinal Compensatory Parameters

Increased resistance to CSF outflow (Rcsf) is commonly recorded in cases of NPH and can be estimated as the difference between baseline and plateau ICP, divided by the respective infusion rate [5]. Elevated Rcsf denotes disturbed CSF circulation [18], with the maximum normal circulation threshold for an elevated Rcsf being 13 mmHg•min/ml [2] or according to other studies, 18 mmHg•min/ml [1].

Estimation of cerebrospinal elasticity is perfomed with calculation of the elastance coefficient (E1), through a time-series analysis for volume-pressure curve retrieval, least mean squares model fitting, and an examination of the relationship between the pulse amplitude and the mean CSF pressure. These calculations are based on the model of cerebrospinal volume compensation [5, 13].

The RAP (R: correlation coefficient, A: amplitude P: mean pressure) is an index representing the dynamic pressure–volume relationship inside the intracranial space,

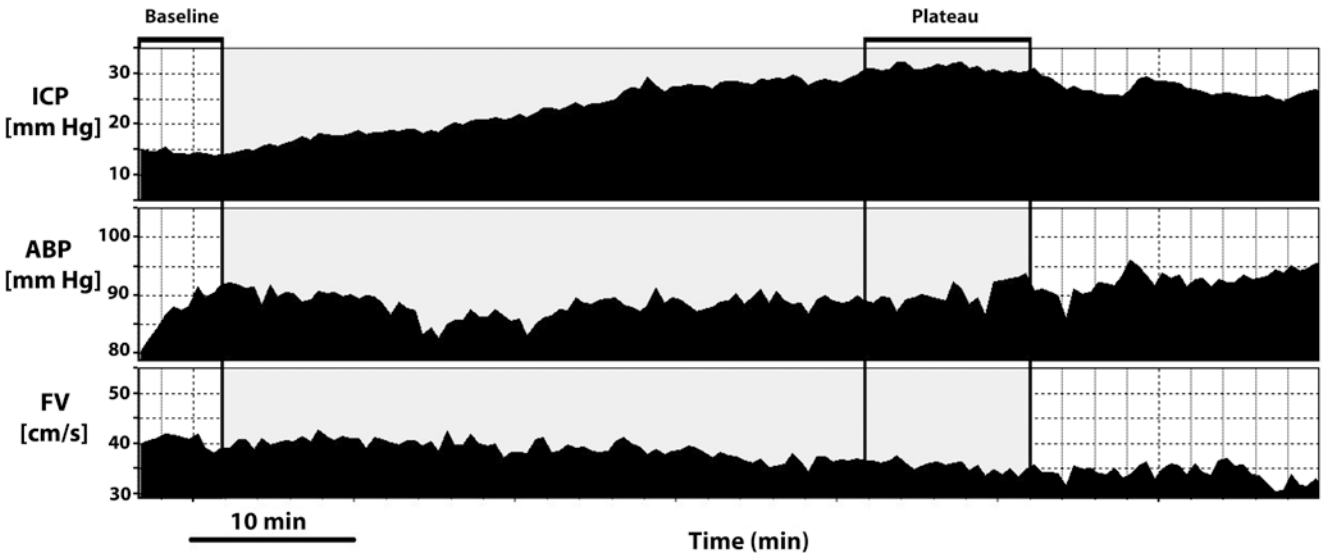

Fig. 1 Example of monitored signals during an infusion test (*ICP* intracranial pressure, *ABP* arterial blood pressure, *FV* blood flow velocity). ICP is demonstrated to rise from baseline to plateau, after the beginning of infusion. The gray area represents the duration of infusion

indicating whether the compensatory reserve is intact or exhausted. RAP can be calculated as a Pearson's moving correlation coefficient between changes in amplitude and mean ICP [6]. The amplitude of the fundamental harmonic of ICP (I1) was derived using 10-s discrete Fourier transformations. RAP around 0 at low ICP (<15 mmHg) indicates good cerebrospinal compensatory reserve, while RAP close to +1 (higher than 0.6) indicates an impaired compensatory reserve.

Critical Closing Pressure Parameters

The CrCP calculations are based on the recently introduced impedance CrCP methodology, requiring simultaneous measurement of TCD blood flow velocity, ICP, and ABP waveforms [16, 17]:

$$\mathrm{CrCP} = \mathrm{ABP} - \frac{\mathrm{CPP}}{\sqrt{\left(\mathrm{CVR}\times\mathrm{Ca}\times\mathrm{HR}\times 2\pi\right)^2 + 1}}\left[\mathrm{mmHg}\right]$$

where CPP is mean cerebral perfusion pressure (estimated as CPP = ABP – ICP); CVR is cerebrovascular resistance; Ca is the compliance of the cerebral arterial bed, while HR denotes the heart rate (beats/s). Although CVR and Ca cannot be measured directly, their product can be estimated using TCD blood flow velocity and ABP or CPP waveforms according to an algorithm described in previous studies [10]. Arterial WT was calculated as the difference between CrCP and ICP [8], whereas CM was the difference between ABP and CrCP [17], both in units of pressure (mmHg).

Table 1 Mean values and standard deviations (mean ± SD) of measured and calculated variables from baseline to plateau

N = 34	Baseline	Plateau	*p* value (*t* value)
ICP (mmHg)	6.67 ± 4.61	24.98 ± 10.49	$p < 0.001$ (13.17)
I1 (mmHg)	1.21 ± 0.87	3.49 ± 2.61	$p < 0.001$ (7.15)
ABP (mmHg)	100.18 ± 32.16	109.32 ± 33.77	$p = 0.005$ (3.04)
CPP (mmHg)	93.50 ± 31.78	84.34 ± 33.78	$p = 0.005$ (3.02)
FV (cm/s)	54.27 ± 18.32	50.37 ± 18.86	$p < 0.001$ (4.70)
HR (beat/s)	69.61 ± 12.45	71.23 ± 14.15	$p = 0.021$ (2.42)*
RAP (a.u.)	0.50 ± 0.33	0.78 ± 0.26	$p < 0.001$ (4.92)
CrCP (mmHg)	50.86 ± 23.46	62.52 ± 23.71	$p < 0.001$ (5.18)
WT (mmHg)	44.20 ± 22.60	37.50 ± 21.60	$p = 0.005$ (3.05)
CM (mmHg)	49.31 ± 17.11	46.80 ± 18.22	$p = 0.070$ (1.87)

ICP intracranial pressure, *I1* amplitude of ICP, *ABP* arterial blood pressure, *CPP* cerebral perfusion pressure, *FV* mean flow velocity, *HR* heart rate, *RAP* correlation coefficient between ICP and I1, *a.u.* auris utraque, *CrCP* critical closing pressure, *WT* wall tension, *CM* closing margin
*The difference becomes insignificant when corrected for multiple comparisons

Statistical Methods

Statistical analysis of the data was performed using the IBM SPSS Statistics 20 package. The analysis consisted of comparing changes in an array of parameters (ICP, I1, ABP, CPP, FV, HR, RAP, CrCP, WT, and CM) from baseline to plateau ICP (Table 1). Results are presented in mean value ± standard deviation (SD) format. Normal distribution was established with the Shapiro–Wilk test and *t* tests were used to conduct the comparison. The level of significance (*p* value) was set at 0.05. When bivariate correlations are used, R denotes Pearson's correlation coefficient.

Results

Mean resistance to CSF outflow was 14.26 mmHg•min/ml (IQR: 9.27–18.13 mmHg•min/ml), with 56 % of the patients ($n=19$) having Rcsf above the normal limit (13 mmHg•min/ml). Cerebrospinal elasticity, expressed as E1, had a mean of 0.25 ml^{-1} (IQR: 0.12–0.36 ml^{-1}).

During infusion tests, mean ICP increased from 6.67 ± 4.61 mmHg to 25.0 ± 10.5 mmHg (mean ± SD; $p<0.001$; Table 1), followed also by an increase in its pulse amplitude I1 ($p<0.001$). This direct relationship between mean and amplitude ICP was reflected in the RAP index, which increased significantly from 0.50 ± 0.33 at baseline to 0.78 ± 0.26 at plateau ($p<0.001$), signifying an increase of 56 %. Mean ABP also rose significantly ($p=0.005$) by 9.12 %, showing a response to rising ICP. The combination of rising ICP and rising ABP resulted in moderate decreases in CPP by 9.80 % ($p=0.005$) and mean FV by 7.19 % ($p<0.001$). Following the rise in ICP, CrCP increased significantly by 22.93 % ($p<0.001$) with WT dropping by 11.33 % ($p=0.005$) owing to compensating vasodilatation. CM showed a tendency to decrease, albeit not significantly ($p=0.070$), as an increase in CrCP was accompanied by a slight rise in ABP. An example of the behavior of CrCP, WT, and CM is presented in Fig. 2. The CM seemed to be inversely correlated to brain elasticity at baseline ICP ($R=-0.358$; $p=0.038$; Fig. 3). This was not the case, however, for either CrCP ($p=0.691$) or WT ($p=0.595$). The predictive power of CM with regard to both normal and high elasticity was assessed using ROC curve analysis; however, the result was areas under the curve (AUC) of below 0.7 in both cases, indicating a low predictive power of CM.

We did not find any relationship between RAP and either CrCP, WT or CM ($p=0.461$; $p=0.889$; $p=0.817$ respectively). Similarly, RAP being lower or higher than 0.6 at baseline ICP was not a differentiator for changes in CrCP, WT or CM from baseline to plateau (ΔCrCP: $p=0.173$; ΔWT: $p=0.937$; ΔCM: $p=0.861$ respectively). An increased Rcsf was not associated with an increased CrCP at baseline ICP ($R=0.218$; $p=0.215$). There was also no significant relationship between Rcsf and either baseline WT or CM ($R=0.141$; $p=0.428$ and $R=-0.184$; $p=0.300$ respectively).

The CM was significantly positive during the whole duration of the infusion tests (mean difference to zero: 52.8 ± 22.82 mmHg; $p<0.001$). The minimal value of CM recorded was 22.22 mmHg in one case at the top of the infusion plateau, after being decreased from 33.63 mmHg at baseline pressure. In this case, ICP rose substantially (from 10.1 to 51.4 mmHg, value of 40 mmHg increased by slow vasogenic waves); however, both the increase in ABP by 8.61 % and the imposed vasodilatation, seen in a reduction in WT by 50.67 %, resulted in FV actually being increased by 1.9 %.

Discussion

During infusion tests, ICP increases significantly because of the extra volume of artificial CSF being infused into the cerebrospinal space. This increase in ICP was resulted in the CrCP being significantly increased at the top of the ICP pla-

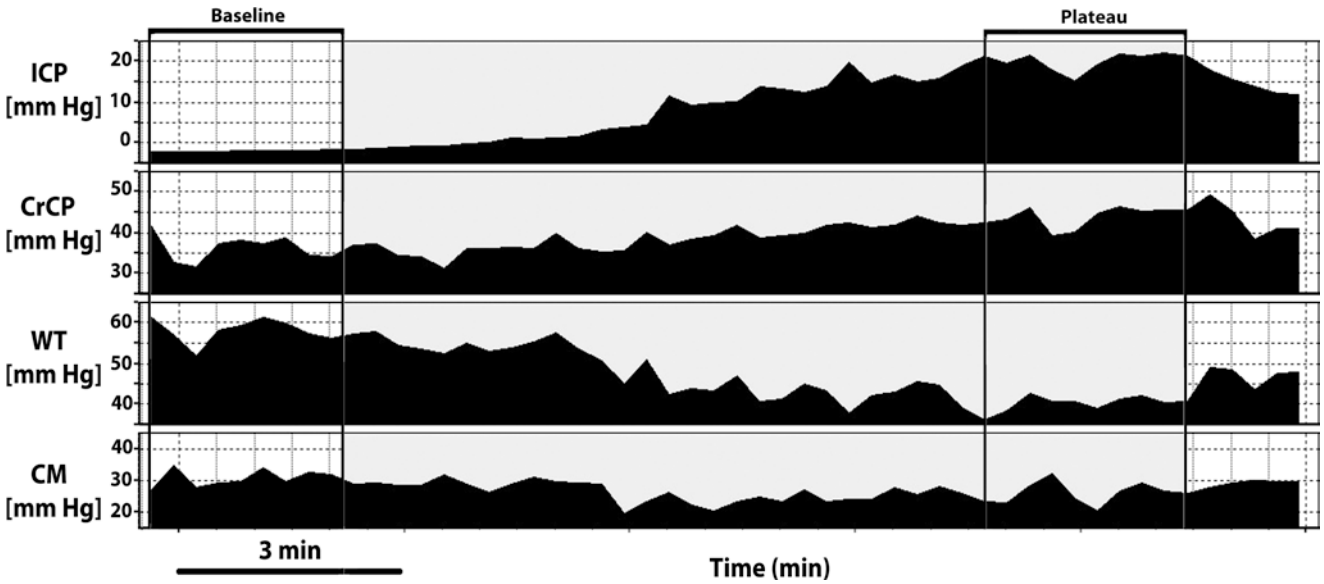

Fig. 2 Infusion-increased intracranial pressure (*ICP*) and the corresponding behaviors of critical closing pressure (*CrCP*), vascular wall tension (*WT*), and the closing margin (*CM*). The gray area represents the duration of infusion

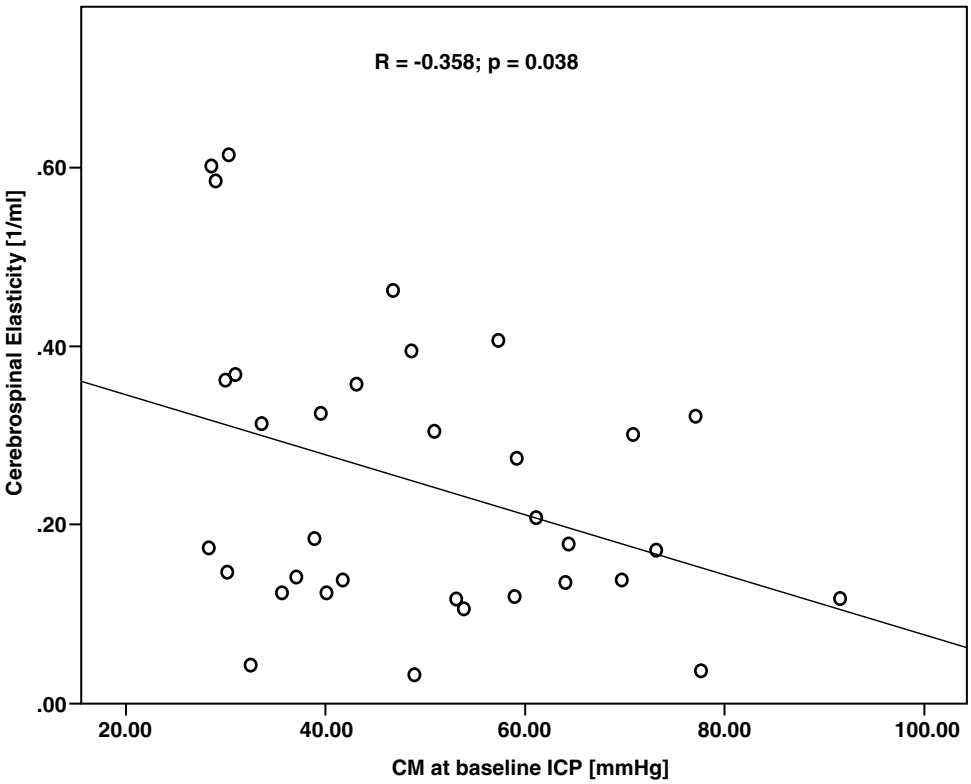

Fig. 3 Closing margin (*CM*) at opening baseline intracranial pressure (*ICP*) of infusion tests ($N=34$) correlates inversely with cerebrospinal elasticity: a lower baseline CM associated with higher elasticity can be an indicator of an impaired compensatory reserve

teau and in the WT being significantly decreased, indicating a compensating vasodilatation occurring in the cerebrovascular system. The opposite changes in ICP and WT, resulting in an increased CrCP, suggest that, compared with changes in WT, changes in ICP might be more pronounced in CrCP during infusion tests. This finding has also been observed in ICP plateau waves in patients following traumatic brain injury [17]. Despite the significant increase in CrCP, the CM did not decrease significantly and this can be explained by ABP showing a slight, but significant, increase. During the infusion tests, CM was always positive and significantly different to zero. These findings, accompanied by the fact that FV did not decrease by a considerable amount, suggest that there might be no elevated risk during the controlled rise of ICP for brain vessels to collapse and for CBF to be adversely affected. This was also confirmed by the case of lowest CM described in the results section; despite a big increase in ICP and decrement of CM, FV was sustained and actually increased owing to rising ABP and imposed vasodilation.

The elasticity can be used as an indicator of impaired cerebrospinal compensatory reserve. Our results signify elasticity to not being associated with either CrCP or WT, but instead being inversely linked to CM; their between correlation being weak, albeit statistically significant. This relationship suggests a possible direct association between a cerebrovascular parameter (CM) and a cerebrospinal compensatory parameter (elasticity), linking the CBF and CSF pathways. The CM at a baseline pressure could therefore potentially act as an indicator of the status of cerebrospinal compensation, i.e., a low CM at baseline pressure being indicative of a high elasticity or consequently of a disturbed compensatory reserve. In terms of physiological interpretation, even with a low predictive power of CM (possibly attributed to the small number of patients), an impaired cerebrospinal system (high elasticity) is then shown to pose a higher risk for small brain vessels to collapse (low CM) during rising ICP, as it is unable to compensate for pressure or volume changes.

The retrospective analysis of data could act as a limiting factor of this study. However, the data used consisted of clinical material that is part of the authors' accumulated experience in hydrocephalus. Further exploiting the existence of these data could form the base for observational studies of different perspectives of cerebral hemodynamics, as in this study assessing critical closing pressure, thus further enhancing the level of understanding of future infusion tests.

Cerebral blood flow was assessed by cerebral blood flow velocity obtained with TCD through the MCA. The main limitation of the TCD technique is the assumption of a constant, albeit unknown, cross-sectional area of the insonated vessel, which can lead to errors in the accuracy of the CBF approximation. However, in our methodology we are not using FV on its own as an approximation of CBF, but instead we use two parameters derived from FV, the Ca and CVR. The product of these two parameters, used in the CrCP model, represents the cerebral arterial time constant (TAU),

which is known to be independent of the size of the artery, as the cross-sectional area of the vessel is crossed out during the multiplication [10, 16].

In terms of CM, owing to the size of the patient sample used ($N=34$), the results presented in this study cannot be treated as being clinically significant, but instead as observations based on the authors' multiyear experience in hydrocephalus. Further clinical studies are required to establish some further thresholds for CM, apart from zero. To fully understand the inverse relationship between CM and cerebrospinal elasticity, the characterization of CM as "low" at the opening pressure should be quantified. This would allow values of CM to be directly used as an indicator of a disturbed cerebrospinal compensatory reserve.

Conflict of Interest Statement ICM+ Software is licensed by Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus/. MC and PS have a financial interest in a fraction of the licensing fee. The corresponding author and the rest of the co-authors do not have any conflict of interest.

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