Spinal CSF absorption in healthy individuals

Mikael Edsbagge,1 Magnus Tisell,1 Lars Jacobsson,2 and Carsten Wikkelso1
1Hydrocephalus Research Unit, Institute of Clinical Neuroscience and 2Department of Radiophysics, Sahlgrenska University Hospital, Göteborg University, S-413 45 Göteborg, Sweden

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Thirty-four healthy volunteers (19 men and 15 women) aged 21–35 yr (mean 25.4) were recruited among medical and dental students and included in the study. None had any history of or ongoing medical disorder, and none was on any medication other than oral contraceptives. While participating in the study, none of the students had any academic affiliation with the Departments of Neurology or Nuclear Medicine. The Göteborg University Ethics Committee approved the study, and informed consent was obtained from all participants. Height, weight, systolic and diastolic blood pressure, and heart rate were registered. The male participants were taller and heavier and had higher systolic and diastolic blood pressure than the female participants (Table 1). Men and women were each randomly assigned to one of two groups: active (7 women and 9 men) and resting (7 women and 10 men) individuals.

**CSF pressure.** The lumbar punctures (LPs) were performed between 3 and 5 PM after 10 min of rest with the individuals in the left lateral recumbent position. The individuals had a pillow placed under the head, no tourniquet of the neck was allowed, and they were requested to remain as still and silent as possible. The dura was, without preceding anesthesia, punctured in the L3–4 interspace with a 0.70 × 75-mm (22 gauge × 3 in.) needle. The needle was connected by a plastic tube (length 80 cm; internal diameter 0.80 mm) to an external pressure gauge and plotted with a Bryans 28000 graph recorder (Biopac Systems, Goleta, CA). In the other 10 individuals, the pressure was registered with a Gealtec nondisposable resistance bridge and the MP 100 WS for Windows data acquisition system (collecting data at 50 Hz) with AcqKnowledge software (Biopac Systems, Goleta, CA) disposable laser-tuned resistance bridge and the MP 100 WS for Windows data acquisition system (collecting data at 50 Hz) with AcqKnowledge software (Biopac Systems, Goleta, CA).

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fast Fourier transformation before filtration with a 3-Hz low-pass filter. The mean ICP was calculated automatically. The frequency of A- and B-waves was identified visually, and mean amplitude and duration were then calculated semiautomatically. For data collected with the Bryans 28000 graph recorder, the mean ICP was calculated for each individual as the mean of two visual examinations obtained by superimposing a cord extrapolated with the best fit onto the printed pressure curve. A- and B-waves were identified visually, and mean amplitude and duration were measured with a ruler.

**CSF production.** CSF production was calculated by a modification of the method originally described by Masserman (35), i.e., the production (ml/min) was calculated as the withdrawn CSF volume (ml) divided by the decrease in ICP immediately after withdrawal of CSF (cmH_{2}O) multiplied by the increase in ICP (cmH_{2}O) per minute during the following pressure registration. The ICP increase per minute was obtained automatically with the Biopac MP 100 WS and with the Bryans 28000 graph recorder by using the visual mean of two observations obtained by superimposing a cord extrapolated with the best fit onto the printed pressure curve.

**CSF dynamics.** Immediately after the pressure recording, the spinal fluid manometer and the transducer were disconnected and 50 MBq of \textsuperscript{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) in a solution of 0.5 ml of NaCl was injected into the spinal SAS via the LP needle. Four \textsuperscript{57}Co markers were fixed to the back of the individuals and kept in the same position during the rest of the investigation (Fig. 1). In the “resting” individuals \textsuperscript{99m}Tc-DTPA was injected with the person lying in the left lateral recumbent position under the gamma camera. After the injection, the individuals slowly turned to the prone position, in which they stayed during the rest of the investigation. They were requested to remain as still as possible. The “active” individuals were instructed to walk around for 1 min after injection of the radionuclide before the first registration was started. They were also requested to walk around between the three subsequent registrations. The radionuclide distribution within the spinal SAS was registered immediately (“0”) and 20, 40, and 60 min after the injection by a gamma camera (Starcam XC/T or Starcam 400 AC/T; General Electric) equipped with a parallel-hole collimator.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
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<td>58–92</td>
<td>66</td>
<td>54–80</td>
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</table>

Values are demographic data of 34 healthy individuals, 19 men and 15 women. *P < 0.05; †P < 0.01; ‡P < 0.001.

**Fig. 1.** Spinal cerebrospinal fluid (CSF) absorption in 1 individual. The 3 frames on left show the radionuclide distribution in the sacral/lumbar (frame 1), the thoracic (frame 2), and the thoracic/cervical (frame 3) parts. Frame 3 has a different upper/lower level of the gray scale because the radionuclide activity in the thoracic/cervical part was very low. The 3 frames were merged into 1 image of the complete spinal subarachnoidal space (SAS), guided by external markers (black dots). Overlapping parts were excluded. A region of interest (ROI) was placed over the spinal SAS (A), and a smaller ROI (B) (registering background activity) was placed over the thoracic region. The cranial limit of the spinal SAS is at the foramen magnum. The foramen magnum level could be visually identified by altering the gray scale. A distal registration border was defined as the cranial limit of the spinal SAS. The radionuclide distribution of 50 MBq of \textsuperscript{99m}Tc-diethylenetriamine pentaacetic acid and background activity were examined immediately (“0”) and 20, 40, and 60 min after injection. After correction for decay and background activity, 4 profiles were obtained from the radionuclide distribution within the spinal SAS ROI (A) and superimposed (right). The caudal and cranial limits of the spinal SAS were mathematically transferred to the profiles. The area under each profile represents the registered amount of radionuclide. The activity registered at 0 min was set to 100%, and the radionuclide reduction in the subsequent registrations was calculated in relation to this. The movement of the radionuclide is expressed by changes in the location of the center of activity, changes in the location of the activity peak, and the cranial border at 60 min (considered to be where the 4 profiles converge). The cranial limit of the profiles was set to 0 and the cranial limit to 100%. The location and movement of the radionuclide within the spinal SAS were related to this scale (C).
with a general-purpose, low-energy collimator. The camera was placed as close as possible over the back of the individual. Because the gamma camera could not cover the entire spinal SAS, three frames were obtained covering the sacral-lumbar, thoracic, and thoracic-cervical parts of the spine. The acquisition time for each frame was 3 min, starting with the sacral-lumbar frame, continuing in a cranial direction, and being registered without interval. The absorption analyses were performed on a General Electric Star 4000 computer. The three frames were merged into one image of the complete spinal SAS with $^{99}$Tc markers. The cranial limit of the spinal SAS was set to the foramen magnum level. This level was recognized through adjustment of the upper/lower level of the gray scale in the frame covering the thoracic-cervical parts of the spine at 60 min, letting the background activity outline the basal parts of the head, the neck, and the shoulders. The foramen magnum level was then visually identified, and the cranial limit was inserted. A distal registration border was defined as the caudal limit of the spinal SAS, excluding the bladder. The distribution and activity of the radionuclide within the spinal SAS was calculated for each registration (0, 20, 40, and 60 min after injection), and a profile of the distribution was produced. The caudal limit was set to 0 and the cranial limit to 100%. The location and movement of the radionuclide within the spinal SAS were related to this scale. The movement of the radionuclide was described by changes in the location of the center of activity (mathematically calculated), changes in the location of the activity peak, and the cranial border at 60 min. The radionuclide activity registered at 0 min was set to 100%, and the radionuclide reduction was calculated in relation to this in the subsequent examinations at 20, 40, and 60 min. The cranial limit of the spinal SAS was not identifiable in the profiles but was identifiable in the radionuclide images of the spinal SAS, as described above, and mathematically transferred to the profiles. The cranial spinal SAS limit in the profile and hence the length of the intraspinal SAS was obtained by 1) calculating the relationship between the length of the profile and the length of the RC registration for the same individual; 2) using this relationship to calculate the intracranial part of the profile from the length of the intracranial part seen in the RC; and 3) subtracting the intracranial part of the profile from the length of the profile (Fig. 1). There was no sign of any radionuclide leakage into the epidural space through the needle passage in two active and one resting individual examined 70 min after the injection of $^{99}$Tc-DTPA. The individuals were in the prone position, and the detector was turned and positioned at 90° against the side of the body, covering the injection site.

To visualize the radionuclide distribution within the SAS during and immediately after the injection phase, two resting individuals were examined with the sacral-lumbar frames. The registration was started when $^{99}$Tc-DTPA was injected and continued for 3 min with 1 frame/s. An accumulation of the radionuclide was found at the site of injection. All registrations were corrected for decay, and an attenuation correction was performed with an attenuation coefficient of 0.14 cm$^{-1}$ (44). The mean distance between the spinal SAS and the outer skin surface was measured on MR images of the spine in 10 age-matched men and women examined at the Department of Radiology for other reasons. Only the resting individuals were included in correlation analyses between CSF dynamics and CSF pressure and production.

Exclusions. Of the initial 34 participants, one was excluded because of LP failure. ICP could not be analyzed in five individuals (Biopac MP 100 WS), and CSF production could not be calculated in one individual (Bryans 28000 graph recorder) because of technical problems. Registration of the CSF dynamics was incomplete in three individuals because of gamma camera malfunction.

Statistics. Statistical analyses were performed with the Wilcoxon rank-sum test and the Spearman correlation test. No corrections for multiple-correlation analyses were conducted. Unless otherwise stated, the level of significance was $P < 0.05$. To test whether the radionuclide reduction was linear, a significance test of linearity (F-test) was performed. The test was calculated by taking the variance of the means (from each time measurement) around the estimated line divided by the variance within each time measurement.

RESULTS

**CSF pressure and production.** ICP was 13.6 ± 3.1 cmH$_2$O (mean ± SD) with a 95% confidence interval (CI) of 12.1–15.1 cmH$_2$O and a range of 9.2–19.1 cmH$_2$O in 19 individuals examined with the Biopac MP 100 WS (Table 2). In the 10 individuals investigated with the Bryans 28000 graph recorder, the ICP was significantly lower (6.9 ± 2.8 cmH$_2$O, range 3.0–11.3 cmH$_2$O). A-waves (plateau waves) were not seen in any of the individuals. B-waves were found in 79% of the individuals examined with the Biopac MP 100 WS, with a mean frequency of 0.6 min$^{-1}$ (95% CI 0.5–0.8 min$^{-1}$; Table 2). ICP did not correlate with the frequency, duration, or amplitude of the B-waves, and ICP was the same in individuals with or without B-waves. Among individuals with B waves, the B-wave amplitude correlated at trend level with the ICP ($r = 0.48, P = 0.07$). No B-waves were found in the individuals examined with the Bryans 28000 graph recorder.

The CSF production rate was the same in individuals examined by the two methods; hence, the CSF production results are from all investigated individuals. The production rate varied between 0.29 and 0.39 ml/min (95% CI) with a mean of 0.34 ± 0.13 ml/min and a range of 0.11–0.73 ml/min (Table 2). The production rate did not correlate with ICP or the B-waves. ICP, B-waves, and CSF production rate were the same in men and women, and there was no correlation between ICP, CSF production rate, and height or weight.

**CSF dynamics.** The center of activity (Fig. 1) moved cranially with a speed of 7 ± 4% (mean ± SD) of the total spinal SAS in 60 min. The 95% CI was 5–8%, and the range was 2–16%. The center of activity progressed more cranially in active than in resting individuals (8 ± 4% vs. 5 ± 4%). The radionuclide activity peak remained at the injection site throughout the whole examination period in all but two patients, in which a cranial movement of 3% and 7%, respectively, was seen. The cranial border had reached the foramen magnum level (100%) 60 min after the injection in 16 of 30 patients (10 active and 6 resting). In the remaining 14 individuals (5 active and 9 resting), the border was still located within the spinal SAS. The mean location for all individuals was 85 ± 20% (mean ± SD), with a tendency to a more cranial location in active compared with resting individuals (92 ± 14% vs. 77 ± 22%; $P = 0.06$). The movement of the center of Table 2. ICP data

<table>
<thead>
<tr>
<th>ICP, cmH$_2$O</th>
<th>Mean</th>
<th>SD</th>
<th>Range 95% CI</th>
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<tr>
<td>B-waves</td>
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<tr>
<td>Frequency, min$^{-1}$ (individuals with B-waves)</td>
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<td>0.3</td>
<td>0.2–1.1</td>
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<td>Duration, s</td>
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<tr>
<td>Amplitude, cmH$_2$O</td>
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<td>1.7</td>
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<tr>
<td>CSF production rate, ml/min</td>
<td>0.34</td>
<td>0.13</td>
<td>0.11–0.73</td>
</tr>
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</table>

Intracranial pressure (ICP) and B-wave parameters (19 individuals) and cerebrospinal fluid (CSF) production (24 individuals) are shown. CI, confidence interval.
activity correlated positively with the location of the cranial border ($r_s = 0.78$). No differences were seen between men and women.

The radionuclide activity within the spinal SAS was gradually reduced by $20 \pm 13\%$ (mean $\pm$ SD) in 60 min with a 95\% CI of 15–24\% and a range of −2 to 45\%. The reduction was greater in active than in resting individuals (27 ± 12\% vs. 13 ± 9\%). The reduction over time was assumed to be linear because nonlinearity could not be proven ($F$-test, $P = 0.13$; Fig. 2).

The radionuclide reduction rate did not correlate with the movement of the center of activity or the location of the cranial border, and there was no difference between genders. Similarly, the radionuclide reduction rate, the movement of the center of activity, and the location of the cranial border did not show any correlation with ICP or CSF production rate.

There were no differences in reduction rate between individuals in whom the cranial border had reached the foramen magnum level and those with all the radionuclide still located in the spinal SAS, irrespective of activity or rest. Furthermore, the reduction rates of all individuals were normalized to a mean reduction rate in the resting and active groups with the cranial border within the spinal SAS of 100\%. No differences were found between individuals with the cranial border within the spinal SAS and those with the cranial border at the foramen magnum or the pooled normalized group ($P = 0.15$ and $P = 0.36$, respectively; Table 3).

Height, but not weight, correlated negatively with the movement of the center of activity (0–60 min, $r_s = −0.43$) and the location of the cranial border ($r_s = −0.49$). Height and weight correlated with each other ($r_s = 0.80$). Eight individuals suffered from temporary post-LP headache.

| Table 3. Spinal radionuclide reduction and movement in resting and active individuals |
|-------------------------------------------------|---------------------|---------------------|
| Cranial Border at Foramen Magnum Level | Cranial Border Within Spinal SAS |
| Active individuals | Resting individuals | Active and resting individuals |
| 29 ± 12\% | 21 ± 9\% | 134 ± 121\% |
| $n = 15$ | $n = 15$ | $n = 30$ |
| 14 ± 11\% | 12 ± 9\% | 100 ± 9\% |
| $n = 6$ | $n = 9$ | $n = 30$ |
| 134 ± 121\% | 100 ± 9\% | 134 ± 121\% |
| $n = 16$ | $n = 14$ | $n = 30$ |

The reduction of radionuclide activity in 15 active and 15 resting individuals is shown. The cranial radionuclide border was at the foramen magnum level in 16 individuals and below this level in 14 individuals. The radionuclide reduction is given in \% (mean ± SD) of injected dose. The reduction rate was higher in active than in resting individuals. There were no differences in reduction rate between individuals with the radionuclide cranial border at the foramen magnum level and those with all radionuclide located in the spinal subarachnoidal space (SAS). Furthermore, the reduction rates of all individuals normalized to a mean reduction rate in the resting and the active groups with the cranial border within the spinal SAS of 100\% did not differ. $n.s.$, Nonsignificant.

**DISCUSSION**

The absorption of CSF in healthy individuals has generally been considered to take place via the arachnoid villi into the sagittal sinus (2, 40). Also, spinal arachnoid villi along the nerve roots have been suggested as an absorption route for CSF (28). In animals, lymphatic drainage pathways have been shown to play an important role for CSF clearance (5, 27, 46). The existence of a lymphatic drainage pathway in humans remains unclear. Spinal CSF absorption has been suggested in animals (20) to account for 25\% (6) to 50\% (31) of the total CSF absorption. In this study we found a 20\% reduction of a radioactive substance injected into the lumbar SAS during the first hour. Because the activity peak was stationary, located at the injection site, and there was no sign of any intracranial displacement of the radionuclide, we conclude that CSF was absorbed from the spinal SAS. We could not measure the lumbar CSF volume in our participants, but other groups have reported the lumbar volume in younger healthy individuals to vary between 28 and 81 ml (8, 26, 30), with a mean of ~50 ml. On the basis of these figures, we estimate a mean spinal CSF absorption of ~10 ml/h, equivalent to 0.17 ml/min and with a range between 0.09 and 0.27 ml/min. The difference in radionuclide reduction between passive and active individuals is equivalent to a calculated mean spinal CSF absorption of 0.11 ml/min in passive and 0.23 ml/min in active individuals. By applying these assumptions to the observed CSF production rate in each individual in this study, we estimated that 38 ± 20\% (mean ± SD) of the CSF absorption in resting healthy individuals and 76 ± 25\% in active individuals was from the spinal SAS. It is interesting to note that active individuals had twice as high a spinal absorption rate as resting individuals. The pressure gradient between CSF and blood in the intracranial and spinal CSF compartment is probably the same in the prone position, whereas in the upright position the gradient should be higher in the spinal compartment. In the upright position, the hydrostatic pressure of the intracranial and spinal column of CSF is added to the spinal CSF compartment,
especially the lumbar part. The extradural veins increase very little in size once the venous pressure has reached 6–9 mmHg (43). An increased transvillus pressure gradient could thus be the reason for the considerably larger spinal absorption in active individuals. Another possibility could be an increased absorption through lymphatic drainage pathways, shown to be pressure dependent (4).

Our calculations presume a correct estimation of the CSF production rate, no radionuclide leakage from the injection site, and no extraspinal CSF absorption. The mean CSF production rate of 0.34 ml/min (95% CI 0.29–0.39 ml/min) calculated in this study by a rather simple method is consistent with most other reports (16, 45), and we therefore regard it as plausible. Furthermore, the results are also concordant with a net inflow of CSF from the ventricular system into the SAS of 0.45 (39) and 0.48 (18) ml/min. We did not find any sign of CSF leakage after LP as we carefully examined three individuals by a special protocol.

How sure can we be that there is no extraspinal CSF absorption since the radionuclide had reached the foramen magnum level in 16 of 30 individuals? The protocol did not include imaging of the intracranial SAS, and therefore it can be argued that a fast intracranial transport of CSF from the basal cisterns into the cranial absorption sites might overestimate the spinal radionuclide reduction.

There are two major arguments against an extraspinal absorption. First, no differences were found in reduction rates between individuals in whom the cranial border had reached the foramen magnum level and those with all radionuclide still located in the spinal SAS. Second, no differences were found when the reduction rates of all individuals were normalized to a mean reduction rate in the resting group and the active group with the cranial border within the spinal SAS of 100% (Table 3). These observations suggest that no significant quantity of radionuclide reached the intracranial SAS, strongly indicating that the reduction is due to a spinal CSF absorption.

Radionuclide activity exceeding 100% of the immediate registration was seen in six individuals in the registration at 20 min and in two individuals in the registration at 60 min. This is most probably due to differences in tissue thickness between our investigated individuals and the calculated distance from MR images in the age-matched men and women. Another reason could be a slight cranial movement of the radionuclide during and between the registrations.

As a result of cardiac cycle-related brain motions there is a pulsatile to-and-fro flow within the spinal SAS. The bidirectional velocities are high in the restricting zones of the spinal canal and low or absent in the lumbar part (17, 21, 41). The upward-directed movement of lumbar-injected radioactively labeled substances and the downward-directed movement of ventricularly injected radionuclide was originally explained by a net forward progression (11, 12) but could also be explained by a diffusion as a result of mixing caused by the pulsative CSF flow (22). A caudal net flow in the ventral and a cranial net flow in the lateral cervical SAS (42) with a tendency of a cranial-directed net flow in the posterior cervical SAS has been described (25). Henning et al. (24) found a caudal-directed flow in the ventral and dorsal cervical compartments and a two-way flow laterally, whereas Greitz et al. (21) could not find any unidirectional two-way transport. Quencer et al. (41) found a constant bidirectional movement of the CSF, with highest flow velocities in the caudal direction.

In our study the radionuclide activity peak is stationary located at the injection site, indicating the absence of a cranial-directed sweeping phenomenon, i.e., the absence of a bulk flow. The cranial movement of the center of activity is explained by a diffusion of the CSF. Because we only followed the radionuclide for 1 h, a minor and slow cranial-directed bulk flow cannot be entirely excluded. The diffusion seems to take place with a constant speed, depending on physical activity. CSF diffusion is more prominent in physically active individuals. This is probably due to an enhanced mixing of CSF secondary to more pronounced pulsations originating from enhanced arterial pulsations andValsalva maneuvers. From the ventricular system there is a net inflow of CSF through the aqueductus cerebri to the SAS (18, 25, 39), and there is no spinal CSF production (33). We find strong support for a spinal CSF absorption and consequently a caudal-directed net flow from the ventricular outflow site of CSF along the spinal CSF compartment toward the spinal absorption sites. The magnitude of this flow could be the same as that of the spinal absorption capacity, 0.11–0.23 ml/min, depending on physical activity. A net flow this small could be difficult to calculate within the multiple higher CSF peak velocities of up to 7 cm/s (25) and might explain some of the inconsistencies in earlier studies regarding the existence and direction of CSF bulk flow.

We found a difference in mean ICP measured by the Bryans 28000 graph recorder and the Biopac MP 100 WS. Similar CSF production rates were obtained by the two methods. We believe that the lower mean ICP achieved with the Bryans 28000 graph recorder is due to a baseline error. The Biopac MP 100 WS was tested repeatedly, and no errors were identified. We therefore decided to exclude ICP measurements derived from the Bryans 28000 graph recorder, except in calculating the CSF production rate. The ICP in our remaining 19 healthy individuals (95% CI 12.1–15.1 cmH2O) is similar to earlier reports by Gilland et al. (19) and Ekstedt (16) and also confirms results from previous studies showing no gender differences (16) and no correlation with weight or height (9). We could not find any correlation between the radionuclide reduction and the ICP. The reason for this could be the small number of healthy individuals, all with a normal ICP within a small range and without any pathological values.

B-waves were seen in the majority of the individuals with a frequency of 0.5–0.8 min⁻¹ (95% CI). The physiological mechanisms behind B-waves are still obscure (1, 15, 29). Originally, Lundberg (32) proposed that B-waves persisting for a long period probably always could be regarded as a sign of cerebral dysfunction, even though some of the recorded patients had a ICP <11 mmHg. B-waves have been reported to be frequent in hydrocephalus (3, 7, 10) but have also been reported in nonhydrocephalic patients with normal ICP (14, 34) and in healthy individuals through study of middle cerebral artery oscillations by transcranial Doppler sonography (13, 36, 38). To our knowledge, this is the first study to report on B-waves measured directly in CSF in healthy young adults, indicating that B-waves should be regarded as a physiological phenomenon.

In conclusion, the spinal radionuclide reduction found in this study indicates a spinal CSF absorption of 0.11–0.23 ml/min, more pronounced in active than in resting individuals. B-waves occur in the majority of awake healthy individuals, and we suggest that B-waves should be regarded as a physiological phenomenon.
ACKNOWLEDGMENTS
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