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Pathophysiological changes in cerebrovascular distensibility in patients undergoing chronic shunt therapy

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Object. Patients undergoing long-term shunt therapy following shunt malfunction often present with acute neurological deterioration, high intracranial pressure (ICP), and yet small or slit ventricles. It is believed that low brain compliance prevents ventricle enlargement in such cases. To elucidate the underlying pathophysiology, the authors estimated compliance as a function of cerebrovascular distensibility in 45 patients undergoing chronic shunt therapy.

Methods. The ICP and pressure–volume index (PVI) were measured at end-tidal CO_2 of 30 mm Hg (PVI_{30}) and 40 mm Hg (PVI_{40}). The ventricle volume was dichotomized as slit/small/normal or dilated based on the frontooccipital horn ratio. In 18 patients PVI_{30} was normal (18.4 $\pm$ 4 ml), whereas in 27 patients it was significantly elevated (45.5 $\pm$ 14 ml). Clinical symptoms or ventricle size at presentation did not correlate with the PVI_{30}. The ICP and PVI at end-tidal CO_2 of 40 mm Hg were significantly higher than those at end-tidal CO_2 of 30 mm Hg ($p < 0.001$ and < 0.02, respectively) suggesting an increased cerebrovascular distensibility.

Conclusions. The authors did not observe a low compliance in patients undergoing chronic shunt therapy who, at shunt malfunction, presented with a slit/small/normal ventricle; however, analysis of the findings strongly indicated that an increased cerebrovascular distensibility was present in these patients. This may explain the high ICP and acute clinical deterioration following shunt malfunction in such cases.

KEY WORDS • pressure–volume index • brain compliance • cerebrovascular distensibility • slit ventricle syndrome • shunt • pediatric neurosurgery

DESPITE clinical symptoms and high ICP, ventricles in patients undergoing long-term shunt therapy may remain slitlike and fail to dilate at the time of shunt malfunction.[3,9,11,30] This not only presents a diagnostic dilemma often putting patients at a grave risk of misdiagnosis but is also a surgical challenge. The pathophysiology remains unclear. It is believed that persistence of slit ventricles at shunt malfunction is a consequence of restrictive periventricular gliosis[10] and altered brain compliance. It is often assumed in such cases that low brain compliance is present, and treatment modalities such as decompressive craniectomy have been recommended to improve compliance.[11] There is, however, insufficient evidence in the literature to support this notion. In fact, in a study conducted by Shapiro and Fried[32] the authors suggested that normal and not low compliance is present in these patients. Part of the confusion stems from incomplete understanding of the structures that influence brain compliance and factors that alter compliance after placing a shunt. Brain parenchyma is deformable but not compressible and is unlikely to contribute to changes in compliance. Cerebrospinal fluid like all fluids is incompressible and, with a very slow rate of formation and resorption, is unlikely to account for the pressure changes secondary to rapid infusion or removal of fluid from the craniospinal axis when compliance is measured. The authors of theoretical work have suggested that compliance is determined by displaceable intracranial blood volume.[5,37] It is possible that change in cerebrovascular distensibility may play a pivotal role in the abnormal compliance seen in patients undergoing chronic shunt therapy.

In this study, we assessed compliance in patients who had presented with symptoms of shunt malfunction by measuring the PVI (compliance = 0.4343 $\times$ PVI/ICP). Cerebrovascular responsiveness was estimated from the difference in the baseline ICP at end-tidal CO_2 of 30 and 40 mm Hg. The PVI was calculated at the two end-tidal CO_2 levels to assess the contribution of vascular respon-

Abbreviations used in this paper: CSF = cerebrospinal fluid; CT = computerized tomography; FOHR = frontooccipital horn syndrome; GCA = Gravity Compensating Accessory; ICP = intracranial pressure; PVI = pressure–volume index; SD = standard deviation.

siveness to the compliance. These parameters were correlated with the ventricle size and clinical data.

Clinical Material and Methods

Forty-five patients (27 males and 18 females, mean age 11.9 years ± 6.8 years [range 9 months–32 years]) in whom a ventricular shunt had been in place for a mean period of 10.9 years ± 7.3 years (range 7.6 months–31.3 years) were studied at the time of shunt revision. In the majority of patients the initial shunt (ventriculoperitoneal in 32, ventriculoatrial in nine, and cystoperitoneal in four) was inserted for congenital hydrocephalus (17 cases) or posthemorrhagic hydrocephalus of prematurity (12 cases). In all patients a differential pressure valve was used (Medos Programmable Valve in nine [Codman, Raynham, MA], and a low pressure PS Medical Valve in 36 [Medtronic, Goleta, CA]). In 14 patients a GCA (NMT Medical, Inc., Atlanta, GA) was used for siphon protection in addition to the differential pressure valve. In the 36 patients with an acute shunt malfunction, 11 were obtunded at presentation, 13 suffered headache and vomiting and the remaining experienced severe headache. Nine patients with a functioning shunt exhibited symptoms secondary to overdrainage with headache and/or vomiting induced while in the upright posture.

Institutional research board approval and informed consent was obtained for the study. Measurements were obtained while the patients were intubated and after induction of general anesthesia (pentothal or propofol). Anesthesia was maintained with isoflurane at 1 to 2%. Blood pressure and pulse rate were monitored noninvasively.

At the time of shunt revision, the ventricular catheter was changed if occluded and then connected to a pressure transducer to measure the opening pressure. The CSF was drained to normalize the ICP. A baseline ICP tracing was then obtained using a strip recorder at a speed of 6 cm/minute. If an ICP monitor (Codman) was placed, it was directly connected to the strip recorder. A variable amount of fluid (2–10 ml) was injected intraventricularly to raise the baseline ICP by approximately 10 mm Hg for reliably estimating the PVI as described in previous studies.[16] The ICP was recorded before and after fluid manipulation at an end-tidal CO_2 of 25 to 30 mm and at an end-tidal CO_2 of 35 to 40 mm Hg. At least two recordings were made at each end-tidal CO_2. All pressures were referenced to the level of the foramen of Monro.

The following information was extracted from the ICP tracings at both end-tidal CO_2 levels: pre- and postmanipulation diastolic/systolic ICP, amplitude of ICP waveform, and the PVI of Marmarou.[36]

Data collected also included ventricle size as measured on CT scans by using the FOHR,[20] head circumference, and spinal length. The last two factors were used to calculate, using a previously described method, the expected normal PVI for each patient.[35]

Based on the CT scan findings, the patients were categorized into those with slit/small/normal ventricles or dilated ventricles. This was necessary because the definition of dilated ventricles is distinct (FOHR > 0.37),[20] whereas no objective criteria, other than visual impression, are available to define slit from small or small from normal ventricles.

Measurements are presented as the means ± SDs.

Results

The ventricle size was deemed slit/small/normal in 31 of the 36 patients in whom the shunt malfunctioned and in six of the nine in whom overdrainage occurred (FOHR = 0.27 [normal = 0.37]). In the remaining eight the dilated ventricles were at FOHR of 0.41.

At presentation the mean ICP was 26 ± 10.7 mm Hg in patients with shunt malfunction compared with 9.3 ± 2 mm Hg in those with overdrainage ($p < 0.001$). In all patients, the mean ICP after ventricular decompression prior to estimation of PVI was 7.6 ± 4 mm Hg at end-tidal CO_2 of 30 mm Hg (PVI_{30}). It was significantly higher (15 ± 6 mm Hg; $p < 0.000$) at end-tidal CO_2 to 40 mm Hg (PVI_{40}) (Table 1).

The mean PVI_{30} was 36.3 ± 20 ml for all patients. In 18 patients, it was normal (18.4 ± 4 ml)—that is, within a 95% confidence limit of the expected PVI for age. In the remaining 27 patients, the mean PVI_{30} (45.5 ± 14 ml) exceeded the expected normal PVI (Fig. 1). Using the Pearson chi-square test, the PVI_{30} was shown not to correlate with the clinical presentation ($p = 0.41$), ventricle size (based on the FOHR) ($p = 0.41$), diagnosis ($p = 0.43$),

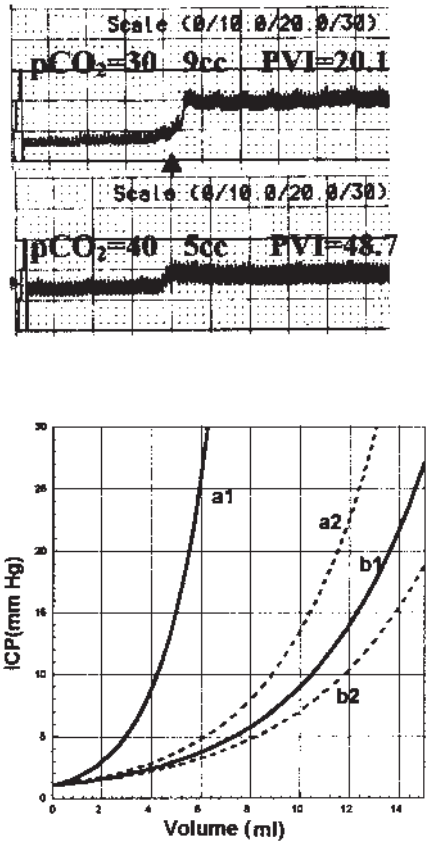

FIG. 1. *Upper:* The PVI at PCO_2 of 30 mm Hg (PVI_{30}) with 9-ml infusion is 20.1 ml. *Center:* The PVI in the same patient at PCO_2 of 40 mm Hg (PVI_{40}) with 5 ml infusion is 48.7 ml. *Lower:* Compliance represented by Curve a1 in 18 patients with a mean PVI_{30} of 18.4 ml increased at higher PCO_2, corresponding to a PVI_{40} of 38.4 ml (Curve a2). Compliance represented by Curve b1 in 15 patients with a mean PVI_{30} of 44 ml, increased at higher PCO_2, corresponding to a PVI_{40} of 60 ml (Curve b2).

TABLE 1

*Summary of pathophysiological changes in patients undergoing long-term shunt therapy**

Variable (no. of cases)	End-Tidal CO_2		p Value
	30 mm Hg	40 mm Hg	
ICP in mm Hg (45)	7.6 ± 4	15 ± 6	<0.000
PVI in ml (45)	36.3 ± 20	44.2 ± 19	<0.020
normal (18)	18.4 ± 4	38 ± 17	<0.000
high (27)†			
15 cases	44 ± 15	60 ± 16	<0.000
12 cases	52.2 ± 20	38.5 ± 13	<0.002

* Values are presented as the means ± SD.

† The breakdown of cases involving a high PVI refers to those with higher PVI values at 40–mm Hg end-tidal CO_2 and those with higher PVI values at 30–mm Hg end-tidal CO_2.

duration of shunt therapy (p = 0.24), age at which the first shunt was placed (p = 0.3), number of ventricular catheters (p = 0.42), type of valve (differential pressure or GCA) (p = 0.67), or number of revisions (p = 0.3).

The mean PVI_{40} (44.2 ± 19 ml) was significantly higher ($p < 0.02$) than PVI_{30}. In all 18 patients in whom PVI_{30} was normal the PVI_{40} was higher (18.4 ± 4 ml to 38 ± 17 ml; $p < 0.000$); in 15 of the 27 patients with high PVI_{30}, the PVI_{40} was even higher (44 ± 15 ml compared with 60 ± 16 ml, respectively; $p < 0.000$) whereas in the remaining 12 patients with high PVI_{30}, the PVI_{40} was lower (52.2 ± 20 ml compared with 38.5 ±13 ml, respectively; $p < 0.002$) (Table 1).

Results of chi-square analysis showed no significant differences in the clinical presentation (shunt malfunction compared with overdrainage [p = 0.19]), clinical symptoms (p = 0.21), ventricle size (p = 0.27), PVI_{30} (p = 0.42), or change in PVI with endtidal CO_2 (p = 0.36) between patients receiving the GCA and those with the differential pressure valve only.

Chi-square test analysis demonstrated that the PVI_{30} and PVI_{40} were not significantly different in the nine patients with a functioning shunt and overdrainage compared with those in whom the shunt malfunctioned (p = 0.43 and p = 0.42, respectively).

Based on results of chi-square analysis, the origin of hydrocephalus was not a significant factor influencing the PVI_{30} (p = 0.3) or changes in PVI with end-tidal CO_2 (p = 0.3), clinical symptoms (p = 0.5), or the ventricle size at the time of presentation (p = 0.7).

The variability in the PVI determinations, expressed as a variation (SD/mean PVI), was 9.7 ± 9%. There was no significant difference in the multiple estimations of the PVI.

Discussion

Brain Compliance and End-Tidal CO_2

Brain compliance is fundamentally a result of expulsion of blood from veins as volume is added to the craniospinal axis (Fig. 2 *upper*).[5,23,33,37] It can be shown that PVI, as a measure of brain compliance, is a function of venous distensibility (that is, stiffness) and venous volume (Appendices 1 and 2). Stiffer veins (lower distensibility) resist compression and result in a low compliance. Studying features in the isolated dog vein, Moreno, et al.,[26] showed that the relationship of venous distensibility to the transmural pressure is represented by a bell-shaped curve (Fig. 2 *lower*). Therefore, in an optimally distended vein (see a in Fig. 3 *upper right*), an increase in transmural pressure due to an increase in end-tidal CO_2 would be expected to result in reduced distensibility and compliance. Such a reduction in brain compliance secondary to hypercarbia is commonly observed in most neurosurgical scenarios and has been confirmed in animal experiments.[7,22] A decrease in transmural pressure due to brain edema or an intracranial mass lesion, likewise, also reduces distensibility and worsens brain compliance.

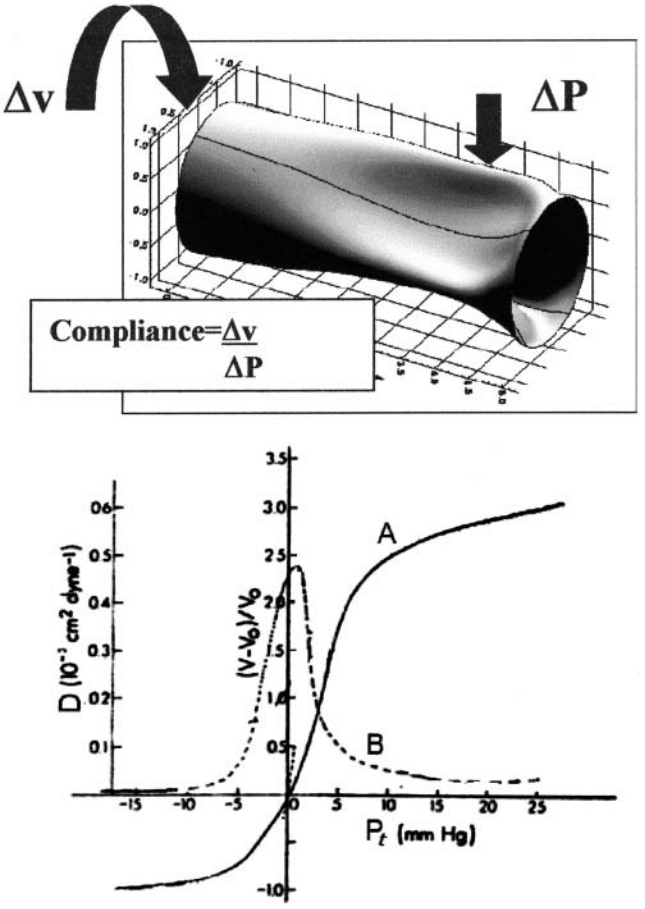

FIG. 2. *Upper:* Schematic drawing showing that addition of fluid *(ΔV)* generates a pressure increase *(Δp)* that drives the blood out of the veins. *Lower:* Curve A: Venous volume change (V − Vo/Vo) to transmural pressure (P_t). Curve B: Distensibility (D) to transmural pressure (P_t) in an isolated dog vein. Adapted from Moreno, et al.

In cases involving chronic shunt therapy in patients who presented with acute deterioration without ventricular enlargement, however, we observed an increase in the PVI with higher end-tidal CO_2 in 18 patients with a normal baseline PVI_{30} and in 15 of the 27 with a high baseline PVI_{30}. The ability of the PVI to increase with an increase in transmural pressure due to high end-tidal CO_2 suggests that these patients experience a high baseline venous distensibility. They are probably best represented on the up-

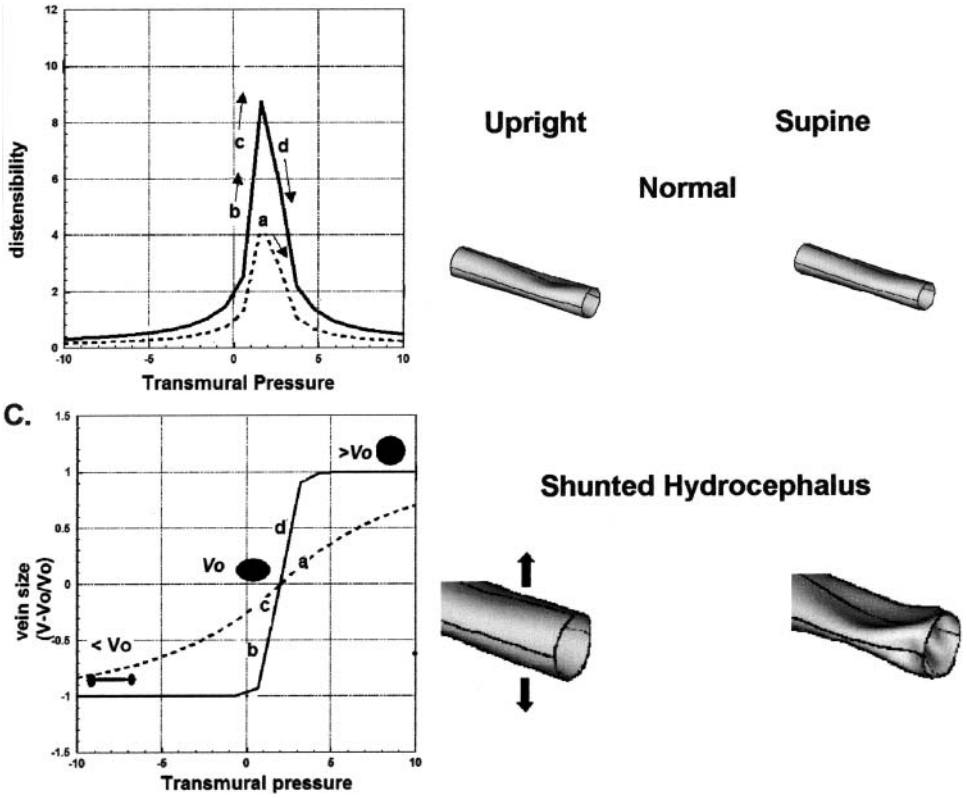

FIG. 3. *Upper Left:* Computer-simulated distensibility curves for 0.2-mm *(dashed curve)* and 0.9-mm *(solid curve)* venous diameter. Points a, b, c, and d, represent the status of normal (a) and shunt-treated (b, c, and d) patients on the distensibility and venous size curves as explained in the text. The *arrows* show the direction of change in the distensibility with increase in transmural pressure. *Lower Left:* Vein size to transmural pressure curves for venous diameter of 0.2 mm *(dashed curve)* and 0.9 mm *(solid curve)*. Note the sharp decrease in lumen volume for a larger vein (solid curve) at transmural pressures between 1 and 4 mm Hg compared with a gradual change for a smaller vein *(dashed curve)*. *Right:* Status of the veins in supine and upright positions; normally, veins are partially collapsed in an upright position due to the Starling resistor relationship of CSF pressure to venous pressure, whereas this is reversed in shunt-treated patients because of the negative pressure caused by CSF siphoning in upright position.

sloping side of the distensibility curve (b and c in Fig. 3 *upper right*). The 12 patients with high PVI_{30}, in whom the PVI decreased with higher endtidal CO_2, exhibited a normal physiological response to increased transmural pressure; however, a high baseline PVI_{30} suggests that even these patients have higher venous distensibility than normal.

Altered Physiology in Shunt-Treated Patients

Certain aspects of altered physiology in shunt-treated patients may contribute to the increases in venous distensibility and PVI. First, there is a loss of the physiological venous-to-CSF pressure gradient due to the presence of the shunt. Overdrainage of CSF and chronically upright position–induced low ICPs cause an increase in the outward transmural pressure gradient across the veins. The result is an increase in venous size over time. This is supported by experimental,[12,18,27] clinical,[21] and radiological[24,25] observations in patients undergoing chronic shunt therapy. In turn, larger veins have a higher distensibility. Furthermore, the loss of physiological Starling resistor relationship between the venous pressure and CSF pressure results in a venous overdrainage in the upright position.[2] A compensatory increase in venous capacitance and blood flow from arteriolar dilation[28] has been demonstrated in upright position on single-photon emission CT scans obtained in shunt-treated patients,[17] further supporting these conclusions. Second, in shunt-treated patients, we believe that the supine position results in a decrease in outward transmural pressure across the veins because of an absence of the negative pressure of siphoning, which is active in the upright position. This causes a partial collapse of veins in the supine position (Fig. 3 *left*) due to a lowered transmural pressure and accounts for the representation of some of these patients on the upsloping side of the distensibility–transmural pressure curve (Fig. 3 *upper right*).

Ventricle Size in Shunt Malfunction

The increase in venous distensibility may also explain the failure of ventricles to enlarge despite high ICP and a normal or high PVI in 31 of the 36 patients who presented with acute deterioration following shunt malfunction. Unlike normal veins (*dashed curve* in Fig. 3 *lower right*),

larger veins have an increased distensibility (*solid curve* in Fig. 3 *upper right*) and collapse more readily.[26] A minimal decrease in transmural pressure secondary to a small increase in CSF pressure after shunt malfunction can cause a rapid reduction in the venous diameter and consequent venous congestion. This could lead to a rapid increase in ICP and acute deterioration. The rapid onset of venous compromise, which is a function of the relationship between the vein size and the transmural pressure, may or may not allow enough time for the loss of periventricular interstitial fluid and resultant ventricular enlargement prior to acute deterioration. Evaluation of our findings suggests that low brain compliance is not a prerequisite for slit ventricular shunt malfunction and that ventricles may fail to dilate despite a normal or a high PVI. This is in accordance with our data and previous observations suggesting a conflicting relationship between ventricle size and brain compliance.[6,19,34,38]

There are alternative explanations given for failure of a ventricle to dilate after shunt malfunction.[3,10,11,30] In 1979 Engel, et al.,[10] proposed the existence of restrictive subependymal gliosis. Although subependymal gliosis occurs in experimental shunt-treated hydrocephalus,[4,39] there is no direct evidence that it can restrict ventricular dilation in humans.[9] In fact in an autopsy report, Del Bigio[8] suggested the that degree of subependymal gliosis is no different in patients with dilated ventricles and those with nonenlarged ventricles after shunt malfunction. The dilation of ventricles in some patients in whom there is slit ventricle shunt malfunction after failure of recently revised shunt further suggests that subependymal gliosis may not be responsible for restricting enlargement of the ventricles.[3,11] Rekate[29] has suggested that in some cases an increased brain turgor secondary to anomalous venous drainage may prevent ventricular enlargement. This may explain why ventricles do not enlarge following post–suture closure shunt malfunction in patients in whom shunts were placed in infancy for hydrocephalus secondary to anomalous venous drainage or high sinus venous pressure;[29–31] however, this does not apply to a majority of patients with normal venous outflow.

The PVI values we recorded in patients with acute shunt failure were higher than the expected PVI for age. This finding is in contrast to those reported by others[13,32] who described a normal PVI in cases involving acute deterioration; however, the mean ICP in our patients with obstructed shunts was twofold as high as that reported by Shapiro and Fried (26.3 $\pm$ 10 and 10.6 $\pm$ 6 mm Hg, respectively). We can only postulate that this higher pressure may have contributed to enhanced buffering capacity in our series. Although counterintuitive, a higher ICP has been observed in experimental and clinical hydrocephalus to correlate with a higher PVI.[16]

There were no clinically different manifestations in the 14 patients with GCA for siphon protection than in those with a differential pressure valve only. Furthermore, there was no difference in the ventricle size at presentation or PVI in either of these two subgroups. This suggests that patients with the GCA suffered from overdrainage and its consequences much like those with only differntial pressure valves. The failure of GCA in providing siphon protection in these patients is in accordance with the bench tests that showed that GCAs intermittently fail during body movements, at which time the ballistic movement of thier metallic balls results in loss of siphon protection.[1]

The cause of hydrocephalus was not a factor influencing clinical presentation, ventricle size, PVI, or changes in PVI with end-tidal CO_2 on chi-square analysis. This result justifies our grouping of patients with a diverse disease origin and suggests that the pathophysiological alterations induced by chronic shunt therapy are probably universal and unrelated to the origin. It further supports the notion that these changes may not be related to the changes in the brain parenchyma per se but rather to extraparenchymal vascular factors as suggested by our findings. The PVI trends were similar in patients with shunt malfunction compared with those with overdrainage at presentation, suggesting that malfunction in itself did not alter the pathophysiology or affect the our data.

Conclusions

Contrary to expectations, brain compliance was normal or high in patients in whom the ventricles had remained slitlike and failed to dilate when the shunt malfunctioned. These patients exhibit an increased cerebrovascular distensibility caused by venous distension due to chronic low ICP when CSF overdrains through the shunt. The failure of ventricles to dilate and an attendant acute clinical presentation could result from venous compromise due to increased cerebrovascular distensibility causing an early collapse of veins when a small change in transmural pressure gradient occurs after shunt malfunction.

Appendix 1

Starling resistor refers to physiological coupling of two fluid systems, wherein one influences the other in such a fashion that the flow through the other remains constant. The bridging vein–CSF pressure coupling is one such relationship.[14] Despite a drop in the sagittal sinus pressure in an upright position, the flow through the bridging veins remains the constant. In their laboratory observations of Starling resistor, Chopp, et al.,[5] found the resistance to flow (R*f*) after addition of volume (Δv) is an exponential function of the initial resistance (R*i*):

$$Rf = Ri \cdot e^{k\Delta v} \qquad \text{(i)}$$

If flow though the veins were to remain constant, multiplying both sides with flow (*f*) yields the following:

$$f \times Rf = f \times Ri \cdot e^{k\Delta v}$$

Because flow multiplied by resistance is equal to the pressure, the change in the pressure following addition of fluid to the system related as follows:

$$Pf = Pi \cdot e^{k\Delta v} \qquad \text{(ii)}$$

Rearranging in log to base 10, the following is seen:

$$\frac{1}{k \cdot \log e} = \frac{\Delta v}{log\ \frac{Pf}{Pi}} = PVI \qquad \text{(iii)}$$

This provides the physical basis for the Marmarou equation of PVI.

The relationship of compliance ($\Delta v/\Delta p$) to PVI is obtained by differentiating equation (ii)

$$\frac{\Delta p}{p} = k\Delta n$$

and rearranging the following:

$$\text{compliance} = \frac{\Delta v}{\Delta p} = \frac{1}{k \bullet p} = \frac{\log e \bullet PVI}{p} = \frac{0.4343 \bullet PVI}{p} \quad \text{(iv)}$$

Appendix 2

Veins are distensible structures. Distensibility (D) of a vein of an area of cross-section (A), length (l), and volume (Vo) is related to the transmural pressure (Δp_t):[15]

$$D = \frac{1}{A}\frac{\Delta A}{\Delta p_t} = \frac{1}{A \bullet l}\frac{\Delta A \bullet l}{\Delta p_t} = \frac{1}{Vo}\frac{\Delta v}{\Delta p_t} \quad \text{(v)}$$

In a closed system such as the craniospinal axis, the Kellie–Monro hypothesis suggests that rapid addition of fluid (Δv) is associated with displacement of blood from the venous system. Furthermore, this addition of fluid generates a transmural pressure (Δp_t) that drives the blood out of the veins (Fig. 2 *upper*). The actual rise in the craniospinal axis pressure is proportional to this transmural pressure. Hence,

$$\Delta p = ki \bullet \Delta p_t \quad \text{(vi)}$$

$\Delta v/\Delta p$ is the compliance of the craniospinal axis, hence from equation (iv), (v), and (vi):

$$D = \frac{1}{Vo \bullet ki}\frac{0.4343 \bullet PVI}{P}$$

and rearranging

$$PVI = 2.303 \bullet ki \bullet D \times Vo \times P \quad \text{(vi)}$$

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