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Age dependence of cerebrospinal pressure–volume compensation in patients with hydrocephalus

MAREK CZOSNYKA, PH.D., D.SC., ZOFIA H. CZOSNYKA, M.SC., PETER C. WHITFIELD, PH.D., F.R.C.S., TIM DONOVAN, B.SC., AND JOHN D. PICKARD, M.CHIR., F.MED.SCI.

Academic Neurosurgical Unit and Wolfson Brain Imaging Centre, Addenbrooke's Hospital, Cambridge, United Kingdom

Object. The dynamics of both drainage and storage capacity become altered during the sequential pathological processes that lead to hydrocephalus. Cerebrospinal fluid (CSF) formation and drainage rate have been reported to be age dependent. The aim of this study was to investigate whether CSF compensatory parameters are dependent on age in patients who have symptoms of hydrocephalus and apparently normal intracranial pressure (ICP).

Methods. Forty-six patients who presented with ventriculomegaly, the clinical symptoms of hydrocephalus, and normal ICPs underwent a computerized CSF infusion test. Parameters used to describe CSF compensation were calculated and correlated with the age of each patient.

The mean ICPs were found to be independent of the age of the patient. Resistance to CSF outflow (Rcsf), however, demonstrated a nonlinear increase with advancing age ($r = -0.57$; $p < 0.0001$) and was associated with a decrease in the CSF production rate, which also occurred with increasing age ($r = 0.49$; $p < 0.002$). Both the pulse amplitude of the ICP waveform and the slope of the amplitude–ICP regression line increased significantly with advancing age ($r = 0.39$; $p < 0.01$ and $r = 0.43$, $p < 0.004$, respectively). The nonlinear increase in the elastance coefficient indicated increasing brain stiffness, which acompanies older ages ($r = -0.31$; $p < 0.04$).

Conclusions. In a study of patients with symptoms of hydrocephalus, but normal ICPs, the increase in Rcsf and decrease in CSF production were most pronounced in patients who were older than 56 years of age. This relationship was more significant than previously suggested.

KEY WORDS • cerebrospinal fluid • pressure–volume relationship • normal-pressure hydrocephalus • age

CEREBROSPINAL fluid, which is formed by active secretion by the choroid plexus, circulates along the craniospinal pathways to be absorbed predominantly via arachnoid granulations into the superior sagittal sinus. The rate of absorption is proportional to the pressure gradient between pressure in the subarachnoid CSF space and venous pressure in the sagittal sinus.[10] Resistance to CSF outflow plays a crucial role in the regulation of CSF flow and pressure. Age-related changes in the formation and absorption of CSF have been previously studied. Although the formation rate of CSF can be measured in humans with limited accuracy,[7,10,16] it has been reported to decrease in healthy persons as they grow older,[16] such that the volume exchange of CSF takes twice as long in the elderly population. It has recently been hypothesized that this leads to accumulation of noxious substances in the CSF, which in turn may contribute to brain atrophy.[19] Indeed, early treatment of Alzheimer disease by implantation of a flow-regulating valve to stimulate increase in CSF production has been postulated.

Abbreviations used in this paper: CSF = cerebrospinal fluid; ICP = intracranial pressure; Rcsf = resistance to CSF outflow.

Measurement of the Rcsf is less problematic, with well-established studies of constant rate infusion, perfusion, or constant-pressure infusion available in the literature.[4,6,9,11] Although almost all authors of clinical studies have emphasized that increased Rcsf is the most powerful predictor of improvement following shunt placement in hydrocephalus, there is no agreement regarding the value above which the Rcsf can be interpreted as increased. Normal values of Rcsf has been variously reported to be 5 to 10 mm Hg/ml/min,[2,11] with the upper limit applicable to the treatment of hydrocephalus being 13 mm Hg/ml/min,[6] or, most recently, 18 mm Hg/ml/min in the well-documented multicenter Dutch trial.[5] The difference between these critical values may be due to technical factors or differences in patient populations such as the average age of patients in these studies. Recently, Rcsf has been reported to increase with age in a group of patients without hydrocephalus, raising caution over interpretation of individual patient results.[1]

There are no data available concerning other age-related properties of CSF compensation. In our hospital we routinely perform computerized infusion studies[9] in patients presenting with symptoms of hydrocephalus. We se-

TABLE 1
*Measurements of CSF compensatory parameters**

Parameter	Mean ± SD	Min	Max
age of patients	58 ± 18	17	86
baseline ICP (mm Hg)	7.9 ± 4	−1	14
Rcsf (mm Hg/ml/min)	18 ± 4	12	29
estimated CSF formation rate (ml/min)	0.34 ± 0.22	0.05	1
elastance coefficient (1/ml)	0.26 ± 0.14	0.01	0.61
pulse amplitude of ICP (mm Hg)	1.93 ± 1.55	0.05	7.7
slope of amplitude–pressure regression line	0.26 ± 0.14	0	0.6

* Max = maximum; Min = minimum.

lected a subgroup of patients in whom a clinical diagnosis of hydrocephalus of various causes had been made who had no symptoms of raised ICP, and we studied the relationships between patient age and craniospinal compensatory parameters.

Materials and Methods

Forty-six patients (25 men and 21 women) ranging in age from 17 to 86 years (mean age 59 years) with clinical symptoms of hydrocephalus (gait disturbance, urinary incontinence, or memory impairment of various degrees) underwent a computerized CSF infusion study. This test is part of the clinically accepted diagnostic procedure in our hospital and, as such, does not require separate approval from the local ethics committee. There were 25 cases of idiopathic hydrocephalus; 13 patients with hydrocephalus related to subarachnoid hemorrhage; six patients with congenital hydrocephalus who had been treated with shunt placement during infancy and in whom the shunts had never been revised; and two patients with posttraumatic hydrocephalus. Five patients had previously undergone ventriculoperitoneal shunt placement but, at the time of the study, all five had nonfunctioning shunts. Computerized tomography or magnetic resonance imaging of the brain was performed close to the time (< 1 month) of assessment of CSF dynamics. All patients had ventricular dilation (the mean bicaudate index was 0.26 ± 0.11 and the mean diameter of the third ventricle was 13 ± 0.6 mm, means ± standard deviations) and/or a degree of brain atrophy, assessed by two independent investigators to be widening of the cortical sulci (J.D.P. and T.D.). None of the patients presented with symptoms of raised ICP.

The infusion study was performed via either the lumbar CSF space or a preimplanted ventricular access device. In both cases two needles were inserted (22-gauge spinal needles for lumbar tests and 25-gauge butterfly needles for ventricular studies). One needle was connected to a pressure transducer via a stiff saline-filled tube and the other to an infusion pump mounted on a trolly built for this purpose, which contained a pressure amplifier (Simonsen & Will, Sidcup, United Kingdom) and an International Business Machines–compatible personal computer that was run by software written in-house.[8] After 10 minutes of baseline measurement an infusion of normal saline at a rate of 1.5 ml/minute, or 1 ml/minute if the baseline pressure was higher than 15 mm Hg, was started and continued until a steady-state ICP plateau was achieved. If the ICP increased to 40 mm Hg, the infusion was stopped. Following cessation of the saline infusion, ICP was recorded until it decreased to steady baseline levels. All compensatory parameters were calculated using computer-supported methods that were based on physiological models of CSF circulation.[4,9,11,15] Baseline ICP and Rcsf can be used to characterize the static conditions of CSF circulation, whereas the cerebrospinal elastance coefficient, and the pulse amplitude of the ICP waveform express dynamic components of CSF pressure volume compensation.

The elastance coefficient is used to describe the compliance of the CSF compartment according to the following formula: compliance of CSF space = $1/[E1 \times (ICP - p_0)]$, where E1 is the elastance coefficient and p_0 is the unknown reference pressure level that represents the hydrostatic difference between the site of ICP measurement and the point of the cerebrospinal axis that is indifferent to pressure.[4,18] Cerebrospinal compliance is inversely proportional to ICP; therefore, a comparison between different patients can be made only at the same level of the difference: $ICP - p_0$. The elastance coefficient is independent of ICP and, thus, this coefficient is a much more convenient parameter to use when comparing individual patients. An elastance coefficient with a low value is specific for a compliant system, whereas an elastance coefficient with a high value indicates a decreased pressure–volume compensatory reserve.

The pulse amplitude of ICP increases proportionally when the mean ICP rises.[4] The proportionality ratio (amplitude/pressure [the AMP/P] index) is used to characterize both the elastance of the CSF space and the transmission of arterial pulsations to the CSF compartment.

Finally, the production of CSF can be estimated using Davson's equation:[10] $ICP = Rcsf \times CSF_{formation} + P_{ss}$, where P_{ss} is a pressure in the superior sagittal sinus. However, the sagittal sinus pressure is unknown and cannot be easily measured without increasing the invasiveness of the whole procedure. Consequently, the P_{ss} and CSF formation are estimated jointly by accessing a nonlinear model that uses the least-square distance method during the computerized infusion test.[10] It is important to mention that such an "estimate" of the CSF production rate approximates CSF absorption, rather than the actual production rate. It is based on the assumption that all circulating CSF is reabsorbed via arachnoid granulations. In cases in which significant CSF leakage into brain parenchyma occurs, CSF production may be grossly underestimated.

Statistical Analysis

Compensatory parameters were tested against patient age by using regression analysis with the threshold for significance being a probability value less than 0.05

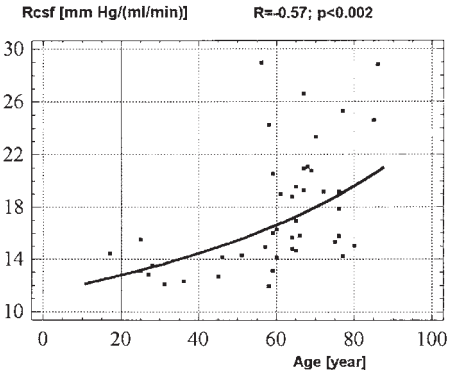

FIG. 1. Graph demonstrating the relationship between Rcsf and age in patients presenting with symptoms of hydrocephalus. The best-fit model is inverse: $y = 1/(a - bx)$.

Results

Measurement of the compensatory parameters of interest are presented in Table 1. There were no significant differences between compensatory parameters among patients suffering from hydrocephalus resulting from different causes.

Patient Age and Rcsf

The result of a regression analysis in which Rcsf and patient age were compared was best described by a reciprocal model ($r = -0.57$; $r^2 = 0.32$ [$p < 0.002$]; Fig. 1). This model indicates that the age dependence of Rcsf be-

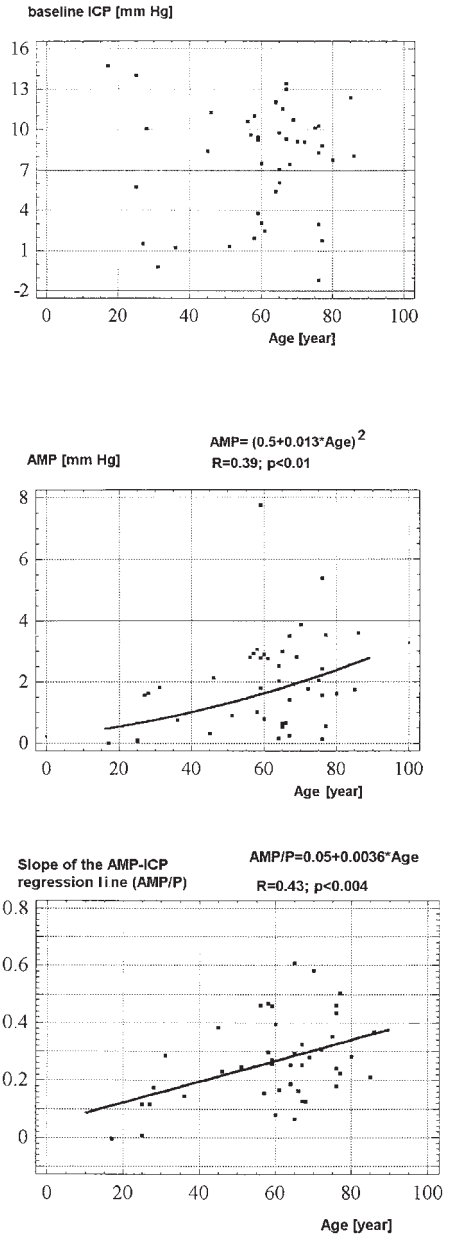

FIG. 2. Graphs depicting the relationship between ICP and patient age. In patients presenting with symptoms of hydrocephalus, baseline ICP does not depend on age *(upper)*. In the same group of patients the pulse amplitude of ICP (AMP; *center*) and the slope of the amplitude–pressure (AMP-ICP) regression line *(lower)* are significantly related to age.

comes more pronounced above a certain age, which, according to our data, is approximately 55 to 57 years.

Patient Age and ICP

The results of a regression analysis in which baseline ICP and patient age were compared indicated no significant relationship (Fig. 2 *upper*); ICP was uniformly distributed among the patients and the configuration of distribution was independent of age. The pulse amplitude of the ICP waveform was significantly age dependent, increasing nonlinearly with advancing age ($r = 0.39$; $p < 0.01$; Fig. 2 *center*). Similarly, the slope of the amplitude–pressure regression line demonstrated a linear increase correlated with advancing age ($r = 0.43$; $p < 0.004$; Fig. 2 *lower*).

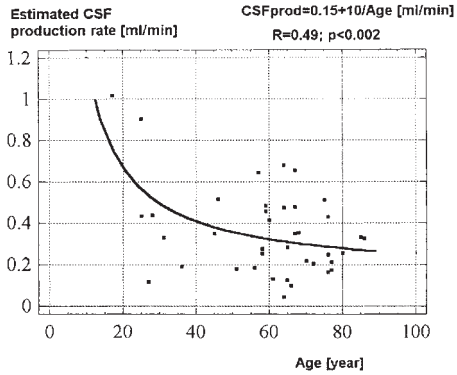

FIG. 3. Graph showing the relationship between CSF production and patient age. In hydrocephalic patients, the estimated CSF production rate is inversely proportional to age.

Patient Age and Estimated Production of CSF

According to Davson's formula, a greater Rcsf in the presence of a normal baseline ICP is associated with a reduction in the rate of CSF production, provided that the sagittal sinus pressure is normal. In our patients the estimate of CSF production demonstrated a significant reduction with increasing age ($r = 0.49$, $p < 0.002$; reciprocal model: Fig. 3).

Patient Age and Elasticity

Parameters used to describe the pressure–volume compensatory reserve also demonstrated significant age dependency. The elastance coefficient increased with patient age in a nonlinear fashion ($r = -0.31$, $p < 0.04$, reciprocal Y model; Fig. 4).

Discussion

Cerebrospinal fluid compensatory parameters are clearly dependent on the specific pathological processes affecting each patient.[4,6,11,15] Any relationship between compensatory parameters and patient age is of a secondary nature. In the absence of information on healthy volunteers, the effect of age on CSF dynamics needs to be studied in a patient population that presents with a homogeneous CSF compensatory reserve. We selected patients with clinical and neuroimaging presentations that were consistent with a diagnosis of hydrocephalus with a normal mean ICP and an Rcsf that exceeded 12 mm Hg/ml/min.

Resistance to CSF Outflow

The relationship between patient age and increasing Rcsf has previously been reported by Albeck, et al.[1] We confirmed this relationship but the rate of age-related increase in Rcsf was also much higher: 0.19 mm Hg/ml/min per year (for patients aged ≥ 56 years) in our study com-

pared with 0.075 mm Hg/ml/min per year in the study of Albeck, et al. Although those researchers studied patients with no known CSF disorders, many of their patients had a resistance to CSF outflow in excess of 15 mm Hg/ml/min, which certainly exceeds the the normal level.[2,6]

Age dependence of CSF compensation in humans has not been recognized by all authors. Ekstedt[11] anticipated that age-dependent changes in the connective tissue of arachnoid villi should affect CSF outflow, but he failed to demonstrate it.

Production of CSF

Our finding that Rcsf increases nonlinearly with age, without a change in baseline ICP, leads to the conclusion that the CSF production rate must decrease, provided sagittal sinus pressure stays constant.[11] Although our method of estimating CSF formation is not precise,[8] its relationship to age has proved to be significant.

This agrees with the study of May and colleagues,[16] who reported a decrease in the CSF formation rate by 50% in elderly persons (mean age 77 years) in comparison with that in young healthy people (mean age 28 years). In contrast, authors of other studies[11,12] have not reported any evidence of age-related decreases in CSF production. Calcification and/or other degenerative changes of the choroid plexus may be responsible for the decrease in CSF production. On the other hand, the lack of a significant decrease in CSF production following plexectomy[17] demonstrates that extrachoroidal sources of CSF formation may easily compensate for a decrease in choroidal CSF secretion. An interesting hypothesis based on the results of experimental studies has been drawn by James and associates,[13] who state that when Rcsf increases acutely, the decrease in CSF production rate may be regarded as a compensatory mechanism. Application of this hypothesis to aging infers that an age-related decrease in CSF production may prevent a rise in baseline ICP when Rcsf increases. If this is true, the hypothesis of Rubenstein[19] that Alzheimer disease–related dementia may be exacerbated by low rates of CSF exchange, resulting in the accumulation of toxins that damage nerve cells,[3] may carry credence.

However, one should keep in mind that the estimate of CSF production we used approximates CSF absorption rather than the CSF production rate. A portion of CSF can leak into brain parenchyma,[10] resulting in an underestimation of the rate of CSF production. Hence, the relationship (Fig. 2 *center*) between estimated CSF production and age may signify increased CSF parenchymal drainage of CSF, rather than a decrease in the CSF production rate, although the mechanism of parenchymal CSF absorption remains unknown.

Brain Compliance and Pulse Amplitude of ICP

Tans and Poortvliet[20] studied the relationship between Rcsf and the pressure–volume units (in milliliter units), an inverse of the elastance coefficient in adults with hydrocephalus. They did not observe any association between pressure–volume index and patient age; however, they reported that the index was inversely correlated with Rcsf. In our patients the correlation between the elastance coefficient and Rcsf was not significant. Instead, both increased with age. This indicates that the brain becomes stiffer with age, which, in turn diminishes the cerebrospinal volume–compensatory reserve.

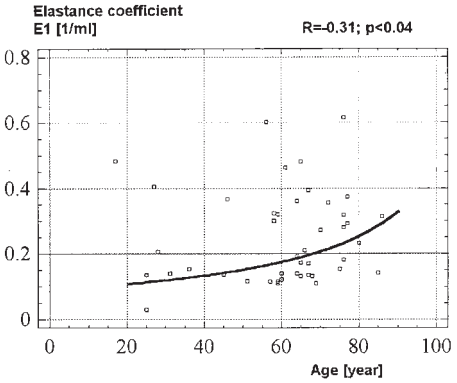

FIG. 4. Graph demonstrating the realtionship between the elastance coefficient of the brain and patient age. The elastance coefficient (E1) increases with age in a nonlinear fashion in hydrocephalic patients. The best-fit model is inversely proportional: $y = 1/(a - bx)$.

The ICP pulse amplitude and the slope of the amplitude/pressure regression line both significantly increase with age. These variables are dependent on the amplitude of the arterial pulse waveform and its transmission through compliant arterial walls to the CSF space. With increasing age, blood pressure tends to rise and arterial pulsatility increases. Little is known about cerebral arterial compliance. Extrapolating data concerning peripheral circulation, we can assume that vessels become stiffer, reducing their compliance. On the other hand, evidence that arterial compliance increases with age as cerebral vessels become more dilated can be found in studies in which transcranial Doppler ultrasonography has been used.[14]

Conclusions

This study provides evidence to support the hypothesis that CSF circulation and pressure–volume compensation are age dependent in patients who present with hydrocephalus without intracranial hypertension. Studies should be initiated to investigate whether the threshold for normal and abnormal CSF compensatory reserve should be age adjusted in patients older than 55 years.

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Dr. Czosnyka is on leave from the Institute of Electronic Systems, Warsaw University of Technology, Poland.

Address reprint requests to: Marek Czosnyka, Ph.D., D.Sc., Academic Neurosurgery, Box 167, Addenbrooke's Hospital, Cambridge CB2 2QQ, United Kingdom. email: MC141@MEDSCHL.CAM.AC.UK.