Postural effects on intracranial pressure: modeling and clinical evaluation

Sara Qvarlander,1,2 Nina Sundström,1,2 Jan Malm,3 and Anders Eklund1,2

1Department of Radiation Sciences-Biomedical Engineering, Umeå University, Umeå, Sweden; 2Centre of Biomedical Engineering and Physics, Umeå University, Umeå, Sweden; and 3Department of Clinical Neuroscience, Umeå University, Umeå, Sweden

Submitted 19 June 2013; accepted in final form 12 September 2013

Qvarlander S, Sundström N, Malm J, Eklund A. Postural effects on intracranial pressure: modeling and clinical evaluation. J Appl Physiol 115: 1474–1480, 2013. First published September 19, 2013; doi:10.1152/japplphysiol.00711.2013.—The physiological effect of posture on intracranial pressure (ICP) is not well described. This study defined and evaluated three mathematical models describing the postural effects on ICP, designed to predict ICP at different head-up tilt angles from the supine ICP value. Model I was based on a hydrostatic indifference point for the cerebrospinal fluid (CSF) system, i.e., the existence of a point in the system where pressure is independent of body position. Models II and III were based on Davson’s equation for CSF absorption, which relates ICP to venous pressure, and postulated that gravitational effects within the venous system are transferred to the CSF system. Model II assumed a fully communicating venous system, and model III assumed that collapse of the jugular veins at higher tilt angles creates two separate hydrostatic compartments. Evaluation of the models was based on ICP measurements at seven tilt angles (0–71°) in 27 normal pressure hydrocephalus patients. ICP decreased with tilt angle (ANOVA: \( P < 0.01 \)). The reduction was well predicted by model III (ANOVA lack-of-fit: \( P = 0.65 \)), which showed excellent fit against measured ICP. Neither model I nor II adequately described the reduction in ICP (ANOVA lack-of-fit: \( P < 0.01 \)). Postural changes in ICP could not be predicted based on the currently accepted theory of a hydrostatic indifference point for the CSF system, but a new model combining Davson’s equation for CSF absorption and hydrostatic gradients in a collapsible venous system performed well and can be useful in future research on gravity and CSF physiology.

normal pressure hydrocephalus; intracranial pressure; cerebrospinal fluid physiology; gravity; visual impairment intracranial pressure syndrome

THERE IS A GAP IN KNOWLEDGE regarding the relationship between changes in body position and intracranial pressure (ICP). ICP is widely studied in the context of trauma and diseases that involve suspicion of disturbed cerebrospinal fluid (CSF) dynamics, such as normal pressure hydrocephalus (NPH) and idiopathic intracranial hypertension (IIH). It is almost exclusively studied in supine or prone position. However, for conditions such as NPH and IIH, it is well justified to study ICP in the upright position, since these patients are generally upright in their daily life. NPH patients also experience their main symptom of gait and balance disturbance while in the upright position. Under normal circumstances, the CSF compartment is a communicating fluid system and, as such, subject to hydrostatic pressure gradients, i.e., although pressure is essentially the same in the entire system in supine position, gravity will give rise to hydrostatic pressure gradients in upright or seated positions. Beyond a furthering of our understanding of the CSF physiology in general, postural effects are of interest because of CSF shunts, where much care has been taken to develop anti-siphon devices to negate gravitational effects. Recently, interests have also been raised with regard to the effect of weightlessness on ICP, since astronauts have presented with symptoms believed to relate to ICP and CSF dynamics (15).

The effects of posture on the cardiovascular system have been studied extensively (1, 5, 11–14, 21), but few corresponding studies of the CSF system exist (3, 16, 18–20). For the venous system, a hydrostatic indifference point (HIPvein) has been defined; it is a point within the system where the venous blood pressure is independent of body position. For changes between supine and upright positions, HIPvein is located close to the top of the diaphragm (11). It has been shown that ICP (i.e., CSF pressure in the ventricles) is reduced when moving from a supine to an upright position, whereas CSF pressure at the lumbar level of the spinal subarachnoid space increases, and it has been hypothesized that there exists a hydrostatic indifference point in the CSF system as well (17). This hypothesis, which was presented by Magnæs, is the generally accepted model of how posture affects ICP. Since the pressure gradients in the CSF system can be predicted from the height of the fluid column, knowledge of the location of a possible hydrostatic indifference point of the CSF system (HIPCSF) would enable us to determine the pressure in the upright position from a measurement made in the supine position. In the study by Magnæs, where the hydrostatic indifference concept was first introduced for the CSF system, a hydrostatic indifference point for changes from a lying to a sitting position was proposed to be located between the C6 and T5 level of the spine for a control group (17). In that study, ICP was only measured at the two extreme positions, however, and, when studying the results of Bergsneider et al. (3), who measured ICP at six different angles of the body (0–55°), we identified a faster reduction of ICP at small angles and a slower reduction at higher angles than predicted by the model presented by Magnæs. These results thus challenge the currently accepted model, and further study of ICP at different body positions is warranted in an effort to explain postural effects on the CSF system.

The main hypothesis of this study was that (baseline) ICP, regardless of body position, is governed by Davson’s equation for CSF absorption and thus dependent on pressure in the venous system, specifically in the dural sinuses (6–8). The hypothesis further incorporates that the dural venous sinus pressure is altered by a collapse of the internal jugular veins when their transmural pressure reaches zero. The aim was to investigate the plausibility of this hypothesis by measuring ICP at seven tilt angles of the upper body (from the supine to a seated position) and compare the data with ICP predicted by...
three different models for the physiological effect of posture on ICP. One model was based on the currently accepted theory of a hydrostatic indifference point for the CSF system, whereas the other two models were based on Davson’s equation and a venous hydrostatic indifference concept with and without effects from collapsed veins at higher tilt angles.

**METHODS**

**Theory.** From Davson’s equation for absorption of CSF (2, 6–9), an expression for baseline ICP in the supine position can be derived:

\[
ICP = R_{out} \cdot I_{formation} + P_d
\]  

(1)

where \(R_{out}\) is the resistance to outflow of CSF, \(I_{formation}\) is the formation rate of CSF, and \(P_d\) is the pressure in the dural venous sinuses. Assuming that \(R_{out}\) and \(I_{formation}\) are unaffected by body position, Eq. 1 should be equally valid in the upright position. The ICP level is then governed by the venous pressure, and the question is raised of how \(P_d\) changes with body position.

The hydrostatic reference point for pressure in the venous system with regard to changes from the supine to upright position is the HIPvein located around the level of the diaphragm (11). At HIPvein, pressure is constant, but generally non-zero, during positive (head-up) tilt. This hydrostatic reference point differs from the zero/reference level for pressure in the venous system, and the question is raised of how \(P_d\) changes with body position.

The hydrostatic reference point for pressure in the venous system, with experimental results that suggest that the pressure just above the vertebrae system (1, 21), maintains an equivalent communication with HIPvein in the upright position, \(P_d\) would still be dependent on the hydrostatic pressure gradient to HIPvein. In addition to the Magnæs model, we have therefore designed and evaluated models for both venous communication alternatives.

**Models of the physiological effect of postural changes on ICP.** Three models describing postural effects on ICP were evaluated in this study. The models were formulated so that ICP could be predicted at any positive (head-up) tilt angle based on the tilt angle (\(\alpha\)) and a single observation of ICP (at a known \(\alpha\)). In this study, ICP in the supine position (0° tilt-angle) was used as this single observation. The parameters of the three models are listed and explained in the glossary, and the models are graphically illustrated in Fig. 1.

**Model I** described the currently accepted concept, which was first introduced by Magnæs (17):

\[
ICP(\alpha) = ICP(0°) - \rho \cdot g \cdot L_{HIPCSF} \cdot \sin(\alpha)
\]  

(2)

Equation 2 assumed that, at a certain point in the CSF system (HIPCSF), the pressure remains constant (independent of tilt angle) and that ICP changes with the height of the hydrostatic column from this point to the auditory canal (Fig. 1, left).

The other two models (**models II and III**) were based on Davson’s equation (6) and assumed that ICP is dependent on dural venous sinus pressure according to Eq. 1 at all tilt angles. Equation 1 was then simplified based on the estimation that \(P_d\) in the supine position was equal to venous pressure at HIPvein (\(P_{HIPvein}\)):

\[
ICP(\alpha) = \rho \cdot g \cdot L_{heart-HIPvein} \cdot \sin(\alpha)
\]  

(3)

\(P_{HIPvein}\) is by definition independent of body position, and is approximately equal to CVP in the supine position.

**Model II** was described by:

\[
ICP(\alpha) = \rho \cdot g \cdot (L_{heart} + L_{heart-HIPvein}) \cdot \sin(\alpha)
\]  

(4)

This was derived from Eq. 3 and the following equation for \(P_d\) as a function of tilt angle:

![Fig. 1. Illustration of the three models of the effect of posture on intracranial pressure (ICP). According to model I (left), there exists a hydrostatic indifference point of the cerebrospinal fluid (CSF) system (HIPCSF) where ICP is independent of body position and ICP changes with the hydrostatic pressure gradient (\(P_{hydrostat}\)) from HIPCSF to the external auditory canal (\(P_{hydrostat} = \rho \cdot g \cdot L_{HIPCSF}\)). According to model II (middle) and III (middle and right), posture affects ICP through venous pressure. In model II, ICP changes with \(P_{hydrostat}\) of the venous system, from HIPvein to the external auditory canal (\(P_{hydrostat} = \rho \cdot g \cdot L_{heart-HIPvein}\)). Model III corresponds to model II below \(a_{lim}\), but for higher tilt angles (right). \(P_{hydrostat}\) corresponds to the distance from the top of collapsed veins in the neck to the external auditory canal (\(P_{hydrostat} = \rho \cdot g \cdot L_{collapse}\)). The critical tilt angle \(a_{lim}\) where veins in the neck collapse, depends on \(P_{HIPvein}\) and the location of venous segments that are exposed to ambient pressure.](image-url)
The model assumed a fully communicating venous system at all tilt angles, and thus that the changes in $P_g$ (Eq. 5), and therefore in ICP (Eq. 4), correspond to the hydrostatic pressure column between HIP vein and the auditory canal (Fig. 1, middle).

Model III included effects of collapsed veins and was described by a system of two equations:

\[
\begin{align*}
\text{ICP} &= \text{ICP}(0°) - P_g \cdot g \cdot (L_\text{heart} + L_\text{heart-HIP vein}) \cdot \sin(\alpha), \\
\alpha &< \alpha_{\text{lim}} \\
\text{ICP} &= \text{ICP}(0°) - P_\text{HIP vein} - \rho \cdot g \cdot L_\text{collapse} \cdot \sin(\alpha), \\
\alpha &\geq \alpha_{\text{lim}}
\end{align*}
\]

Equation 8 implies that, at $\alpha < \alpha_{\text{lim}}$, $P_g$ was equal to the hydrostatic pressure gradient between the top of the collapsed segment and the auditory canal (i.e., $P_g = 0$). Above $\alpha_{\text{lim}}$, changes in ICP then corresponded only to the change in this hydrostatic pressure gradient (Fig. 1, right). The tilt angle where the collapsed segment was determined (\(\alpha_{\text{lim}}\)) was the tilt angle where the hydrostatic pressure gradient between the top of the collapsible segment and HIP vein reached $P_{\text{HIP vein}}$, i.e., when the internal pressure in this segment decreased to zero. Thus $\alpha_{\text{lim}}$ was described by:

\[\alpha_{\text{lim}} = \sin^{-1}\left(\frac{\rho \cdot g \cdot (L_\text{heart} + L_\text{heart-HIP vein} - L_\text{collapse})}{P_\text{HIP vein}}\right)\]

Patients. Patients undergoing investigation for suspected normal pressure hydrocephalus (NPH) at Umeå University Hospital were invited to participate in this study. In total, 27 patients (7 women/20 men; mean age of 73 ± 7 yr) underwent successful ICP measurement at different tilt angles. All patients had communicating CSF systems according to MR or CT scans performed before the procedure. The study was approved by the regional ethical board at Umeå University, and all patients gave informed, written consent.

Measurement protocol. The CSF space was accessed through lumbar puncture at the L3-L4 level using an 18-gauge needle, and pressure was measured through the needle with a CELDA infusion apparatus (Likvor, Umeå, Sweden), which uses a fluid catheter system. The hydrostatic zero level for the pressure measurement was set to the level of the external auditory canal in supine position.

At the start of the investigation, ICP was measured at baseline for 15 min with the patient in the supine and horizontally aligned position. The patient was then shifted from the supine to a seated position in seven steps, with 2 min of measurement at each tilt angle of the back rest of the patient bed. The back rest was tilted with the built-in system of the bed, using an inclinometer (ADXL105, Analog Devices, Norwood, MA) to aim for the predetermined angles of the research algorithm. As a result, the patient went from a supine horizontal position to a seated position with the knees bent. For each level, the height of the external auditory canal relative to the hydrostatic zero level of the sensor was measured using a laser sight and used to adjust the zero level for the pressure measurement. Thus, for all tilt-angles, ICP was referenced to the level of the auditory canal.

With the patient in the supine position, the horizontal distance between the middle of the sternum (as an anatomical landmark for the heart) and the auditory canal was measured; this was denoted $L_\text{heart}$ (Fig. 1).

Pressure analysis. All post-processing and calculations except statistics were performed using MATLAB (version R2007b, The Mathworks, Natick, MA). The pressure at each tilt angle was low-pass filtered to reduce disturbances (fifth-order Butterworth filter, cut-off frequency of 10 Hz implemented using MATLAB’s “filtfilt” algorithm for zero-phase digital filtering) before the mean ICP was calculated.

Estimation of patient-independent distances. The distance between the auditory canal and HIP vein cannot be measured without invasive venous pressure via central venous catheter. In this study, the distance was therefore estimated as $(L_\text{heart} + L_\text{heart-HIP vein})$, where $L_\text{heart}$ was measured individually, and the distance $L_\text{heart-HIP vein}$ was approximated as equal for all patients. According to model III, segments of the venous system may collapse at higher tilt angles, and therefore some of the mean ICP values may not be appropriate for calculation of $L_\text{heart-HIP vein}$. Based on the expected locations of collapsed segments of veins at the neck and HIP vein at the diaphragm, as well as a normal $P_\text{HIP vein}$ (equal to supine CVP), the venous system was only assumed to be fully communicating at the lowest two tilt angles (0° and 12°). Thus the mean ICP values for the supine position and the 12° head-up tilt were used to calculate a group value of $L_\text{heart-HIP vein}$ according to:

\[L_{\text{heart-HIP vein}} = \frac{[\text{ICP}(0°) - \text{ICP}(12°)]}{\rho \cdot g \cdot \sin(12°)} - L_{\text{heart}}\]

using the group mean value of $L_{\text{heart}}$.

For model III, an estimate of $L_\text{collapse}$, i.e., the distance between the auditory canal and the top level of the collapsed segments of the veins, was also needed. The calculation was based on Eq. 7, which is only valid when the collapse has occurred (at $\alpha \geq \alpha_{\text{lim}}$). Using the same argument as above, only the five mean values of ICP not used in Eq. 10 (tilt angles of 27°–71°) were assumed to correspond to collapsed veins. The estimate of $L_\text{collapse}$ was thus determined by an iterative nonlinear curve fitting, based on a Levenberg-Marquardt least-squares algorithm (MATLAB’s “nlinfit” function), using these five mean values and the initial guess of 10 cm [4.5 mmHg as initial guess for $P_{\text{HIP vein}}$ (10)]. An approximated 95% confidence interval for $L_\text{collapse}$ was calculated based on the assumption of an asymptotic normal distribution for the $L_\text{collapse}$ estimate (MATLAB’s “nlparci” algorithm).

Prediction of ICP. Predicted ICP based on model I depended on patient-specific estimates of the distance between the auditory canal and HIP vein. The distances were calculated as:

\[L_{\text{HIP vein}} = \frac{[\text{ICP}(0°) - \text{ICP}(71°)]}{\rho \cdot g \cdot \sin(71°)}\]

The choice of using only the lowest and highest tilt angle for the estimation, rather than a regression based on all angles, was made as the original study suggesting the model measured only in the supine and seated position (17).

In model II, ICP was predicted using the estimated group value of $L_\text{heart-HIP vein}$ and the individually measured ICP(0°) and $L_\text{heart}$. In model III, ICP prediction also included the group estimate of $L_\text{collapse}$ and the individually estimated $P_{\text{HIP vein}}$. Patient-specific $P_{\text{HIP vein}}$ values were estimated by iterative nonlinear curve fitting of model III separately for each individual. This curve fitting was based on the Levenberg-Marquardt algorithm described earlier (with the same initial guesses). Individual confidence intervals were also estimated using the algorithm mentioned above. As a consequence of individual variation in $L_\text{heart}$ and $P_{\text{HIP vein}}$, $\alpha_{\text{lim}}$ was also patient specific (Eq. 9).

A sensitivity analysis was performed for models I and II based on simple derivation on Eqs. 2 and 4, respectively. For model III, sensitivity of the model to each parameter was analyzed separately.
Thus, since each parameter only affected the model below or above \( \alpha_{\text{lim}} \), in addition to the value of \( \alpha_{\text{lim}} \) (Eq. 9), Eqs. 6 and 7 could be treated separately.

**Statistics.** Each model was evaluated using an adjusted lack-of-fit test: the residuals for each individual were calculated as the difference between measured ICP and ICP predicted by each model, and one-way ANOVA was applied to all residuals, using tilt angle as the categorical factor. At every tilt angle, the group means and standard deviations (SD) were calculated for the predicted ICP of each model, as well as for measured ICP. One-way ANOVA was used to evaluate whether ICP was affected by tilt angle. Values of \( P < 0.05 \) were considered statistically significant. All statistical calculations were performed using PASW Statistics (version 18, SPSS, Chicago, IL).

**RESULTS**

ICP decreased significantly with tilt angle (ANOVA: \( P < 0.01 \)). Figure 2 and Table 1 show the group means for the measured and the predicted ICP of each of the three models with confidence intervals (Fig. 2) and SD (Table 1). Table 2 shows the estimated values of the model parameters and the measured values of \( L_{\text{heart}} \). The estimate of \( P_{\text{HIP CSF}} \), which is equivalent to CVP in the supine position, was \( 5.3 \pm 2.5 \) mmHg (model III, mean \( \pm \) SD). The confidence intervals for the individual \( P_{\text{HIP CSF}} \) estimates had a mean width of \( 2.1 \pm 0.8 \) mmHg (mean \( \pm \) SD). The estimate of \( L_{\text{collapse}} \) was \( 11.0 \) cm, with a confidence interval of \( \pm 2.0 \) cm.

The sensitivity analysis showed that ICP predicted by models I and II varied \(- \rho \cdot g \cdot \sin(\alpha) \) mmHg per 1 cm of increase in \( \rho \cdot g \cdot \sin(\alpha) \) mmHg per 1 cm of change in \( L_{\text{hip}} \) at tilt angles up to \( \alpha_{\text{lim}} \), with no change above \( \alpha_{\text{lim}} \). Conversely, predicted ICP varied \(- \rho \cdot g \cdot \sin(\alpha) \) mmHg per 1 cm of change in \( L_{\text{collapse}} \) at \( \alpha \geq \alpha_{\text{lim}} \) but not at all below \( \alpha_{\text{lim}} \). Predicted ICP also varied \(- 1 \) mmHg with every 1-mmHg change in \( P_{\text{HIP CSF}} \) at \( \alpha \geq \alpha_{\text{lim}} \) but not at all at \( \alpha < \alpha_{\text{lim}} \). The angle \( \alpha_{\text{lim}} \) varied nonlinearly with all three parameters. For a variation around the mean value, the change in \( \alpha_{\text{lim}} \) corresponded to approximately \(-1^\circ \) per 1 cm of change in \( L_{\text{hip}} \) or \( L_{\text{collapse}} \), and \(+3.5^\circ \) per 1 mmHg of change in \( P_{\text{HIP CSF}} \).

**DISCUSSION**

By proposing and evaluating a model that combined two well established physiological observations (Davson’s equation and the collapse of the jugular veins in upright positions), this study provided a new description of postural and gravita-

---

**Table 2. Estimated values of model parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ( \pm ) SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>( L_{\text{HIP CSF}} ), cm</td>
<td>18.4 ( \pm ) 4.7</td>
<td>10.6–27.2</td>
</tr>
<tr>
<td>( L_{\text{heart}} ), cm</td>
<td>24.9 ( \pm ) 2.5</td>
<td>19–29</td>
</tr>
<tr>
<td>( L_{\text{heart}} + L_{\text{HIP CSF}} ), cm</td>
<td>33.8 ( \pm ) 2.5</td>
<td>28.0–38.0</td>
</tr>
<tr>
<td>( L_{\text{collapse}} ), cm</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>( P_{\text{HIP CSF}} ), mmHg</td>
<td>5.3 ( \pm ) 2.5</td>
<td>0.7–10.1</td>
</tr>
<tr>
<td>( \alpha_{\text{lim}} ), degrees</td>
<td>19 ( \pm ) 10</td>
<td>3–41</td>
</tr>
</tbody>
</table>

---

**Fig. 2.** Mean values with confidence intervals (of the mean) at each tilt angle for measured ICP (filled squares) and simulated ICP of model I (circles), model II (diamonds), and model III (shaded triangles).
tional effects on ICP. The results showed the feasibility of the hypothesis that Davson’s equation, which includes dural venous sinus pressure, governs ICP at all body positions. The study also supported that, during changes in body position, this dural venous sinus pressure was influenced by hydrostatic pressure gradients and was significantly altered by effects of the collapse of the jugular veins.

In a study measuring subinuim pressure during neurosurgery, the pressure was found to decrease ~13.7 mmHg (18.6 cmH2O) when the patient was moved from a supine to a seated position (90°) (14). This is very similar to the ICP decrease of 12.8 mmHg identified in this study and to the Pa reduction estimated by model III (Table 1). Model III was further supported by the estimated values of HIPvein, P HIPvein, and L collapse (Table 2). P HIPvein was considered equal to CVP in the supine position, and all estimated values were reasonable in relation to normal CVP (10). The estimated average location of HIPvein at ~9 cm below the middle of the sternum was in agreement with the published reference level for adults, which places HIPvein slightly below the highest point of the diaphragm (11). L collapse suggested that the top of the collapsed venous segments was located 11 cm below the auditory canal and thus at the level of the neck, which is in accordance with the established observation of where the jugular veins collapse in upright positions (5, 12, 21). This is also approximately at the level where the jugular venous valves are located (22), indicating that they can be a critical point for the collapsing jugulars.

Studies have shown that venous outflow from the brain is dominated by the internal jugular veins in the supine position, whereas a major part of the outflow is redirected to the vertebral veins in upright positions (1, 21). Potentially, the hydrostatic pressure gradient should then not be altered by the collapse of the jugular veins. The model based on Davson’s equation without effects from collapsed veins (model II) predicted an average decrease of ICP and Pa of 23.6 mmHg compared with the measured 12.8 mmHg (Fig. 2). Model II thus severely underestimated ICP at higher tilt angles and consequently ICP predictions based solely on the hydrostatic compensation related to HIPvein could not be used. If the dominant path the blood flow takes is altered in upright positions, the higher resistance to venous flow in these pathways may cause an increase in the nonhydrostatic (i.e., resistive) pressure drop from the intracranial veins to the heart. However, we believe that the jugular veins still control the intracranial venous pressure because it was previously demonstrated that the shift of flow from the jugular veins to alternate routes was gradual (21). Continued but diminishing flow through the jugular veins implies that the collapsible venous segments alternates between open and closed and that pressure at this segment thus fluctuates around zero. If this is the case, the top of the collapsed segment remains the reference level for upstream venous pressure, independent of other flow pathways, and the interpretation of model III holds. If all venous flow passed through alternate vessels, model III would be invalid, but this is not supported by the experimental data.

The Magnæs model (model I) based on a hydrostatic indifference concept of the CSF system overestimated ICP at all tilt angles not used to determine HIPCSF, thus implying that a single hydrostatic indifference level cannot be determined for the CSF system for changes in upper body tilt angle. According to the hydrostatic indifference concept, the change in ICP should be a sinusoidal function of the angle of the upper body (Eq. 5). This sinusoidal shape did not fit the ICP data measured in this study. Since the sensitivity analysis demonstrated the ICP predicted by model I at each tilt angle varies linearly with a change in L HIPCSF and thus regardless of the specific value of this distance, predicted ICP would still be a sinusoidal function of tilt angle. Even though the location of HIPCSF estimated in this study was consistent with that of the Magnæs study (17), the lack-of-fit analysis demonstrated that the model did not accurately describe the gravitational effects on ICP and that the concept of a hydrostatic indifference point for the CSF system was not valid.

Models II and III neglect the resistance-related pressure drop from the dural venous sinuses (Eqs. 3 and 5) and veins in the neck (Eq. 9) to the veins at HIPvein. The rationale for this is that these pressure differences should be relatively small and independent of tilt angle as long as the venous system is communicating. The exception is for α = αlim in model III, where the resistive pressure drop from the dural venous sinuses may change with the collapse of certain segments of the veins, but in this case Pa is no longer considered to relate to P HIPvein, and thus this pressure drop is irrelevant.

A limitation of this study was that no measurements of the diameter, pressure, or flow in the jugular veins were performed even though the interpretation of model III is based on the collapse of these veins. The model was, however, designed to include a change in hydrostatic gradients related to venous collapse at an arbitrary location, and the excellent match of the estimated location to previous experimental data on collapsing jugular veins supports the feasibility of the interpretation. Furthermore, the model without effects of collapsed veins performed poorly, suggesting that neglecting these effects was not viable. A future study evaluating model III using both ICP measurements and ultrasonic measurements of flow and diameter of the jugular veins has also been planned.

The estimations of L collapse and L heart-HIPvein could have been performed for each patient, since these distances are likely patient-specific. However, the variation between individuals is likely to be relatively small and approximately normally distributed. In accordance with the sensitivity analysis, the ICP predicted by model III at any specific angle varies linearly with these distances either below αlim (L heart-HIPvein) or above it (L collapse), as long as P HIPvein is held constant. The ICP values resulting from individual variation in these distances would then be distributed around the presented ICP values in the same fashion as the individual distances were distributed around the group estimates. The mean ICP values would thus be very similar, and the residuals should remain independent of tilt angle, although the ranges of the residuals would change. If the P HIPvein values were allowed to vary, these values would compensate for changes in L collapse and the range of residuals would likely decrease. However, assuming these distances were patient independent increased the degrees of freedom for patient-specific prediction in model III decreased, and the risk of falsely good individual prediction due to overfitting.

The age and suspected NPH status of the study population may have an effect on some of the model parameters of this study. Vessel compliance may be altered, which could in turn affect P HIPvein the location of HIPvein, and L collapse. Thus the specific parameter values estimated in this study may not be
applicable for a general population, but the model evaluations are unlikely to be affected by the current population characteristics. It is crucial that the patients did not suffer from noncommunicating hydrocephalus, which would have affected both the ICP measurements and the determination of hydrostatic gradients within the system.

It is not surprising that the combined model (model III) produced good results. Davson’s equation (6–8) is one of the fundamental assumptions used in CSF dynamic studies, and as such regarded as an axiom when ICP is analyzed in infusion investigations (2, 4, 9). Infusion studies have been performed almost exclusively in supine or recumbent position, however, with the dural venous sinus pressure regarded as constant and therefore not in focus. For the cardiovascular physiologist, it has been equally accepted that venous pressure has a hydrostatic indiffERENCE point just below the heart and that, when the body is in upright position, the jugular veins will collapse (5, 12, 21), which disconnects the hydrostatic pressure coupling of the cranial venous system from the central venous system (13). Since the CSF and venous systems historically have been studied for purposes related to different research fields and with different postures, they have, to our knowledge, not previously been linked together to explain ICP behavior in relation to posture. Having done so in this study, with promising results, offers potential insight into conditions with CSF dynamic disturbances and may improve basic physiological understanding of the cerebral circulation. Patients with NPH or idiopathic intracranial hypertension spend most of their time in an upright position, but their pathophysiology is investigated in the supine position. This study shows that, in the future, it is feasible to conduct and interpret results from investigations of CSF dynamics in an upright position, which may help to identify pathophysiological aspects, which are overlooked with the present investigational conventions. The presented description of the postural effects on ICP also has implications for the design of CSF shunts and anti-siphon devices, which are used to compensate for such effects, as well as for research into the effects of space flight and related conditions such as the Visual Impairment Intracranial Pressure (VIIP) syndrome, where postural effects are absent due to the lack of gravitational field.

This study showed that postural changes in ICP could not be predicted based on a hydrostatic indiffERENCE point for the CSF system. However, prediction based on hydrostatic pressure gradients in the venous system was feasible if the formation of a separate hydrostatic compartment above collapsed veins in the neck was included at higher tilt angles. The effects of changes in body position in relation to the gravitational field could thus be included in a mathematical model of ICP, which can be used as a basis for future research into connections between gravity, or the lack of gravity, and different aspects of CSF pathology.

ACKNOWLEDGMENTS
We thank Tomas Bäcklund for valuable assistance with the measurement setup.

GRANTS
This project was financed by the Swedish Research Council, VINNOVA, and the Swedish Foundation for Strategic Research through their common initiative: “Biomedical engineering for improved health” (grant no. VR3011-2006-7551); the Swedish Research Council (grant no. 221-2011-5216); and the European Union through ERDF: Objective 2, Northern Sweden (grant no. 158715-CMTF).

DISCLOSURES
Professor Malm, Professor Eklund, and Dr. Sundström are listed as inventors on a patent re: CSF dynamic investigation apparatus, for which they have received royalties from Likvor. Professor Eklund has received honorary for lecturing from DePuy.

AUTHOR CONTRIBUTIONS
Author contributions: S.Q., N.S., J.M., and A.E. conception and design of research; S.Q. and N.S. performed experiments; S.Q. and A.E. analyzed data; S.Q. and A.E. interpreted results of experiments; S.Q. prepared figures; S.Q. drafted manuscript; S.Q., N.S., J.M., and A.E. edited and revised manuscript; S.Q., N.S., J.M., and A.E. approved final version of manuscript.

REFERENCES

