Intracranial pressure and cerebrospinal fluid outflow conductance in healthy subjects

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Conductance of cerebrospinal fluid (CSF) outflow (C_{out}) is an important parameter to be considered in patients with CSF circulation abnormalities. In patients with normal-pressure hydrocephalus it is the single most important parameter in determining if the patient needs CSF shunting. The lower normal limit for C_{out} has been estimated from the effect of shunting in patients with normal-pressure hydrocephalus, from patients retrospectively reevaluated after recovering from illness, and from patients with known abnormalities in the brain or the CSF system. The true value of C_{out} in normal individuals, however, has hitherto not been reported.

In the present study, C_{out} has been measured by a lumbar infusion test in eight young volunteers with no suspicion of disease. The mean intracranial pressure (ICP) was 11 mm Hg and a linear relationship was found between CSF absorption and ICP. The mean C_{out} was 0.11 ml/min/mm Hg and the lower 95% confidence level was 0.10 ml/min/mm Hg. These values are in accordance with those obtained from previous studies.

Key Words: cerebrospinal fluid outflow, cerebrospinal fluid dynamics, intracranial pressure, hydrocephalus

The relationship between intracranial pressure (ICP) and formation and absorption of cerebrospinal fluid (CSF) was given by Davson, et al., in the following equation: ICP = R_{out} \times FR_{ce} + P_{sa}, where R_{out} is the resistance of CSF outflow, the reciprocal value of conductance to CSF outflow (C_{out}), FR_{ce} is the formation rate of CSF, and P_{sa} is the pressure in the sagittal sinus. This means that a decrease in C_{out} leads to increased ICP, which may result in ventricular enlargement. In most clinical situations, FR_{ce} is considered constant and only subject to pathological changes in rare conditions like papilloma of the plexus or when ICP is greatly increased. On the other hand, a decrease in C_{out} is often an important pathogenetic factor in disorders with intracranial hypertension or hydrocephalus. During the formation of hydrocephalus in patients with normal-pressure hydrocephalus, ICP decreases as the size of the ventricles increases, a phenomenon which may be explained by the law of Laplace. For this reason, determination not only of ICP but also of C_{out} in hydrocephalic conditions with normal or close to normal ICP is essential.

Probably C_{out} is mainly determined by the resistance to outflow of CSF from the subarachnoid space through the arachnoid villi to the superior sagittal sinus, but resistances exist all over the CSF transport system. Alternative pathways exist along the perivascular space to the lymphatic vessels in smaller animals and via the spinal roots in man.

The C_{out} value can be measured by techniques involving bolus injection infusion, or perfusion testing and has been shown to be a useful parameter in clinical practice. A study by Schmidt, et al. of reproducibility in measuring C_{out} showed that the constant-pressure constant-infusion-rate technique is a reliable and reproducible method for measurement of C_{out} in patients with normal-pressure hydrocephalus.

Normal values of C_{out} have been estimated from patients investigated with suspicion of disease or abnormal CSF circulation. The true upper and lower limits of C_{out} in normal persons are not known, as conductance studies have never been performed in healthy subjects. The purpose of the present study was to measure C_{out} in normal persons together with an estimation of normal lumbar (intracranial) steady-state pressure. A lumbar constant-pressure constant-infusion-rate method was used.

Clinical Material and Methods

Eight healthy volunteers aged 22 to 28 years (two men and six women) were examined. Each volunteer was placed in a lateral recumbent position with a pillow
under the head to obtain an equal level of the ventricular system and the lumbar subarachnoid space. No torsion of the neck was allowed. After local anesthesia was initiated with 5 to 10 ml lidocaine (10 mg/ml), a midline lumbar puncture was made with a 1.2 mm No. 18 needle between the L-4 and L-5 vertebrae. All punctures were uneventful and no blood contamination of the CSF was present. After puncture, the cannula was connected to a transducer which was fixed to the back of the subject at the same level as the cannula. The transducer was connected to an amplifier and to a paper recorder.

A baseline measurement of the lumbar pressure was performed for 30 minutes followed by a lumbar infusion study. The cannula was connected to two tubes. Artificial CSF (Ringer's lactated solution) was delivered via one tube by an infusion pump with a constant rate \( V_{\text{in}} \) of 1.82 ml/min or 4.55 ml/min. The outlet of the other tube was elevated in steps to increase the lumbar pressure. At each pressure level, the volume of CSF from the outlet of the tube \( V_{\text{out}} \) was measured for 5 minutes and a minimum of 2 minutes was allowed between each measurement to obtain a steady-state ICP on the next level. Four to eight ICP levels were examined in each volunteer. The procedure was completed within 2 to 2.5 hours, after which the volunteer rested in bed for 4 to 6 hours.

A constant formation rate of 0.4 ml/min was assumed, and the CSF absorption rate \( V_{\text{abs}} \) was calculated from the formula: \( V_{\text{abs}} = V_{\text{in}} + 0.4 - V_{\text{out}} \). Corresponding values of \( V_{\text{abs}} \) and \( V_{\text{out}} \) were plotted and the linear regression line was calculated by the method of least squares. The slope of the regression line is an expression of \( C_{\text{out}} \), and the reciprocal value is the resistance to outflow \( R_{\text{out}} = 1/C_{\text{out}} \).

Statistics were calculated on the SPSS/PC+ software.† The investigation was approved by the Ethics Committee of Science of Copenhagen.

**Results**

The mean ICP from all eight studies was 11 ± 2 mm Hg (± standard deviation, range 7 to 15 mm Hg). The pulse wave amplitude was 1 to 3 mm Hg.

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**Definitions of Abbreviations**

- \( C_{\text{out}} \) = conductance of CSF outflow
- CSF = cerebrospinal fluid
- \( FR_{\text{out}} \) = formation rate of CSF
- \( P_{ss} \) = sagittal sinus pressure
- \( R_{\text{out}} \) = resistance to CSF outflow
- \( V_{\text{abs}} \) = CSF absorption rate
- \( V_{\text{in}} \) = constant infusion rate
- \( V_{\text{out}} \) = volume of outflow

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<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Mean ( C_{\text{out}} ) (ml/min/mm Hg)</th>
<th>Regression Coefficient</th>
<th>ICP (mm Hg)</th>
<th>Baseline Range</th>
<th>No. of ICP Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.14 ± 0.01</td>
<td>0.99 (p &lt; 0.001)</td>
<td>7</td>
<td>12-32</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>0.11 ± 0.01</td>
<td>0.97 (p &lt; 0.002)</td>
<td>9</td>
<td>11-32</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>0.11 ± 0.01</td>
<td>0.99 (p &lt; 0.001)</td>
<td>11</td>
<td>13-26</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>0.13 ± 0.01</td>
<td>0.99 (p &lt; 0.001)</td>
<td>12</td>
<td>21-28</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>0.04 ± 0.01</td>
<td>0.95 (p &lt; 0.001)</td>
<td>15</td>
<td>8-28</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>0.14 ± 0.01</td>
<td>0.99 (p &lt; 0.001)</td>
<td>12</td>
<td>8-29</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>0.14 ± 0.01</td>
<td>1.00 (p &lt; 0.001)</td>
<td>12</td>
<td>14-28</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>0.16 ± 0.01</td>
<td>0.99 (p &lt; 0.001)</td>
<td>11</td>
<td>14-28</td>
<td>5</td>
</tr>
</tbody>
</table>

* \( C_{\text{out}} \) = conductance to cerebrospinal fluid outflow (± standard error of the mean); ICP = intracranial pressure (lumbar pressure); range = minimum and maximum steady-state level of lumbar pressure during examination; no. of ICP levels = number of steady-state lumbar pressure levels measured for each subject.

The values for mean \( C_{\text{out}} \), regression coefficient (R), baseline and range of ICP, and numbers of ICP levels for each individual are shown in Table 1. Plots of \( V_{\text{abs}} \) against ICP for all eight investigations show that the points from seven of the eight investigations fall almost on the same straight line (Fig. 1). In investigation No. 5 intense fluctuations of ICP were present, and it was not possible to obtain reliable steady-state ICP levels. Furthermore, a resting pressure of 15 mm Hg was uncovered. To exclude intracranial pathology, a computerized tomography (CT) scan was performed 3 days later; however, this was normal.

When the results from all eight examinations were

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**TABLE 1**

*Individual \( C_{\text{out}} \) and ICP from eight healthy subjects*

**FIG. 1.** Corresponding values of intracranial pressure (ICP) measured by lumbar puncture and absorption rate of cerebrospinal fluid. Seven of the eight studies fall almost on the same straight line, while one study (No. 5) is deviant.
Cerebrospinal fluid outflow conductance

**TABLE 2**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mean ( C_{out} ) (ml/min/mm Hg)</th>
<th>95% Confidence Interval (ml/min/mm Hg)</th>
<th>Regression Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>all</td>
<td>0.11 ± 0.01</td>
<td>0.10 - 0.13</td>
<td>0.90 (p &lt; 0.001)</td>
</tr>
<tr>
<td>all except subject 5</td>
<td>0.12 ± 0.01</td>
<td>0.11 - 0.14</td>
<td>0.92 (p &lt; 0.001)</td>
</tr>
</tbody>
</table>

* \( C_{out} \) = Conductance to cerebrospinal fluid outflow (± standard error of the mean).

joined to one regression line, a mean \( C_{out} \) of 0.11 ml/min/mm Hg was obtained, the corresponding 95% confidence interval was 0.10 to 0.13 ml/min/mm Hg (Table 2). If the results of examination in Subject 5 are excluded from the calculation, a mean \( C_{out} \) of 0.12 ml/min/mm Hg with a 95% confidence interval of 0.11 to 0.14 ml/min/mm Hg is obtained.

Four of the eight volunteers had severe postlumbar-puncture headache, eventually demanding treatment with an epidural spinal blood patch. After this the headache quickly disappeared, but one woman experienced tinnitus for 8 weeks.

**Discussion**

Measurement of conductance of CSF outflow is important in evaluating the necessity for a shunt operation in patients with normal-pressure hydrocephalus. It has also been employed as a clinical parameter and in research concerning the pathogenesis of diseases such as hydrocephalus following subarachnoid hemorrhage, pseudotumor cerebri, and meningitis and in pediatric neurosurgery.

When using \( C_{out} \) in the assessment of CSF abnormalities, a normal limit is arbitrarily set. Values below this level are considered pathological. In the study by Gjerris, *et al.*, a lower "normal" level was based on the results obtained after shunt operation. In that study of 240 patients with normal-pressure hydrocephalus, no patient with a \( C_{out} \) above 0.08 ml/min/mm Hg derived any benefit from CSF diversion, irrespective of preoperative clinical symptoms, CT findings, and the results of ICP measurements. Ekstedt published values of 58 patients from a series of 820 patients. These patients were retrospectively reevaluated and found not to have any neurological or systemic vascular disorders. He found a mean conductance of 17.98 cu mm · kPa⁻¹ · sec⁻¹, corresponding to a \( C_{out} \) of 0.14 ml/min/mm Hg; 90% of the values fell within 0.10 to 0.21 ml/min/mm Hg. Sklar proposed a lower normal limit between 0.1 and 0.2 ml/min/mm Hg based on clinical experience, and suggested that a \( C_{out} \) less than 0.13 ml/min/mm Hg is probably abnormal. In a study by Tans and Poortvliet, 18 of 26 patients had a \( C_{out} \) lower than 0.10 ml/min/mm Hg; 83% of these patients improved after shunting. Eight patients within a \( C_{out} \) above 0.1 ml/min/mm Hg were clinically and radiologically stable without shunting, except for one patient with progressive brain atrophy. All of these studies were carried out in patients with brain disorders, however, suggesting possible abnormalities in the CSF dynamics. This lack of true normal values motivated the present study, and our finding of a lower 95% level of 0.10 ml/min/mm Hg is in accordance with estimated values from the previous studies (Table 3).

An upper normal 90% limit of \( C_{out} \) of 0.21 ml/min/mm Hg was found in the study by Ekstedt. In our study an upper 95% confidence limit of 0.13 ml/min/mm Hg was discovered, but no disorder has ever been associated with increased \( C_{out} \). In our series of 240 patients with normal-pressure hydrocephalus, we found more than 40 patients with a \( C_{out} \) above 0.2 ml/min/mm Hg. The symptoms in these patients did not differ from those in patients with a low \( C_{out} \).

A constant formation rate of 0.4 ml CSF/min is assumed. The correct rate may be a little lower or higher, but the absolute value has no influence on the calculated value of \( C_{out} \); it will only change the intercept of the regression line. Alteration of \( FR_{osf} \) during the infusion study will influence the calculation of \( C_{out} \), however, changes in \( FR_{osf} \) must be considerable to produce a substantial change in \( C_{out} \). In the subjects studied, a 50% reduction of \( FR_{osf} \) when ICP is increased from the lowest to highest steady-state level, would reduce the calculated \( C_{out} \) by less than 10%. However, the upper and lower limits of ICP studied are so narrow and the maximum pressure so low, that a significant change in \( FR_{osf} \) is not to be expected.

The mean ICP in our eight subjects was 11 mm Hg, in accordance with the results of 10 to 12 mm Hg obtained in normal individuals described in other studies. A linear relationship between \( V_{abs} \) and ICP in the investigated range of ICP is assumed, and the good curve fit in this study confirms the linear relationship between ICP and \( V_{abs} \).

We observed a high rate of adverse reactions. Four of the volunteers complained of headache, dizziness, and tinnitus so severe that they required treatment with a spinal epidural blood patch. The reasons for the high rate of adverse effects are not clear, but are probably caused by continuous CSF leak through the dural lesion at the puncture site. In more than 500 perfusion studies...
performed in our department in patients with normal-pressure hydrocephalus and benign intracranial hypertension, we have experienced these adverse effects in only a very few cases. The greater susceptibility in this investigation may be explained by the younger age of the volunteers compared to that of the normal-pressure hydrocephalus patients, who, furthermore, are often bedridden. Patients with benign intracranial hypertension do often benefit from lumbar puncture, so adverse effects due to CSF leakage would not be expected in these patients. Also, the cannula used in the study was rather thick (1.2 mm) to minimize resistance.

The present study shows that the normal values of $C_{out}$ obtained from healthy volunteers are in accordance with the clinical experience from patients with abnormalities of CSF dynamics. We therefore recommend the use of $C_{out}$ measurement in patients with a suspicion of abnormal CSF circulation.

References


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