Influence of Lumbosacral Cerebrospinal Fluid Density, Velocity, and Volume on Extent and Duration of Plain Bupivacaine Spinal Anesthesia

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Background: **The current study was designed to investigate the influence of lumbosacral cerebrospinal fluid (CSF) density, velocity, and volume on the extent and duration of plain bupivacaine spinal anesthesia.**

Methods: **Forty-one patients scheduled to undergo orthopedic surgery with spinal block were enrolled. Lumbosacral CSF volumes were calculated from low thoracic, lumbar, and sacral axial magnetic resonance images. CSF velocity at the L3–L4 level was derived from phase-contrast magnetic resonance images. Spinal anesthesia was performed in the lateral decubitus position. CSF (2 ml) was sampled to measure CSF density before injection of 3 ml plain bupivacaine (0.5%). Statistical correlation coefficients (ρ) between CSF characteristics and measurements of spinal anesthesia were assessed by Spearman rank correlation. In addition, stepwise multiple linear regression models were used to select important predictors of measures of spinal anesthesia.**

Results: **There was a significant correlation between CSF density and peak sensory block level (ρ = 0.33, P = 0.034). Lumbosacral CSF volume inversely correlated with peak sensory block level (ρ = −0.65, P < 0.0001) and positively correlated with onset time of complete motor block (ρ = 0.42, P = 0.008). CSF volume also inversely correlated with time required for regression of the sensory block to L1 (ρ = −0.35, P = 0.026) and L2 (ρ = −0.33, P = 0.039). There was a significant inverse correlation between peak diastolic CSF velocity and duration of motor blockade (ρ = −0.44, P = 0.005). Multiple regression analysis revealed that weight and CSF volume significantly contributed to the peak sensory block level (R² = 0.46).**

Conclusions: **These findings indicate that CSF density and volume influence the spread of spinal anesthesia with plain bupivacaine and that CSF volume also influences the duration of spinal anesthesia. CSF velocity might also influence the duration of plain bupivacaine spinal anesthesia.**

SUBARACHNOID injection of local anesthetic solution, especially plain spinal anesthetic solution, produces anesthesia of unpredictable extent and duration.[1,2] At least 25 factors are thought to influence the spread of spinal anesthesia.[2] Assuming that the cerebrospinal fluid (CSF) is the diluent for drugs delivered by the subarachnoid route, the physical characteristics of CSF, such as volume and density, are among these 25 factors governing the distribution of local anesthetic solutions in the subarachnoid space.[2] For example, Carpenter *et al.*[3] reported a correlation between lumbosacral CSF volume and peak sensory block level of hyperbaric lidocaine (r = −0.91 by linear regression analysis) using magnetic resonance imaging (MRI). In addition, Schiffer *et al.*[4] recently reported that CSF density is an important factor influencing the peak sensory block level of plain bupivacaine spinal anesthesia. However, the correlation between CSF density and the peak sensory block level of plain bupivacaine is not predictive (R² = 0.37 by multiple regression analysis). Therefore, Schiffer *et al.*[4] speculated that lumbosacral CSF volume is another important factor influencing subarachnoid distribution of plain bupivacaine, although a significant relation between lumbosacral CSF volume and the extent of sensory block by plain bupivacaine remains to be demonstrated.

In addition to the measurement of CSF volume by MRI, other important considerations include the recent observation on MRI that CSF is not static but vigorously oscillates with arterial pulsations.[5–9] These wave-like movements might be another important factor in the distribution and clearance of spinal agents.[2,10] To date, however, there is no information on the relation between lumbosacral CSF volume or velocity and the spread and duration of plain bupivacaine anesthesia. The current study was designed to investigate the influence of lumbosacral CSF density, velocity, and volume on the block spread and duration of plain bupivacaine spinal anesthesia.

Materials and Methods

The current study was conducted at the Self Defense Force Hanshin Hospital in Hyogo, Japan, and was approved by the Hospital Ethics Committee. Written informed consent was obtained from each patient before participation in the study. There were 41 patients with American Society of Anesthesiologists physical status class I who were scheduled to undergo orthopedic lower limb surgery with a thigh tourniquet and plain bupivacaine spinal anesthesia. Apart from the usual contraindications to spinal anesthesia, patients with obvious spinal postural abnormalities (kyphosis) or neurologic disturbances were excluded from the study.

Low thoracic and lumbosacral axial MRIs for the measurement of CSF volume and velocity were obtained using an MRI system (Excel Art; Toshiba, Tokyo, Japan) operating at 1.5 T. Posterior–anterior lumbar spine radiographs were used for the identification of the spinal
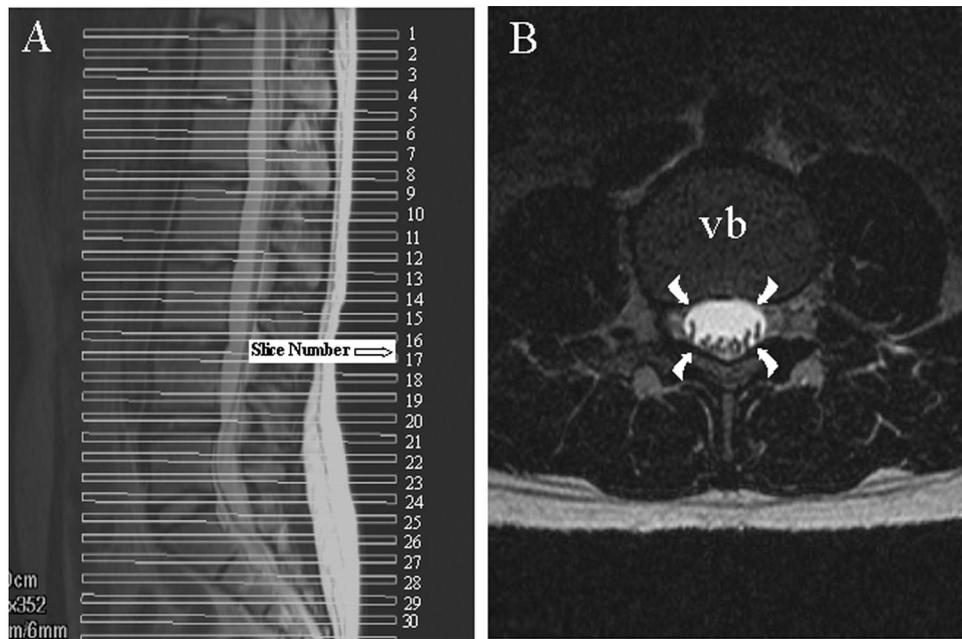
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Fig. 1. Examples of magnetic resonance images used to determine cerebrospinal fluid volume. (*A*) Sagittal scout image showing levels of axial images. (*B*) Axial image at the L2 level (*slice 15* in *A*) showing bright cerebrospinal fluid containing nerve roots observed as *gray defects*. The area enclosed by the perimeter of the cerebrospinal fluid (*arrows*) is measured to determine the dural sac volume. Cord volume (none shown at this level) is subtracted to determine the volume of cerebrospinal fluid and roots. The dural area at this level was 2.44 cm². (Orientation is anterior up.) vb = vertebral body.

level, marking the intersection of a line joining the iliac crests. MRIs and radiographs were obtained a few days before anesthesia. Low thoracic, lumbar, and spinal axial MRIs were obtained at 8-mm increments with a fast-spin echo sequence, which highlights CSF, using the modified method reported by Hogan *et al.*[11] Briefly, technical specifications included a 10,000-ms repetition time, a 160-ms echo time, a 15-cm field of view, a 160×256-image matrix, and 3-mm slices at 5-mm intervals. The dural sac and spinal cord areas were determined by a radiologist (J. H.), who was blinded to the purpose of this study, for each image using a digital analysis system that came equipped with the MRI system. The area of the sac minus the area of the cord constituted the area of the CSF and roots; this area multiplied by 8 mm resulted in the CSF/root volume. The level of the disk between the eleventh and twelfth thoracic vertebrae was determined, and the CSF/root volume was measured caudal from this site. Although this calculated volume includes the roots, it is hereafter referred to as the CSF volume (fig. 1, A and B).

Measurements of CSF velocity at the L3–L4 level were derived from phase-contrast MRI by scans oriented approximately perpendicular to the CSF direction of flow, using the modified method reported by Greitz *et al.*[5] Briefly, technical specifications included a 30-ms repetition time, a 16-ms echo time, a 128×256-image matrix, and 5-mm slices (fig. 2A). Electrocardiography triggering was used for prospective gating of the acquisition. Cardiac gating produced a series of phase-contrast images at different cardiac phases. The CSF velocity (CSFV) profile at this site shows systolic ($CSFV_{systolic}$) and diastolic

($CSFV_{diastolic}$) components. From these phase-contrast images, a blinded investigator (J. H.) measured peak $CSFV_{systolic}$, $CSFV_{diastolic}$, and average CSFV at the L3–L4 level (fig. 2, B and C).

Thirty minutes before transfer to the operating room, all patients received an intramuscular injection of atropine (0.5 mg). After placement of standard noninvasive
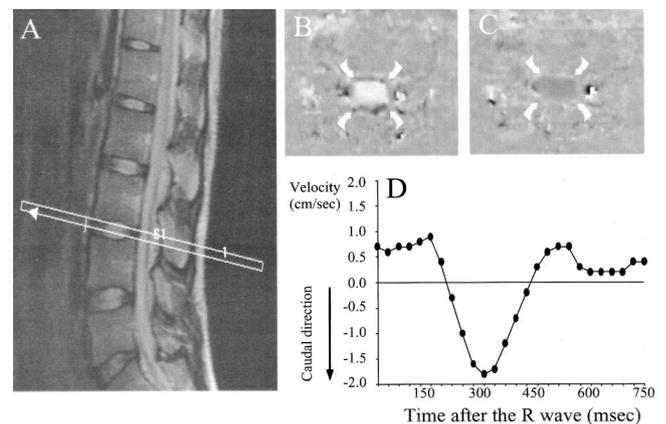
Fig. 2. Examples of magnetic resonance images used to determine cerebrospinal fluid (CSF) velocity and CSF velocity wave form during the cardiac cycle. (*A*) The examination of the plane for the phase-contrast magnetic resonance images perpendicular to the CSF flow direction at the L3–L4 level is indicated on the scout image. (*B* and *C*) Axial images of caudally and cephalad-directed CSF flows at the L3–L4 level. Bright (*arrow*) indicates caudally directed CSF flows (*B*), and dark (*arrow*) indicates cephalad-directed CSF flows (*C*). (*D*) The graph represents CSF velocity (cm/s) after the R wave. The negative deflections represent caudal systolic CSF flow, and the positive deflections represent cephalad diastolic CSF flow.

monitoring devices, a lumbar puncture was performed using a 25-gauge pencil-type needle (Pencan®; B Braun, Tokyo, Japan) at the L3–L4 level, with the patient in the lateral decubitus position with the operated side up. The L3–L4 level interspace was identified by counting the spines of the vertebrae and palpation of the iliac crest. After obtaining free CSF reflux, 2 ml CSF was sampled, immediately stored in closed tubes to avoid evaporation, and frozen at −80°C. Spinal injection of 3 ml (15 mg) plain bupivacaine, 0.5% (4-ml vial, 0.5% Marcaine®; AstraZeneca, Osaka, Japan), with the needle aperture directed toward the nondependent (operated) side was then performed over 15 s, and the patient was immediately turned to the supine position and remained horizontal until the end of the operation. The extent of the sensory block was assessed by pinprick (23-gauge) on the skin on the midline from top to bottom of the body up to T12 and on the nondependent side thereafter. For practical reasons, motor block was only evaluated on the nonoperated side by the previously described modified Bromage scale (0 = able to move hip, knee, ankle, and toes; 1 = unable to move hip, able to move knee, ankle, and toes; 2 = unable to move hip and knee, able to move ankle and toes; 3 = unable to move hip, knee, and ankle, able to move toes; 4 = unable to move hip, knee, ankle, and toes).[4] Hemodynamic data (mean arterial pressure, heart rate) were also recorded. Data sampling was performed every 5 min for the first 30 min after spinal injection and then every 15 min until the end of the observation period, which was defined as regression of the sensory block level to L5. After complete motor block was obtained, patients were encouraged to urinate every 15 min. Time to urinate was recorded. These data were recorded by the nurses of the operating room and the orthopedic ward in charge of the patient, who were unaware of the purpose of the study, and who were instructed to accurately report the sensory block level and the degree of the motor block. Acetated Ringer's solution, 5 ml/kg, was administered at 1 h before spinal anesthesia, and $1 \cdot kg^{-1} \cdot h^{-1}$ was administered during and after anesthesia. Ephedrine (5 mg) was administered intravenously when mean arterial pressure decreased by more than 30% of the baseline value. A decrease in heart rate to less than 45 beats/min was treated with 0.5 mg intravenous atropine. The relation between peak sensory block level and maximal decrease in mean arterial pressure during the 60 min after spinal injection was calculated.

Cerebrospinal fluid density with a resolution of up to four digits at 37°C was measured using a volumetric method.[12] All samples were warmed to 37.0°C in a water bath before weight measurements with an electronic balance, Ribror R AEU-210 (Shimadzu, Tokyo, Japan). These measurements were performed in triplicate for each sample, and mean values were calculated. The limit of detection of the balance used in this study was 0.0001 g/ml.

The patient sample size of the current study was determined by power analysis ($\alpha = 0.05$, $\beta = 0.20$) to reveal a significant correlation coefficient. Power analysis indicated that 37 patients were required to obtain a significant correlation coefficient, assuming that the two variables were continuous data and the correlation coefficient between the CSF volume and onset time of complete motor block was 0.45, which was based on a preliminary study. Continuous data were expressed as mean ± SD, and discrete data were expressed as medians with ranges. Statistical correlation coefficients (ρ) were assessed by Spearman rank correlation among the CSF variables such as volume and density; peak sensory block level to pin prick; time until development of peak sensory level to pin prick and complete motor block; time required for peak sensory block level to regress across two segments; time required for pin prick analgesia to regress to the L1, L2, L3, L4, and L5 dermatomes; time until complete motor recovery; time until spontaneous voiding; and maximal decrease in mean arterial pressure. A P value of less than 0.05 was considered significant. In addition, multiple linear regression analysis was used to examine the relative importance of patient and CSF variables to the aforementioned measures of spinal anesthesia. Age, height, weight, body mass index (BMI), CSF density, CSF volume, peak $CSFV_{systolic}$, $CSFV_{diastolic}$, and average CSFV were considered independent variables. Multicolinearity among the variables can hinder the interpretation of results; therefore, forward and backward stepwise selections were used to identify the independently associated variables. For adding and deleting variables, the F ratio criterion was 4.0, which is the squared value obtained from a t test for the hypothesis that the coefficient of the variable in question equals zero.[13]

Results

Demographic and CSF characteristics of all patients are presented in table 1. The volume of lumbosacral CSF ranged from 20.5 to 61.6 ml. Although the CSF velocity profile in the lumbar spine at the L3–L4 level was more irregular than previously reported in the cervical and thoracic region,[5–9] the systolic and diastolic components are still shown (fig. 2D). The caudal systolic flows started at 90–420 ms. The caudal systolic and cephalad diastolic velocities varied from 0 to 2.7 cm/s and 0.1 to 1.6 cm/s, respectively. The average CSF velocity was 0.1 cm/s, which was caudally directed.

None of the patients needed general anesthesia or adjuvant anesthesia as a result of unsuccessful spinal anesthesia. All patients developed complete motor block on the nonoperated side. No patient required urinary catheterization for urinary retention. Only one patient was given intravenous ephedrine (10 mg) because of a

Table 1. Patient Demographics and CSF Characteristics

| | Age, yr | Height, cm | Weight, kg | BMI, kg/m^2 | CSF Density, g/ml | CSF Volume, ml | CSF Velocity (cm/sec)* | | |
							Peak Systolic Velocity	Peak Diastolic Velocity	Average Velocity
Mean ± SD	30 ± 10	170 ± 7	67 ± 9	23 ± 3	1.0005 ± 0.0002	41.7 ± 9.3	−1.1 ± 0.6	0.8 ± 0.4	−0.1 ± 0.2

* The negative values represent caudal systolic cerebrospinal fluid (CSF) flow, and the positive values represent cephalad diastolic CSF flow.
BMI = body mass index.

decrease in mean arterial pressure of more than 30% from the baseline value. The main spinal anesthetic and hemodynamic data are summarized in table 2.

Correlations between the values of CSF characteristics and the measures of spinal anesthesia, and among the measures of spinal anesthesia, assessed by Spearman rank correlation, are presented in table 3. There was a positive correlation between CSF density and peak sensory block level ($\rho = 0.33$, $P = 0.034$; fig. 3A). There was no correlation between CSF density and other measures of spinal anesthesia (table 3). Lumbosacral CSF volumes inversely correlated with the peak sensory block level ($\rho = -0.65$, $P < 0.0001$; fig. 3B) and positively correlated with the onset of motor block ($\rho = 0.42$, $P = 0.008$; fig. 4A). There was no significant correlation between peak CSFV$_{systolic}$ and measures of sensory and motor anesthesia. Average CSFV correlated with onset of complete motor block ($\rho = 0.38$, $P = 0.015$; fig. 4B). There was a significant inverse correlation between peak CSFV$_{diastolic}$ and the duration of motor blockade ($\rho = -0.44$, $P = 0.005$; fig. 5).

Cerebrospinal fluid volume positively correlated with time required for the sensory level to regress from the peak block level across two segments ($\rho = 0.31$, $P = 0.048$; fig. 6A), whereas CSF volume inversely correlated with regression to L1 ($\rho = -0.35$, $P = 0.026$; fig. 6B), regression to L2 ($\rho = -0.33$, $P = 0.033$; fig. 6C), and time to spontaneous voiding ($\rho = -0.41$, $P = 0.010$; table 3). There were significant inverse correlations between peak sensory block level and onset time of the sensory block ($\rho = 0.35$, $P = 0.029$) and between peak level and onset of the motor block ($\rho = 0.44$, $P = 0.006$; table 3). Peak sensory block level inversely correlated

Table 2. Main Anesthetic and Hemodynamic Data

Peak sensory block level	T7 (T2–T12)
Onset time of peak sensory block level, min	45 (15–75)
Onset time of complete motor block, min	25 (10–60)
Time to two segments' regression from peak sensory block level, min	135 (60–210)
Time to regression to L1, min	210 (150–270)
Time to regression to L5, min	360 (285–465)
Duration of motor block, min	285 (180–375)
Time to spontaneous voiding, min	440 (240–620)
Maximal decrease in mean arterial pressure, % of baseline value	88 ± 7

Values are median with range in parentheses or mean ± SD. n = 41.

with time required for the sensory block level to regress from the peak block level across two segments ($\rho = 0.56$, $P = 0.0004$; fig. 6D and table 3) and the decrease in mean arterial pressure from baseline ($\rho = 0.43$, $P = 0.007$; table 3). In contrast, the peak sensory block level positively correlated with BMI ($\rho = -0.33$, $P = 0.035$) and time required for regression to L1 ($\rho = -0.53$, $P = 0.001$; fig. 6E), L2 ($\rho = -0.56$, $P = 0.0004$; fig. 6F), and L3 ($\rho = -0.49$, $P = 0.002$; table 3). Average CSFV correlated with regression to L1 ($\rho = -0.32$, $P = 0.045$) and L2 ($\rho = -0.33$, $P = 0.038$; table 3).

There was no significant multiple linear regression coefficient between each variable and the time of regression to L3 and L4 as dependent variables. The significant multiple linear regression coefficients are shown in table 4. Multiple regression analysis revealed that weight and CSF volume significantly contributed to the peak sensory block level (predicted peak sensory block level = $4.48 - 0.08 \times$ weight $+ 0.18 \times$ CSF volume; $R^2 = 0.46$, $P < 0.0001$; table 4). CSF volume was the only significant predictive variable for time to spontaneous voiding ($R^2 = 0.15$, $P = 0.007$). BMI and peak CSFV$_{systolic}$ were significant predictive variables for the time required for the sensory block level to regress from the peak block level across two segments ($R^2 = 0.29$, $P = 0.001$). BMI and average CSFV were significant predictive variables for the time required for the regression of the block to L2 ($R^2 = 0.15$, $P = 0.016$) and for the complete motor block onset time ($R^2 = 0.29$, $P = 0.001$). BMI was the only significant predictive variable for onset time of the sensory block ($R^2 = 0.30$, $P = 0.001$) and for the decrease in mean arterial pressure ($R^2 = 0.25$, $P = 0.001$). Peak CSFV$_{diastolic}$ was the only significant predictive variable for the duration of motor block ($R^2 = 0.23$, $P = 0.001$). Although average CSFV and peak CSFV$_{diastolic}$ were the only significant predictive variables for the time required for regression of the block to L1 and L2, respectively, each R^2 was quite low (table 4).

Discussion

Many studies have investigated the factors that influence the extent of plain local anesthetic solutions because of the inability to predict the peak sensory block level of spinal anesthesia with plain anesthetic solutions.

Table 3. Correlations between CSF Characteristics and Measures of Spinal Anesthesia

	P Value of Correlation*					
	CSF Density	CSF Volume	Peak CSFV$_{systolic}$	Peak CSFV$_{diastolic}$	Average CSFV	Peak Sensory Block Level
Patient characteristics						
Age	0.219	0.245	0.310	0.612	0.965	0.740
Height	0.899	0.065	0.161	0.628	0.581	0.592
Weight	0.489	0.934	0.115	0.794	0.771	0.100
Body mass index	0.297	0.206	0.267	0.995	0.997	0.035
Measures of spinal anesthesia						
Peak sensory block level	0.034	<0.0001	0.923	0.510	0.587	
Onset time of peak sensory block level	0.161	0.924	0.417	0.568	0.971	0.029
Onset time of complete motor block	0.092	0.008	0.246	0.897	0.015	0.006
Time to two segments' regression from peak sensory block level	0.194	0.048	0.471	0.537	0.769	0.0004
Time to regression to L1	0.236	0.026	0.749	0.419	0.045	0.001
Time to regression to L2	0.107	0.039	0.674	0.470	0.038	0.0004
Time to regression to L3	0.128	0.105	0.708	0.814	0.103	0.002
Time to regression to L4	0.850	0.899	0.936	0.130	0.142	0.185
Time to regression to L5	0.737	0.554	0.243	0.087	0.910	0.644
Duration of motor block	0.947	0.697	0.081	0.010	0.805	0.614
Time to spontaneous voiding	0.636	0.010	0.533	0.256	0.803	0.117
Maximal decrease in mean arterial pressure, % of baseline value	0.772	0.352	0.643	0.855	0.539	0.007

* Values were determined by Spearman rank correlation.

CSF = cerebrospinal fluid, CSFV = cerebrospinal fluid velocity.

These studies reported that dose of local anesthetics,[14,15] orientation of spinal needle aperture,[16] or site of injection influence the extent of plain local anesthetics,[17] whereas speed of injection[18] or patient demographic data[19] did not. In the current study, we injected an identical dose of plain bupivacaine with the needle aperture directed toward the nondependent (operated) side. Therefore, it is unlikely that the dose, site of injection, or technique influenced the results of the current study.

The lumbosacral CSF volume in the current study, 41.7 ml, was comparable with that obtained in previous studies, 36.3–53.7 ml.[3,20] The MRI technique used in this study (3-mm-thick slices, two-dimensional fast-spin echo) was similar to that described by Hogan *et al.*[11] Although this method was validated in a previous study

by measurement of known volumes and reliable duplication with repeated measurement,[11] Lee *et al.*[20] recently reported a new method using three-dimensional fast-spin echo, in which slice spatial resolution (1-mm sagittal partitions) was improved. Although the CSF volume measured by these MRI techniques included the cauda equina, this contributes to only approximately 15% of the total volume of the dural sac at this level.[21]

After spinal anesthetic solution is injected in the CSF, the dilution of spinal anesthetic solutions by CSF occurs before arrival at effect sites in the central nervous system. Consistent with the results obtained by Carpenter *et al.*,[3] who demonstrated a strong relation between CSF volume and peak sensory block level after the administration of hyperbaric lidocaine ($r = -0.91$), there was a
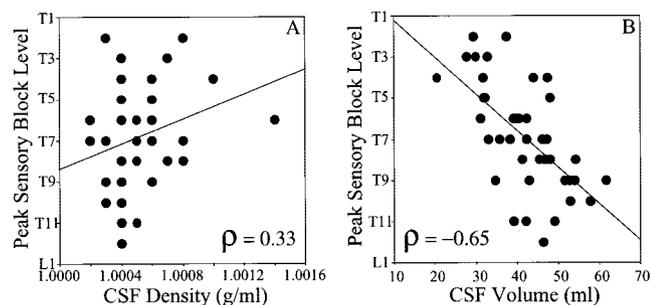

Fig. 3. (*A*) Correlation between cerebrospinal fluid (CSF) density and peak sensory block level ($\rho = 0.33$, $P = 0.034$). (*B*) Inverse correlation between CSF volume and peak sensory block level ($\rho = -0.65$, $P < 0.0001$). Although correlation coefficients (ρ) and *P* values were calculated using Spearman rank correlation, the linear regression lines are presented in these graphs.
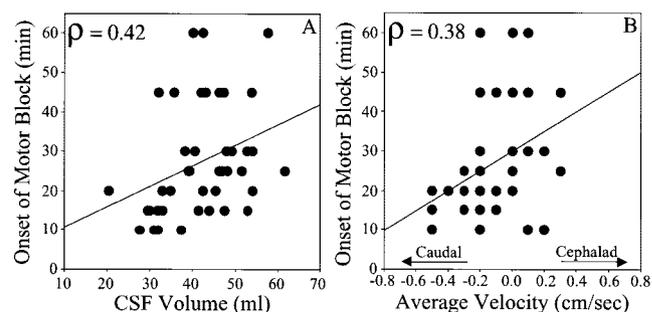

Fig. 4. (*A*) Correlation between onset of complete motor blockade and cerebrospinal fluid (CSF) volume ($\rho = 0.42$, $P = 0.008$). (*B*) Correlation between onset of complete motor blockade and average CSF velocity ($\rho = 0.38$, $P = 0.015$). Although correlation coefficients (ρ) and *P* values were calculated using Spearman rank correlation, the linear regression lines are presented in these graphs.
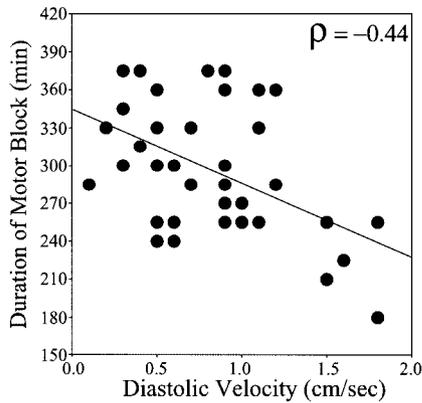
Fig. 5. Inverse correlation between peak diastolic cerebrospinal fluid velocity and the duration of motor blockage ($\rho = -0.44$, $P = 0.005$). Although the correlation coefficient (ρ) and P value were calculated using Spearman rank correlation, the linear regression line is presented in this graph.

significant relation between CSF volume and the peak sensory block level in the current study ($\rho = -0.65$, $P < 0.0001$). In addition, CSF volume correlated with the onset time of the motor blockade, which is not consistent with the findings of Carpenter *et al.*[3] These results suggest that CSF volume is the important factor influencing the extent of plain bupivacaine. Further, it is also generally believed that after dilution occurs, the distribution of hyperbaric solutions away from the site of injection is governed mainly by the effects of gravity, whereas plain solutions are not.[2] The results of the current study confirmed those of the Schiffer *et al.*,[4] who reported that higher densities are associated with a higher cephalad level. Taken together with the results of CSF volume, the current study indicated that the lower the CSF volume is and the higher the CSF density is, the higher the peak sensory block levels for plain bupivacaine solutions are.

After an intrathecal injection of a local anesthetic, plain local anesthetic is more likely to remain where it was injected, and a concentration gradient develops with a progressive decrease in anesthetic concentration away from the injection site.[22] Therefore, more cephalad afferent nerves within the thecal sac would encounter increasingly dilute concentrations of plain bupivacaine, resulting in an earlier ebb of the peak sensory level. Indeed, the time required for the sensory block level to regress from the peak block level across two segments inversely correlated with the peak sensory level in the current study, *i.e.*, the higher the level of the spinal block is, the shorter time to regress across two segments is. On the other hand, in the lumbar region where local anesthetic remains, the local anesthetic would be more diluted by a larger lumbosacral CSF volume, resulting in a shorter duration of lumbar sensory anesthesia. The results of previous studies by Carpenter *et al.*[3] and Urmey *et al.*[16] can be explained by this mechanism. Carpenter *et al.*[3] demonstrated that the lower peak sensory block levels are and the greater the CSF volume is, the shorter the duration of tolerance of transcutaneous electronic stimulation at the ankle (L5–S1) is. Urmey *et al.*[16] reported that orientating the aperture of the needle directly caudally prolonged the duration of sensory anesthesia and motor block and time to urinate. They speculated that this prolongation is due to a greater amount of the local anesthetic being concentrated near the lower lumbar and sacral nerve roots where the injection is directed caudally. We demonstrated that the lower sensory block level is associated with a greater CSF volume and less time required for regression to L1–L3, and CSF volume inversely correlates with the regression of the block to L1 and L2 and time to spontaneous voiding. Therefore, this mechanism might explain the recovery profile of the current study. The lack

Fig. 6. (*A*) Correlation between cerebrospinal fluid (CSF) volume and time of two segments' regression from peak sensory level ($\rho = 0.31$, $P = 0.048$). (*B*) Inverse correlation between CSF volume and time of regression to L1 ($\rho = -0.35$, $P = 0.026$). (*C*) Inverse correlation between CSF volume and time of regression to L2 ($\rho = -0.33$, $P = 0.033$). (*D*) Inverse correlation between peak sensory block level and time of two segments' regression from peak sensory block level ($\rho = 0.56$, $P = 0.0004$). (*E*) Correlation between peak sensory block level and time of regression to L1 ($\rho = -0.53$, $P = 0.001$). (*F*) Correlation between peak sensory block level and time of regression to L2 ($\rho = -0.56$, $P = 0.001$). Although correlation coefficients (ρ) and P values were calculated using Spearman rank correlation, the linear regression lines are presented in these graphs.
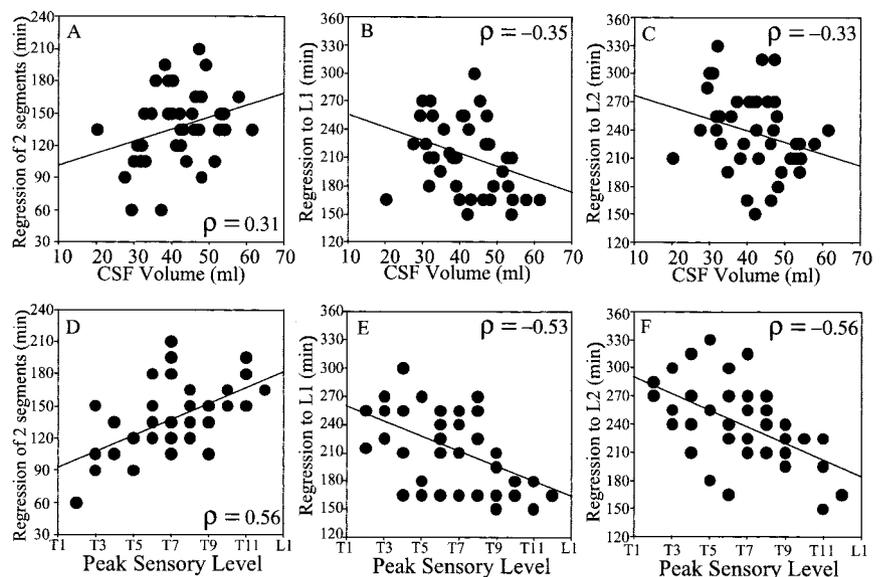
Table 4. Results of Multiple Linear Regression Analyses for Predictive Variables*

Dependent Variable	Adjusted R^2	P Value	Intercept	Independent Variable	Regression Coefficient	SE	Standard Regression Coefficient
Peak sensory block level	0.46	<0.0001	4.48			2.51	
				Weight, kg	−0.08	0.03	−0.29
				CSF volume, ml	0.18	0.03	0.63
Onset time of peak sensory block level, min	0.30	0.0001	130.40			21.90	
				BMI, kg/m²	−3.97	0.94	−0.56
Onset time of complete motor block, min	0.29	0.001	88.41			17.62	
				BMI, kg/m²	−2.51	0.75	−0.45
				Average CSFV, cm/s	24.99	9.54	0.35
Time to two segments' regression from peak sensory block level, min	0.29	0.001	316.24			43.35	
				BMI, kg/m²	−6.96	1.77	−0.53
				Peak CSFV$_{systolic}$, cm/s	16.39	6.97	0.32
Time to regression to L1, min	0.09	0.036	203.78			6.74	
				Average CSFV, cm/s	−65.51	30.19	−0.33
Time to regression to L2, min	0.15	0.016	116.34			56.33	
				BMI, kg/m²	4.94	2.41	0.30
				Average CSFV, cm/s	−68.10	30.51	−0.33
Time to regression to L5, min	0.08	0.046	394.05			15.37	
				Peak CSFV$_{diastolic}$, cm/s	−34.62	16.76	−0.31
Duration of motor block, min	0.23	0.001	345.07			15.18	
				Peak CSFV$_{diastolic}$, cm/s	−58.92	16.56	−0.50
Time to spontaneous voiding, min	0.15	0.007	577.70			53.12	
				CSF volume, ml	−3.54	1.23	−0.42
Maximal decrease in mean arterial pressure, % of baseline value	0.25	0.001	1.23			0.09	
				BMI, kg/m²	−0.02	0.00	−0.52

* Only statistically significant correlations are presented.
BMI = body mass index; CSF = cerebrospinal fluid; CSFV = cerebrospinal fluid velocity.

of a correlation between CSF volume and the regression to L3–L5 might be related to the high degree of interindividual variability at these segments. Recent autopsy and microscopic studies indicate that as the root size at the segments of L3–S2 increases, the interindividual variability in root size also increases. For example, the posterior L5 area, the most variable root, ranges from 2.2 to 7.4 mm³.[21]

Time to regression of the block to L1, L2, and L3 correlated with peak sensory level, *i.e.*, the higher the level of the spinal block was, the more time was required for regression of the block to L1, L2, and L3 in the current study. These correlations between the peak sensory block level and time of regression to L1–L3 contradict the results obtained by Schiffer *et al.*,[4] who demonstrated an inverse correlation between peak sensory block level and the time of regression to L4, *i.e.*, higher cephalad levels are associated with a shorter time for the block to regress to L4. It is difficult to explain this discrepancy. The protocols of the two studies were identical except for the measurement of sensory block.

The extent of sensory block was assessed by pinprick in the current study, whereas Schiffer *et al.*[4] used ether drops. However, the difference in the measurement of the sensory block does not account for the discrepancy because loss of temperature discrimination occurs one or two dermatomes higher, but its onset and regression closely parallel those of the sensory level assessed by pin prick.[19] Further study is required.

On the basis of the assumption that the direction of flow of the 500 ml CSF produced daily is mainly intracranial from the site of production in the choroid plexus to the principal sites of vascular absorption through intracranial arachnoid villi and that downward flow of CSF through the spinal subarachnoid space is minimal, involving perhaps less than 10% of the 500 ml CSF produced, the subarachnoid space is classically portrayed as a "limited pool" of CSF gently bathing the delicate neuraxial structures.[2,10] However, recent MRI observations reveal that CSF vigorously oscillates with arterial pulsations.[5–9] The amplitude of CSF movement is approximately 0.9 cm/beat in the cervical (C6–C7) CSF

and approximately 0.4 cm/beat at the thoracolumbar junction, with minimal movement in the distal lumbosacral sac. The net flow from the site of production of CSF to the absorption site at the C2 level is 0.02 ml/beat, which is only 2% of the CSF pulsatile flow.[5] Oscillatory CSF pulsation is a possible but unexplored mechanism for local anesthetic distribution after subarachnoid injection.[10] The CSF pulsations might be an important factor in the distribution and clearance of spinal agents because the epidural venous plexus flow, which probably has a significant role in the absorption and generation of CSF pulsations, is closely coupled to CSF flow.[7] Because CSF oscillation is also amplified with increased intraabdominal pressure, this effect might be an important means by which the anesthetic effect is extended in pregnant and obese patients.[10]

In the current study, the mean systolic and diastolic velocities were 1.1 (0–2.7) and 0.8 (0.1–1.6) cm/s, respectively, similar to those obtained in previous reports. Greitz et al.[5] reported that the systolic velocities varied from 0 to 2.0 cm/s at the L3 level. Enzmann et al.[6] reported that the mean systolic and diastolic velocities just anterior to the conus were both 1.0 cm/s. Although there was no significant relation between peak $CSFV_{systolic}$ and measures of sensory and motor anesthesia, there was a significant relation between peak $CSFV_{diastolic}$ and the duration of motor blockade and between average CSFV and duration of sensory blockade. These findings suggest that CSFV influences the extent and duration of plain bupivacaine spinal anesthesia. However, the CSF velocity findings in the current study must be interpreted cautiously. We used electrocardiography triggering for prospective gating of the acquisition in the current study. The disadvantage of prospective gating is that the acquisition is stopped within approximately 200 ms of the next R wave for accurate direction of the next trigger. Therefore, the diastolic phase is not fully recorded,[23,24] and the diastolic and average velocities in the current study might be inaccurate. In addition, there might be other methodologic inaccuracies, such as the influence of arterial venous waveform amplitude. Improved flow analysis with new MRI technology will reveal greater detail regarding the patterns of CSF motion and factors that influence the extent of the movement.[23,24]

Other potential study limitations include the following: Although we assumed that the spinal puncture was performed at the L3–L4 level, we must consider the possible influence of the injection site because of the uncertainty of the injection level.[25,26] The possible influence of spinal puncture on the peak sensory level was discussed in the article by Schiffer et al.[4] In the current study, 2 ml CSF was sampled in all patients. Although 5 ml CSF, but not 3 ml, removed before spinal injection has an impact on the spread of spinal anesthesia with plain bupivacaine,[27] the effect of 2 ml CSF removal on the spread and duration of spinal anesthesia might not have been equivalent in all patients because there was great interindividual variability of CSF volume with a threefold difference.[3] Finally, there are inaccuracies in the volumetric method used in the current study[12] compared with the well-established accuracy (± 0.00001 g/ml) and high level of precision of the mechanical oscillation technique for the measurement of density.[28,29] Schiffer et al.[4], who demonstrated a highly significant relation between CSF density and peak block level, measured CSF density with a resolution of up to six digits using a densitometer, whereas we measured only four digits using a less accurate volumetric method. In addition, the temperature control during CSF density measurements in the current study was also less precise (37.0°C). Strict temperature control (37.00°C) during CSF density measurements is required for increased accuracy.[28,29] Therefore, reduced accuracy and precision of mass, volume, and temperature measurements limit the findings of CSF density in the current study.

Multiple linear regression analysis in the study of physiologic systems provides a powerful statistical tool for sorting out the relations among several variables. Although all selected predictive values must ideally be uncorrelated, there are no completely independent variables among age, height, weight, BMI, CSF density, CSF volume, peak $CSFV_{systolic}$, $CSFV_{diastolic}$, and average CSFV. Rather, it is important to select parameters that produce an R^2 close to 1.0 in multiple linear regressions. Multicolinearity among variables makes regression analyses difficult to interpret. Therefore, we used forward and backward selection to identify the most useful variables for predicting the extent and duration of plain bupivacaine spinal anesthesia.[13,30] Although CSF density correlated with the peak sensory block level by Spearman rank correlation (table 3 and fig. 3A), according to multiple linear regression modeling, it was not a predictor of the peak sensory block level (table 4), possibly because of the weak correlation between CSF density and the peak block level because of inaccuracies in the CSF density measurement methods.

Although our findings provide valuable insight into the mechanism of plain bupivacaine spinal anesthesia, they will not be helpful for guiding clinical practice. For example, the R^2 of the peak sensory block level was 0.46, which means that only 46% of the peak sensory block level can be explained with our selected parameters of weight and CSF volume. Further, CSF volume is not always measured before anesthesia. On the other hand, BMI can routinely be calculated before anesthesia. However, multiple linear regression analysis indicates that the correlation between BMI and onset time of sensory block is statistically significant ($P = 0.001$) but poorly predictive ($R^2 = 0.30$). Therefore, our results cannot be expected to improve the ability to predict the spread or duration of plain bupivacaine spinal anesthesia

in clinical practice, although they provide a better explanation of the unpredictability of extent and duration of plain bupivacaine spinal anesthesia.

In summary, the lower the CSF volume is with a higher CSF density, the higher the peak sensory block level is for plain bupivacaine solutions, indicating that CSF density and volume are main factors that influence the spread of spinal anesthesia with plain bupivacaine. The current study also indicates that CSF volume is associated with the duration of the sensory block. The results of the current study also suggest that CSF velocity influences the extent and duration of plain bupivacaine spinal anesthesia.

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