Assessment of Craniospinal Pressure-Volume Indices

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BACKGROUND AND PURPOSE: The PVI_{CC} of the craniospinal compartment defines the shape of the pressure-volume curve and determines the damping of cyclic arterial pulsations. Despite no reports of direct measurements of the PVI_{CC} among healthy elderly, it is believed that a change away from adequate accommodation of cardiac-related pulsations may be a pathophysiological mechanism seen in neurodegenerative disorders such as Alzheimer disease and idiopathic normal pressure hydrocephalus. In this study, blood and CSF flow measurements are combined with lumbar CSF infusion measurements to assess the craniospinal PVI_{CC} and its distribution of cranial and spinal compartments in healthy elderly.

MATERIALS AND METHODS: Thirty-seven healthy elderly were included (60–82 years of age). The cyclic arterial volume change and the resulting shift of CSF to the spinal compartment were quantified by PC-MR imaging. In addition, each subject underwent a lumbar CSF infusion test in which the magnitude of cardiac-related pulsations in intracranial pressure was quantified. Finally, the PVI was calculated by using a mathematic model.

RESULTS: After excluding 2 extreme values, the craniospinal PVI_{CC} was calculated to a mean of 9.8 ± 2.7 ml and the estimated average 95% confidence interval of individual measurements was ± 9%. The average intracranial and spinal contributions to the overall compliance were 65% and 35% respectively ($n = 35$).

CONCLUSIONS: Combining lumbar CSF infusion and PC-MR imaging proved feasible and robust for assessment of the craniospinal PVI_{CC}. This study produced normative values and showed that the major compensatory contribution was located intracranially.

ABBREVIATIONS: ECG = electrocardiogram; ΔICP = intracranial pulse pressure magnitude; ΔPVI_{CC} = relative width of the 95% confidence interval of the calculated PVI_{CC}; ΔRPPC = width of the 95% confidence interval of the calculated RPPC; ΔV_{ART} = arterial volume change; ΔV_{bolus} = volume infused in a lumbar CSF bolus infusion test; ΔV_{IC} = volume accommodated by the intracranial compartment; ΔV_{SC} = volume displaced to the spinal compartment; ΔICP = intracranial pressure; ICP_{end} = ICP after lumbar CSF bolus infusion test; ICP_{start} = ICP before lumbar CSF bolus infusion test; P_{1} and P_{0} = pressure constants; PC-MR imaging = phase contrast MR imaging; PVI = pressure-volume index; PVI_{bolus} = PVI of the craniospinal cavity estimated from a lumbar CSF bolus infusion test; PVI_{CC} = PVI of the craniospinal cavity; PVI_{IC} = PVI of the intracranial compartment; PVI_{SC} = PVI of the spinal compartment; RPPC = relative pulse-pressure coefficient.

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and have not been applied to human subjects. In general, lumbar CSF infusion tests cannot provide information on how the compliance is distributed within the craniospinal cavity. By measuring flow of blood and CSF using flow-sensitive PC-MR imaging, it is possible to quantify both the pulsating blood flow to the brain and the resulting CSF volume shift to the spinal compartment that occurs naturally within every cardiac cycle.9 PC-MR imaging alone has been used to derive parameters related to compliance, but without a direct measurement of ICP, the PVICC cannot be explicitly calculated (equation 1).9,10 In this study, we propose and evaluate a combination of lumbar CSF infusion tests and PC-MR imaging flow measurements to assess PVICC and its distribution between the intracranial and spinal compartments. We use this method to describe the normal compensatory capacity in a group of healthy elderly.

Materials and Methods
A property of the craniospinal system, consistent with the mathematical model of equation 1, is the linear relationship between mean ICP and ΔICP (Fig 1).7 The slope of the linear relationship, denoted RPPC, can be assessed during a lumbar CSF infusion study.11 Assessment of RPPC in combination with a measurement of the ΔVART occurring during a heart cycle enables calculation of PVICC (see Appendix for derivation). The relationship can be written as

$$PVICC = \frac{\Delta V_{\text{ART}}}{\log(RPPC + 1)}.$$  

Furthermore, assuming a communicating system without any differences between RPPC measured intracranially and in the spinal compartment enables calculation of the compliances of the intracranial and spinal compartments (PVICC and PVISC, respectively) by replacing ΔVART with the ΔVSC in equation 1. ΔVART and ΔVSC can be measured with PC-MR imaging.10,12 Moreover, the difference between the arterial volume increase and the volume shifted to the spinal compartment is the ΔVSC. It follows that PC-MR imaging and lumbar CSF infusion measurements can be combined to calculate PVICC, PVISC, and PVISC. In this study, initial MR imaging measurements for anatomic assessments of the brain were conducted, immediately followed by flow quantification with PC-MR imaging (Fig 2A). If no contraindication was revealed from the MR imaging investigation, the subject continued to the lumbar CSF infusion investigation (Fig 2B). The output from the PC-MR imaging measurements and the lumbar CSF infusion investigation was combined by using equation 2 (Fig 2C).

Subjects
An ad was put in the local paper inviting healthy volunteers (60–82 years of age) to apply for a research project regarding MR imaging and lumbar puncture (including a lumbar CSF dynamic investigation). Of the 149 that answered the ad, 59 persons were called for an interview, including a neurologic examination. Fifty subjects qualified. All had a Mini-Mental State Examination score of >28 points, and none had >2 of the vascular risk factors, smoking, hypertension, or hyperlipidemia.13 Advanced vascular diseases (eg, diabetes, previous stroke, or myocardial infarction) were exclusion criteria, as well as use of anticoagulants, benzodiazepines, or antidepressants. Five of the volunteers were excluded after the MR imaging, and the lumbar CSF infusion investigations could not be carried out in 4 individuals. Two MR imaging flow measurements were discarded because of cardiac synchronization difficulties and 2 lumbar CSF infusion investigations could not be used because of needle problems (different subjects). Thus, the studied group consisted of 37 healthy elderly (22 women and 15 men). Fifteen subjects had their lumbar CSF infusion investigation within 1 hour following the MR imaging; 21, the next day; and 1 subject, 6 days after the MR imaging. The mean age was 71 ± 6 years. The local ethics committee approved the study. Informed consent was obtained from all participants.

MR Imaging Measurements
Measurements were performed on a 3T Achieva scanner (Philips Healthcare, Best, the Netherlands). Routine sequences (T1, T2, and fluid-attenuated inversion recovery) were performed to assess criteria set for inclusion as a healthy subject. The PC-MR imaging sequences had a scan matrix of 128 × 128–160 × 160, a 5- to 6-mm section thickness, a 10- to 16-ms TR, a 6- to 11-ms TE, a flip angle of 10°–15°, and a 2-fold signal-intensity averaging. The velocity sensitization was set to 70 cm/s for blood assessments and 7 cm/s for CSF assessments. Retrospective triggering, ECG or peripheral, was used to synchronize the PC-MR imaging sequence to the cardiac cycle for proper sampling. Thirty-two phases were reconstructed. CSF and blood flows were quantified at the level of the first and second cervical vertebrae (thus proximal to the anterior spinal artery branch). Vessel lumen segmentation was performed manually in ImageJ (rsb.info.nih.gov/ij).14 ΔVART was calculated from the sum of the blood flows in the internal carotid and vertebral arteries (Fig 3). The CSF flow at the cervical level was used to estimate ΔVSC. Subtraction of the spinal CSF flow from the summed arterial flow curve was used to calculate ΔVSC.

Lumbar CSF Infusion Investigation
A fully automatic lumbar CSF infusion apparatus, in which the subject is in a supine position, was used.15 It uses 2 needles inserted in the lumbar canal, 1 for infusion of a Ringer acetate solution and 1 for pressure measurements. Investigations started with a recording of the resting ICP. This was followed by a CSF infusion phase in which the pressure was regulated to 6 predetermined and constant pressure levels, separated by 0.4 kPa (Fig 4). In a few exceptions (n = 4) with partial obstruction of the infusion needle, the operator switched to a pattern with a constant infusion rate of 1.5 mL/min for 20 minutes.
The pressure was sampled at 100 Hz. In 26 subjects, the heart rate was monitored by ECG for evaluation of agreement with the heart rate of the MR imaging investigations. There was no significant difference between the heart rate measured during the MR imaging and during the lumbar CSF infusion test (63.9 versus 63.1 beats per minute; mean difference, 0.8 beats per minute; paired t test, \( P = .5 \)). To calculate RPPC, we estimated a ΔICP by calculating a pulse pressure as the difference between the maximum and minimum ICP in 1.5-second time windows after applying a forward-backward fifth-order high-pass Butterworth filter with a cutoff frequency of 0.5 Hz. For all pressure levels of the constant pressure infusion pattern, including baseline, the ΔICP was defined as the median pressure pulse. The RPPC was calculated by least squares linear regression between the ΔICP and median ICP of the different pressure levels. \( P_0 \) was determined as the crossing between the regression line and the pressure axis (Fig 1).

In the case of a constant infusion, ΔICP and average ICP for all 1.5-second intervals of the infusion phase were used in the regression. The uncertainty of the RPPC parameter, denoted \( \sigma_{\text{RPPC}} \), was approximated for each investigation by calculating the width of the 95% confidence interval from the regression analysis.

At the end of the investigation, 32 of the subjects were additionally investigated with a single bolus infusion (Fig 4), in which a 5.6-mL-volume \( \Delta V_{\text{bolus}} \) was rapidly administered while the pressure response was recorded.\(^1\,\text{16}\) Equation 8 in the Appendix was used for calculating the PVI\(_{\text{bolus}}.\)^17 The ICP\(_{\text{start}}\) and ICP\(_{\text{end}}\) were measured as the average ICP during the 10-second periods directly before the start and imme-

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**Fig 2.** An overview of how the infusion and MR imaging modalities are combined to estimate compliance indices.

**Fig 3.** A, Total cerebral arterial blood flow (summed flow of the internal carotid and vertebral arteries). B, Cumulative integration of the curve in A with the average flow subtracted yields the arterial volume change during a cardiac cycle. \( \Delta V_{\text{art}} \) was defined as the largest volume difference during a cardiac cycle.

**Fig 4.** An ICP recording from a lumbar CSF infusion test. A, Baseline ICP recording. B, Infusion to predetermined ICP levels. C, Relaxation phase allowing ICP to normalize. D, A bolus test (rapid infusion of a 5.6-mL artificial CSF).
After the end of the bolus infusion phase. A $P_0$, from the RPPC slope of the infusion test performed before the bolus test was used. 

$$\Delta PVI_{bolus}$$ was calculated by using propagation of error analysis applied on equation 2, together with $\Delta RPPC$ as described above and with an assumed precision in the volume displacement estimation of an $\Delta V_{ART}$ of $\pm 0.1 \text{ mL}$.

**Results**

From the PC-MR imaging investigation, $\Delta V_{ART}$ was measured to a mean of $1.98 \pm 0.43 \text{ mL}$ and $\Delta V_{IC}$ and $\Delta V_{SC}$ were measured to $1.36 \pm 0.44 \text{ mL}$ and $0.68 \pm 0.23 \text{ mL}$, respectively ($n = 37$). The estimations from the lumbar CSF infusion tests yielded a mean RPPC of $0.62 \pm 0.25$ with a mean $\Delta RPPC$ of $\pm 0.07$ ($n = 37$). By combining the parameters from the lumbar CSF infusion test and the PC-MR imaging investigation, we calculated $PVI_{CC}$ to $11.8 \pm 9.0 \text{ mL}$, $PVI_{IC}$ to $8.4 \pm 8.1 \text{ mL}$, and $PVI_{SC}$ to $3.9 \pm 2.5 \text{ mL}$ ($n = 37$). Two subjects with extreme $PVI_{IC}$ estimations contributed strongly to the variation in $PVI_{CC}$ (Fig 5). Without extreme values, $PVI_{CC}$ was $9.8 \pm 2.7 \text{ mL}$, $PVI_{IC}$ was $6.7 \pm 2.6 \text{ mL}$, and $PVI_{SC}$ was $3.4 \pm 1.2 \text{ mL}$ ($n = 35$). In relative figures, $65\%$ (range, $44\%$–$89\%$) of the compensating capacity was located intracranially and the remaining $35\%$ (range, $11\%$–$56\%$) was located spinally ($n = 35$). The average $\Delta PVI_{bolus}$ was calculated to $\pm 9\%$. The average $PVI_{bolus}$ was calculated to $11.2 \pm 6.9 \text{ mL}$ ($n = 32$). Without extreme values, the $PVI_{bolus}$ was $10.2 \pm 3.7 \text{ mL}$ ($n = 30$). Although the mean values for $PVI_{CC}$ and $PVI_{bolus}$ were similar, the correlation of individual observations was low (Fig 5).

**Discussion**

A method to combine data collected from PC-MR imaging measurements and lumbar CSF infusion studies was presented. This provided a different analysis of the craniospinal compliance properties than that achieved by analyzing results from the different measurement techniques separately. The methodology only required minor additions to the routine procedure for patients referred for a lumbar CSF infusion study because almost all undergo an MR imaging investigation that may easily include PC-MR images. Estimations of $PVI_{CC}$ were obtained from the combined methodology and estimations of $PVI_{bolus}$ from a single bolus test. The average $PVI_{CC}$ and average $PVI_{bolus}$ were comparable with previous reports of constant-rate infusion studies in subjects with hydrocephalus but were lower than those in previous reports of bolus investigations performed in admitted neurologic and neurosurgical subjects (Table). This may be an indication of actual differences in $PVI_{CC}$ between healthy elderly and other groups of patients. If so, it seems as if healthy subjects had a $PVI_{CC}$ in the lower end of the spectrum. This was not expected because the general hypothesis is that $PVI_{CC}$ would be higher among the healthy and that a low $PVI_{CC}$ is pathologic. However, in the Table, studies using a slightly different pressure-volume model without a constant term account for the reports of high $PVI_{CC}$ values, while those using a pressure-volume model with a constant term (as used in this study) have produced reports of $PVI_{CC}$ more similar to that generated in this study. Aside from differences potentially originating in the choice of model, aging is known to influence the compliance of the craniospinal cavity, and thus addition of normative data of elderly subjects is crucial.

The $\Delta V_{ART}$ indicated the robustness of the method. How compliance was distributed between the intracranial and spinal compartments was investigated. To our knowledge, such reports of basic physiology are missing in the literature. In terms of average compliance, $65\%$ was found intracranially and $35\%$ spinaly. This observation was in agreement with reported values in cats ($68\%$ and $32\%$ intracranially and spinaly, respectively). This might reflect the fact that compressible intracranial veins were a major compliance in the system. While the intracranial compartment was the predominant contributor to the $PVI_{CC}$, the individual variations of this distribution were large.

Assessment of the cardiac-related pulsatile intracranial dynamics is increasingly used to understand the physiology and pathology of the CSF system. $PVI_{CC}$, together with $\Delta V_{CC}$ determines the impact on the brain caused by the arterial pulsations (approximately 30 million each year). With increasing age, arterial physiology changes. Arterial stiffness and wind-kessel dysfunction of the aorta stresses the microcirculation. The cyclic $V_{ART}$ increases. $PVI_{CC}$ is a quantification of how well these increased pulsations are cushioned. Ventricular dilation is associated with cognitive and gait impairment. That inadequate absorption of the arterial pulse can promote ventricular dilation is a persistent hypothesis on the etiology regarding the development of communicating hydrocephalus. Moreover, the growing concept of pulse wave encephalopathy has been attributed to several other disorders (Alzheimer disease, mild cognitive impairment, age-related white matter changes). This mechanism may involve a pathologic combination of altered $PVI_{CC}$ with or without increased $V_{ART}$. Because the combined MR imaging and lumbar CSF infusion test quantify both parameters (in a time regime of a cardiac cycle), this approach would be particularly useful in studying the occurrence and nature of pulse wave encephalopathy.

Because measurements of $PVI_{CC}$ entirely based on lumbar infusion tests are associated with within-subject systematic errors, a new approach is desirable. A challenge with current infusion tests is that induced pressure variations are slow.
During a time window much wider than a cardiac cycle, autoregulatory vasogenic volume variations will cause both systematic and randomized errors in the estimated PVI_{ICC}, a possible explanation of previously reported discrepancies between different infusion patterns within subjects.30

This study was based on several assumptions that deserve specific attention. We assumed that it is possible to separate the MR imaging and infusion measurements in time. This requires the measured parameters of equation 2 to remain unchanged between the measurements. Within limits, RPPC is independent of ICP, which might change between the measurements.7 Furthermore, the pressure-volume model of equation 1 together with the well-determined RPPC (ie, a small ΔRPPC) indicates that ΔV_{ART} is, in fact, also independent of ICP. These parameters might, however, be altered by a change in heart rate, affecting the cardiac output between the measurements. In this study, no significant difference between the heart rate measured at the different modalities was observed. The calculations rely on the assumption that RPPC agrees between the intracranial and spinal compartments. This requires a low resistance between the 2 compartments, a likely situation except in spinal stenosis.

The craniospinal system is built up with active components generating volume variations and passive components absorbing these variations. The sum of all passive components will form the compliance of the system. In this study, we have considered 2 types of active components. The first consists of craniospinal arterial vessels. These arterial vessels expand during each cardiac cycle. The second active component is external lumbar CSF infusion. If any of these active volume changes are known, the pressure response they generate can be used to quantify the compliance of the system. In this article, we assumed that the volume change, measured with PC-MR imaging of the internal carotid and vertebral arteries, will be entirely transferred as heart-beat-related craniospinal arterial volume changes. This view is in accordance with having arterial pulsations transmitted through the arterial wall in a way that blood at some point in the capillary network flows without oscillations.31 By measuring blood flow at the cervical level, we assumed that the entire arterial volume increase of the craniospinal system could be calculated. This is a generalization because arterial supply to lower parts of the spinal cord is not included (eg, the anterior spinal artery is included but segmental and radicular arteries are not included). The magnitude of the missing spinal arterial flow is difficult to estimate because there are no reliable reports of this quantity.52 However, this missing flow is likely a small fraction compared with the blood flow to the brain, and thus the resulting underestimation of PVI_{ICC} is also small.

Regarding the comparison between the new methodology and the bolus test, the average PVI_{ICC} and average PVI_{bolus} agreed but individual observations did not correlate (Fig 5). A likely explanation is that a single bolus test does not estimate the craniospinal compliance with precision, whereby a series of boluses are a common choice.16,33 In fact, the combined MR imaging and lumbar CSF infusion data to determine PVI_{ICC} are in analogy with an averaging of hundreds of pressure responses caused by physiologic bolus excitations. Thus, this method potentially generated a more robust and accurate estimate than that of the single external bolus excitation.

In Fig 5, two extreme values were identified. One had a low ICP response from the bolus test together with a very low RPPC (the upper right extreme value), while the other had a normal ICP response during the bolus test but a low RPPC. Without these measurements, the variance in PVI_{ICC} and PVI_{bolus} was greatly decreased and the reduced dataset was believed to be representative of an elderly population. However, it could not be exclusively deduced if the extreme measurements were physiologic or due to needle problems. Nevertheless, extreme values appear in the measurements, and their origin should be further investigated.

Conclusions

The combination of PC-MR imaging measurements and a lumbar CSF dynamic test with an established mathematic model of the craniospinal system proved feasible and robust for assessing the compensatory mechanisms of the craniospinal system and its intracranial and spinal compartments. This study produced normative PVI values for healthy elderly and showed that the major compensatory contribution is located intracranially.

Appendix

The RPPC slope can be mathematically derived by investigating the pressure response following a change in volume:

\[ ICP + ΔICP = P_V (V_{ICC} + ΔV_{ART}) / (0.4343 \cdot V_{ICC}) + P_0. \]

This can be re-expressed to define RPPC as

\[ ΔICP / ICP - P_0 = e^{ΔV_{ART} / (0.4343 \cdot V_{ICC})} - 1 = RPPC, \]

where ΔV_{ART} is the cyclic volume displacement related to cardiac pulsations. This can be rewritten to express the PVI as

<table>
<thead>
<tr>
<th>Subjects</th>
<th>PVI_{ICC} (mL)</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pressure hydrocephalus (n = 69)16</td>
<td>16.4</td>
<td>Repeated bolus injections</td>
</tr>
<tr>
<td>Idiopathic normal pressure hydrocephalus (n = 47)16</td>
<td>16.7</td>
<td>Repeated bolus injections</td>
</tr>
<tr>
<td>Head injury: ICP, &lt;20 mm Hg (n = 9)16</td>
<td>20.8</td>
<td>Bolus injection/CSF withdrawal</td>
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<td>Hydrocephalus, ventriculomegaly (n = 27)19</td>
<td>9.6</td>
<td>Constant-rate infusion</td>
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<tr>
<td>Hydrocephalus, ventriculomegaly (n = 27)19</td>
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<td>Relaxation preceding infusion</td>
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<tr>
<td>Mechanically ventilated, pathologic autoregulation (n = 35)34</td>
<td>20.0</td>
<td>Bolus injection</td>
</tr>
<tr>
<td>Mechanically ventilated, functioning autoregulation (n = 24)34</td>
<td>31.6</td>
<td>Bolus injection</td>
</tr>
<tr>
<td>Hydrocephalus, ventriculomegaly (n = 46)20</td>
<td>8.9</td>
<td>Constant-rate infusion</td>
</tr>
<tr>
<td>Adult patients without intracranial masses (n = 7)1</td>
<td>25.9</td>
<td>Bolus injection/CSF withdrawal</td>
</tr>
</tbody>
</table>

Reports of PVI_{ICC} in various states

Finally, $PVI_{bolus}$ is presented. Starting with equation 3 and by letting the volume displacement represent that of a bolus infusion, we can rewrite the relationship as

$$\frac{\Delta V}{\log(RPPC + 1)} = \frac{\Delta V_{bolus}}{\log(0.434 \cdot PV_{bolus})}.$$ 

where $ICP_{start}$ represents the resting pressure preceding the bolus infusion. The pressure response can be expressed as

$$\frac{\Delta ICP_{bolus} + ICP_{start} - P_0}{ICP_{start} - P_0} = e^{\Delta V_{bolus}/(0.434 \cdot PV_{bolus}),}$$

where $ICP_{end}$ is the pressure when the bolus volume is administered. It follows that $PVI_{bolus}$ can be expressed as

$$PVI_{bolus} = \frac{\Delta V_{bolus}}{\log(I\neg\neg\neg C P_{end} - P_0)}.$$