Anesthesiology 2004; 101:451–60

Factors Affecting the Spread and Duration of Epidural Anesthesia with Ropivacaine

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Background: **Epidural anesthesia has an unpredictable extent and duration. Differences in the surface area of the lumbosacral dura, epidural fat volume, and epidural venous plexus velocity might explain the variability in the extent and duration of epidural anesthesia with ropivacaine.**

Methods: **Twenty-six healthy patients, aged 18–45 y, undergoing peripheral orthopedic surgery were enrolled. Dural surface area and posterior epidural fat volume were calculated from low thoracic, lumbar, and sacral axial magnetic resonance images obtained at 8-mm increments. Epidural venous plexus velocity at the L3–L4 disk level was derived from phase-contrast magnetic resonance images. The patients received 100 mg ropivacaine (1.0%) epidurally. The spread and duration of sensory anesthesia was assessed by pinprick, and that of motor block was assessed using a modified Bromage scale. Statistical correlation coefficients (ρ) between magnetic resonance imaging and epidural anesthesia measurements were assessed by Spearman rank correlation. Stepwise multiple linear regression models were used to select important predictors of measures of epidural anesthesia.**

Results: **Dural surface area correlated with peak sensory block level ($\rho = -0.73$, $P = 0.0003$) and onset time of caudal and cephalad block ($\rho = 0.62$, $P = 0.002$; $\rho = -0.63$, $P = 0.002$). Fat volume correlated with the regression to L5–S3 ($\rho = -0.44$ to -0.54, $P = 0.029$ to 0.007). Epidural venous plexus velocity was significantly correlated with the regression to L3 ($\rho = -0.42$, $P = 0.038$) and L4 ($\rho = -0.48$, $P = 0.017$). Multiple regression analysis revealed that dural surface area was a significant predictive variable for the peak sensory block level ($R^2 = 0.61$, $P < 0.0001$).**

Conclusions: **These findings indicate that dural surface area influences the spread of epidural anesthesia with ropivacaine and posterior fat volume influences the duration of epidural anesthesia in healthy patients within a narrow age range. Epidural venous plexus velocity might also influence the duration of epidural anesthesia with ropivacaine.**

THE spread of epidural anesthesia is highly variable among individuals.[1–4] A large number of studies have attempted to clarify the reason for this variability.[1,2] Some of the variability is intrinsic to patients and not dependent on variations in technique or the drugs administered. Some intrinsic factors, such as age, are poorly correlated with the spread of anesthesia.[1,2,4] Intrinsic factors governing the spread of solutions in the epidural space are best understood if the epidural space is considered to be a cylindrical reservoir, the volume of the reservoir being determined by such factors as length and diameter of the cylinder and size of the structures normally contained in it.[1,2] Although the spread of local anesthetic solutions in the epidural space is not completely understood, Hogan[5,6] demonstrated that solutions injected into the epidural space usually spread freely through the epidural space and coat the cylindrical dural sac while partly passing through the foramina. On the other hand, there is interindividual variability in cerebrospinal fluid (CSF) volume, which is calculated by multiplying the area of the dural sac by the length, and there is a significant correlation between lumbosacral CSF volume and the peak sensory block level of spinal anesthesia.[7,8] Therefore, differences in the surface area (SA) of the lumbosacral dura among patients might account for the interindividual variability in the spread of epidural anesthesia because a greater dural SA might result in a lower epidural longitudinal distribution of local anesthetics. In addition, epidural fat might also influence the pharmacokinetics of drugs injected into the epidural space because local anesthetics might have considerable affinity for epidural fat; thereby a significant portion of an injected dose of local anesthetic might be prevented from reaching the site of action.[9,10] Therefore, interindividual variability in the amount of fatty tissue might account for the varying spread and intensity of epidural anesthesia.[9,10]

Similar to the spread of anesthesia, there is great interindividual variability in the duration of epidural anesthesia.[1–4,11] The process of drug removal from the site of administration influences the duration of anesthesia.[3] Because local anesthetics after epidural injection are deposited mainly in CSF, blood vessels, especially the epidural venous plexus (EVP), and epidural fat,[1,2,12] the rate of absorption and disposition in these three sites affects the duration of epidural anesthesia. Therefore, epidural fat volume or epidural blood flow (EBF) of local anesthetics or both might influence the duration of epidural anesthesia.[3,9,13] In addition to the measurement of dural SA and posterior epidural fat volume, magnetic resonance (MR) imaging can demonstrate both the magnitude and the direction of pulsatile flow in various regions using the cardiac gating phase-contrast technique.[8,14–17] Using this technique, we recently reported that CSF velocity (CSFV) might influence the duration of plain bupivacaine spinal anesthesia.[8] Like CSFV, EVP velocity (EVPV) can be demonstrated by phase-contrast MR imaging.[14,15]

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Received from the Department of Anesthesia, Self Defense Force Hanshin Hospital, Hyogo, Japan. Submitted for publication January 20, 2004. Accepted for publication April 12, 2004. Support was provided solely from institutional and/or department sources.

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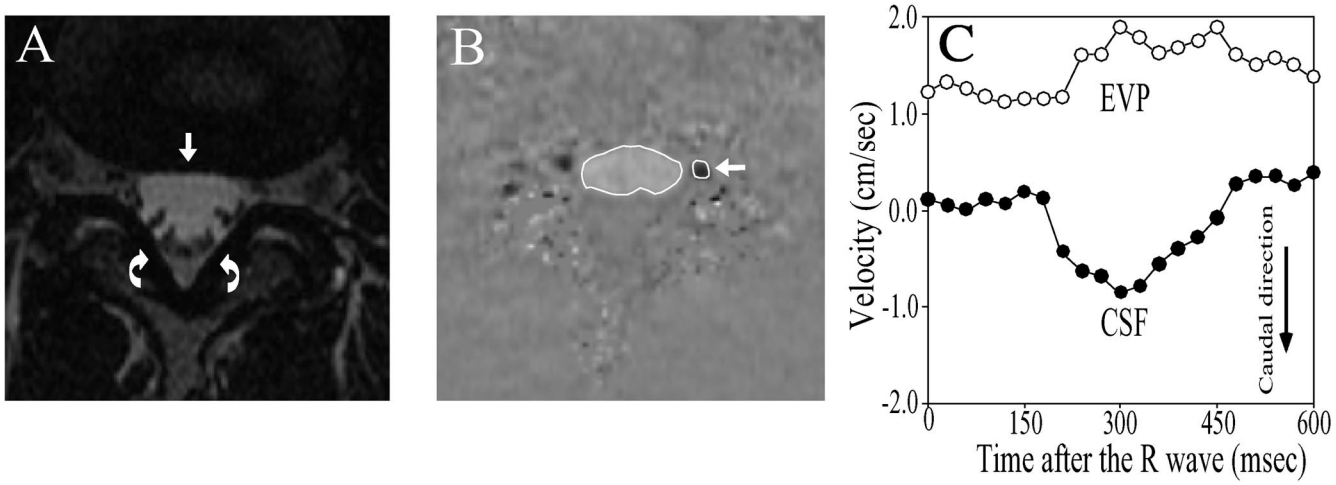

Fig. 1. Examples of magnetic resonance images used to determine various measurements and graph representing velocities. (*A*) Axial image at the L3–L4 intervertebral foramen level showing bright cerebrospinal fluid (CSF) containing nerve roots observed as gray defects and triangle-shaped posterior epidural fat (*curved arrow*). The perimeter of the CSF (*straight arrows*) was measured to determine the dural surface area. The area of the posterior epidural fat was measured to determine the posterior epidural fat volume. The CSF perimeter and the posterior epidural fat areas at this level were 0.52 cm and 0.15 cm^2, respectively. (*B*) Axial image of CSF and epidural venous plexus (EVP) flows at the L3–L4 disk level. Bright imaging indicates caudad flow, and dark imaging indicates cephalad flow. Cephalad EVP flow (*straight arrow*) is observed adjacent to caudad CSF flow. The regions of interest were defined by tracing the outlines of CSF and EVP, seen as bright and dark, respectively. (*C*). Graph representing CSF and EVP velocities (cm/s) after the R wave. The negative deflections represent caudad systolic CSF flow, whereas the positive deflections represent cephalad diastolic CSF flow. Therefore, the CSF velocity profile had both caudad systolic and cephalad diastolic components. On the other hand, the EVP velocity profile had a mostly cephalad component.

The goal of the current study was to investigate the influence of dural SA, posterior epidural fat volume, CSFV, and EVPV on the extent and duration of epidural anesthesia with ropivacaine using MR imaging.

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. Twenty-seven patients with American Society of Anesthesiologists physical status I, who provided written informed consent, were enrolled in the study. Under epidural anesthesia with ropivacaine, they underwent orthopedic lower limb surgery with a thigh tourniquet. Apart from the usual contraindications for epidural anesthesia, patients with obvious spinal postural abnormalities (kyphosis) or neurologic disturbances were excluded from the study.

Low thoracic and lumbosacral axial MR images for the measurement of dural SA, EVPV, and other measurements were obtained using an MR imaging system (Excel Art; Toshiba, Tokyo, Japan) operating at 1.5 T. Posterior–anterior lumbar spine radiographs were used for the identification of the spinal level, marking the intersection of a line joining the iliac crests. MR images and radiographs were obtained a few days before anesthesia. Axial MR images were obtained at 8-mm increments with a fast-spin echo sequence using a method similar to that previously described.[8] One of the authors (Y. A.), who was not involved in the assessment of the patients receiving epidural anesthesia with ropivacaine, determined the dural sac and spinal cord areas for each image using the NIH Image 1.63 program for Macintosh (Research Services Branch of the National Institutes of Mental Health, Bethesda, MD). The level of the disk between the 11th and 12th thoracic vertebrae was determined, and the perimeter length of the sac and the area of the sac minus the area of the cord were measured caudal from this site. This perimeter length and area multiplied by 8 mm resulted in the dural SA and CSF volume, respectively. Similarly, posterior epidural fat volume was measured by multiplying the area of epidural fat by 8 mm (fig. 1A). Although the posterior epidural fat is not continuous with that of the lateral compartment in general,[9] caudal to the L3–L4 disk, the fat is sometimes interconnected. In such cases, the back of the superior articular process was defined as posterior. In addition, the area of the spinal canal was measured to compare with the area of the sac at the lamina of L3. Measurements of CSFV and EVPV at the L3–L4 disk levels were derived from phase-contrast MR imaging by scans oriented approximately perpendicular to the CSF direction of flow, using the method similar to that used previously except for the definition of the region of interest (ROIs).[8] Briefly, electrocardiography triggering was used for prospective gating of acquisition. Cardiac gating produced a series of phase-contrast images at different cardiac phases. Al-

though fixed circular ROIs of 10 mm^2 were used in our previous study as reported by Greitz *et al.*,[16] ROIs in the current study were defined by tracing the outlines of the CSF and EVP, which were observed adjacent to the CSF, as reported by Bhadelia *et al.*,[17] because of the small size of the EVP (normal, 0.5–3 mm; fig. 1B). The CSFV profile at this site had both caudad systolic ($CSFV_{systolic}$) and cephalad diastolic ($CSFV_{diastolic}$) components. From these phase-contrast images, we measured peak $CSFV_{systolic}$, peak $CSFV_{diastolic}$, and average CSFV at the L3–L4 levels. In contrast to the caudad and cephalad CSF flow, the EVPV profile had a mostly cephalad flow (figs. 1B and C). Accordingly, we calculated only average EVPV.

Thirty minutes before transfer to the operating room, all patients received an intramuscular injection of atropine (0.5 mg). After placement of standard noninvasive monitoring devices, an epidural puncture was performed using a 20-gauge Tuohy needle (Perican®; B. Braun, Tokyo, Japan), at the L3–L4 level, using the loss-of-resistance technique with saline, taking care not to inject more than 1 ml saline. A medial approach with the patient in the lateral decubitus position with the operated side up was used. The L3–L4 level interspace was identified by counting the spines of the vertebrae and palpation of the iliac crest. After ensuring no aspiration of CSF or blood, a test dose of 3 ml ropivacaine, 1.0%, was administered with the bevel of an epidural needle positioned cephalad. Three minutes later, when there were no signs of inadvertent or subarachnoid injection, 7 ml ropivacaine, 1.0%, was administered at a rate of 0.5 ml/s. The patient was then turned in the supine position and remained horizontal until the end of surgery. The time of administration in all patients was approximately 1:00 PM. The spread 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 using 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).[8] Data sampling was performed every 5 min for the first 45 min after epidural injection and then every 15 min until the end of the observation period, which was defined as regression of the sensory block level to S3. 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 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 was administered at 5 ml/kg 1 h before epidural anesthesia and at 1 $ml \cdot kg^{-1} \cdot h^{-1}$ during and after anesthesia. Ephedrine (5 mg) was administered intravenously if 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 patient sample size was determined by power analysis ($\alpha = 0.05$, $\beta = 0.10$) to reveal a significant correlation coefficient. Power analysis indicated that 25 patients were required to obtain a significant correlation coefficient, assuming that the two variables were continuous data and the correlation coefficient between dural SA and onset time of the peak sensory block was 0.60, which was based on a preliminary study. Continuous data were expressed as mean ± SD, and discrete data were expressed as median and range. Statistical correlation coefficients (ρ) were assessed by Spearman rank correlation among patient demographics, measures of MR imaging such as dural SA, the peak sensory block level to pinprick, the time until the development of the peak sensory level to pinprick and maximum motor block, the degree of motor block, the time required for the peak sensory block level to regress across two segments, the time required for pinprick analgesia to regress to the L3, L4, L5, S1, S2, and S3 dermatomes, the time until complete motor recovery, and the time until spontaneous voiding. A P value of less than 0.05 was considered statistically significant. In addition, multiple linear regression analysis (forward stepwise selection) was used to examine the relative importance of patient and MR imaging variables to the aforementioned measures of epidural anesthesia. Age, height, weight, body mass index, dural SA, CSF volume, fat volume, average EVPV, peak $CSFV_{systolic}$, peak $CSFV_{diastolic}$, and average

Table 1. Patient Demographics and Measures of Magnetic Resonance Imaging

								Velocity, cm/s*			
								EVP	CSF		
	Age, yr	Height, cm	Weight, kg	BMI, kg/m^2	Dural Surface Area, cm^2	CSF Volume, ml	Posterior Epidural Fat Volume, ml	Average	Peak Systolic	Peak Diastolic	Average
Mean ± SD (n = 26)	26 ± 8	169 ± 5	65 ± 7	23 ± 2	11.4 ± 1.4	39.6 ± 7.3	3.2 ± 1.4	0.8 ± 0.5	−0.9 ± 0.4	0.6 ± 0.3	−0.1 ± 0.2

* The negative values represent caudal flow, whereas the positive represent cephalad flow.

BMI = body mass index; CSF = cerebrospinal fluid; EVP = epidural venous plexus.

Table 2. Main Anesthetic Data

Variables of sensory block	
Peak sensory block level	T9 (T4–L2)
Onset time of peak caudal block level, min	15 (10–30)
Onset time of peak cephalad block level, min	30 (15–60)
Time to two segments' regression from peak sensory block level, min	105 (90–315)
Time to regression to L3, min	263 (135–495)
Time to regression to L4, min	338 (150–510)
Time to regression to L5, min	375 (285–555)
Time to regression to S1, min	428 (300–570)
Time to regression to S2, min	473 (255–645)
Time to regression to S3, min	480 (255–645)
Variables of motor block	
Maximum degree of motor block, 0–4*	2 (1–4)
Onset time of maximum motor block, min	18 (5–60)
Duration of motor block, min	210 (120–420)
Time to spontaneous voiding, min	438 (210–630)

Data are presented as median with ranges in parentheses; n = 26.

* Modified Bromage scale (0 = no block, 4 = complete motor block); see text for details.

CSFV were considered independent variables. For adding 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.[8]

Results

Twenty-six (25 men, 1 woman) of 27 patients, aged 18–45 y, who received epidural ropivacaine were analyzed. One patient was excluded from the analysis because a spinal tap occurred. Demographics and characteristics of variables measured by MR imaging are presented in table 1. The caudad systolic and cephalad diastolic components of CSF flow in the lumbar spine at the L3–L4 level are shown, whereas the direction of lumbar EVP flow was consistently cephalad. In general, the caudal direction increased when CSF flow became caudal, although the relation between EVP and CSF flow remained the same (figs. 1B and C).

Although one patient experienced tourniquet pain and two patients had mild discomfort at the site of surgery, they were treated with a single dose of fentanyl (50–100 μg), and none of the patients required general anesthesia. No patient required intravenous ephedrine because of a decrease in mean arterial pressure of more than 30% from the baseline or urinary catheterization for urinary retention. The main epidural anesthetic data are summarized in table 2.

Correlations between the values of patient characteristics and the measures of MR imaging, and the measures of epidural anesthesia, assessed by Spearman rank correlation, are presented in table 3. There was an inverse correlation between dural SA and peak sensory block level ($\rho = -0.73$, $P = 0.0003$; fig. 2). Dural SA positively correlated with the onset time of caudal block ($\rho = 0.62$, $P = 0.002$; fig. 3A) and inversely correlated with the onset time of cephalad block ($\rho = -0.63$, $P = 0.002$; fig. 3B). CSF volume also correlated with the peak sensory

Table 3. Correlations between Predictive Variables and Measures of Epidural Anesthesia

	P Value of Correlation							
	Surface Area	CSF Volume	Fat Volume	EVPV	Peak $CSFV_{systolic}$	Peak $CSFV_{diastolic}$	Average CSFV	Peak Sensory Block Level
Patient characteristics								
Age	0.559	0.493	0.393	0.203	0.864	0.707	0.342	0.389
Height	0.985	0.393	0.034*	0.304	0.775	0.758	0.794	0.450
Weight	0.956	0.883	0.209	0.980	0.079	0.021*	0.277	0.694
Body mass index	0.586	0.922	0.861	0.508	0.084	0.004*	0.075	0.446
Measures of epidural anesthesia								
Peak sensory block level	0.0003*	0.0001*	0.058	0.142	0.840	0.665	0.546	
Onset time of peak caudal block level	0.002*	0.004*	0.541	0.011*	0.598	0.714	0.801	0.001*
Onset time of peak cephalad block level	0.002*	0.0003*	0.616	0.173	0.972	0.200	0.371	0.011*
Time to two segments' regression from peak sensory block level	0.280	0.061	0.551	0.912	0.484	0.475	0.638	0.219
Time to regression to L3	0.417	0.536	0.359	0.038*	0.417	0.770	0.379	0.414
Time to regression to L4	0.426	0.641	0.199	0.017*	0.184	0.321	0.534	0.928
Time to regression to L5	0.953	0.560	0.019*	0.371	0.231	0.129	0.407	0.790
Time to regression to S1	0.687	0.466	0.029*	0.728	0.424	0.238	0.491	0.719
Time to regression to S2	0.993	0.785	0.008*	0.527	0.274	0.098	0.328	0.987
Time to regression to S3	0.876	0.555	0.007*	0.750	0.264	0.089	0.335	0.805
Maximum degree of motor block	0.880	0.804	0.018*	0.525	0.479	0.014*	0.849	0.912
Onset time of maximum motor block	0.419	0.248	0.008*	0.283	0.279	0.005*	0.689	0.920
Duration of motor block	0.555	0.227	0.401	0.276	0.664	0.403	0.822	0.757
Time to spontaneous voiding	0.667	0.772	0.072	0.859	0.960	0.929	0.767	0.847

* $P < 0.05$, Spearman rank correlation.

CSF = cerebrospinal fluid; CSFV = cerebrospinal fluid velocity; EVPV = epidural venous plexus velocity.

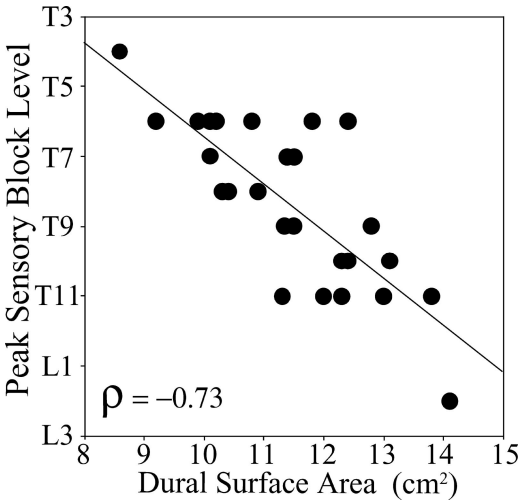

Fig. 2. Inverse correlation between dural surface area and peak sensory block level ($\rho = -0.73$, $P = 0.0003$). Although the correlation coefficient (ρ) and P value were calculated using the Spearman rank correlation, the linear regression line is presented in this graph.

block level ($\rho = -0.77$, $P = 0.0001$), the onset time of the caudal block ($\rho = 0.57$, $P = 0.004$), and the onset time of the cephalad block ($\rho = -0.72$, $P = 0.0003$; table 3). Posterior fat volume correlated with the degree of motor block ($\rho = -0.47$, $P = 0.018$; fig. 4A) and with the onset time of maximum motor block ($\rho = -0.53$, $P = 0.008$; fig. 4B). There were significant correlations between posterior epidural fat volume and the regression to L5 ($\rho = -0.47$, $P = 0.019$), S1 ($\rho = -0.44$, $P = 0.029$), S2 ($\rho = -0.54$, $P = 0.008$; table 3), and S3 ($\rho = -0.54$, $P = 0.0007$; fig. 5). These correlations between fat volume and measures of epidural anesthesia were significant, even if the score from the patient with the highest fat volume (7.1 ml) was excluded. Average EVPV correlated with the onset of the peak caudal block level ($\rho = 0.51$, $P = 0.011$), and the regression to L3 ($\rho = -0.42$, $P = 0.038$; table 3) and L4 ($\rho = -0.48$, $P = 0.017$; fig. 6). Neither peak $CSFV_{systolic}$ nor average CSFV correlated with the epidural anesthesia measures (table 3). There were significant inverse correlations between peak $CSFV_{diastolic}$ and the degree of motor blockade ($\rho = -0.49$, $P = 0.014$) and between peak $CSFV_{diastolic}$ and the onset of maximum motor blockade ($\rho = -0.56$, $P = 0.005$; table 3).

Among the variables considered to be independent in the multiple linear regression analysis, there were several significant correlations between patient characteristics and MR imaging measures (table 3). Besides these correlations, there were significant correlations between dural SA and EVPV ($\rho = 0.53$, $P = 0.008$), between fat volume and peak $CSFV_{diastolic}$ ($\rho = 0.56$, $P = 0.005$), and between peak $CSFV_{diastolic}$ and peak $CSFV_{systolic}$ ($\rho = -0.61$, $P = 0.002$). There was also a highly significant correlation between dural SA and CSF volume ($\rho = 0.88$, $P < 0.0001$). CSF volume was significantly correlated with EVPV ($\rho = 0.50$, $P = 0.012$). The significant multiple linear regression coefficients are shown in table 4. Multiple regression analysis revealed that dural SA significantly contributed to the peak sensory block level ($R^2 = 0.61$, $P < 0.0001$; table 4), suggesting that dural SA is the primary determinant of sensory block of epidural anesthesia with ropivacaine. Dural SA was the only significant predictive variable for the onset of the peak caudal block level ($R^2 = 0.38$, $P = 0.0005$; table 4). On the other hand, CSF volume was the only significant predictive variable for the onset of the peak cephalad block level ($R^2 = 0.46$, $P < 0.0001$; table 4). In addition to being the only significant predictive variable for the regression to L5–S3, fat volume was also the only significant predictive variable for the onset of maximum motor block ($R^2 = 0.24$, $P = 0.006$; table 4). Peak $CSFV_{diastolic}$ was the only significant predictive variable for the degree of motor block ($R^2 = 0.26$, $P = 0.005$; table 4).

Discussion

The most striking finding of the current study was the significant correlation between dural SA and the peak sensory block level achieved after epidural injection of 100 mg ropivacaine. Furthermore, multiple regression analysis indicated that the R^2 of the peak sensory block level was greater than 0.5, suggesting that dural SA is the

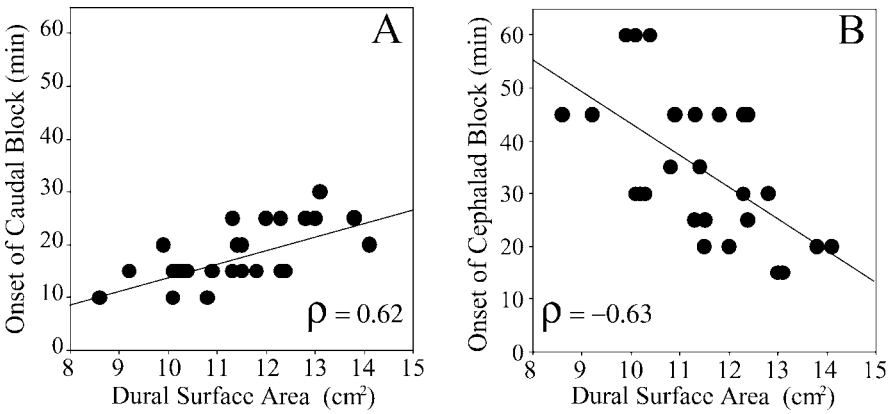

Fig. 3. (*A*) Correlation between surface area of the dura and the onset of peak caudal sensory block level ($\rho = 0.62$, $P = 0.002$). (*B*) Inverse correlation between of dural surface area and the onset of peak cephalad sensory block level ($\rho = -0.62$, $P = 0.0002$). Although the correlation coefficients (ρ) and P values were calculated using the Spearman rank correlation, the linear regression lines are presented in these graphs.

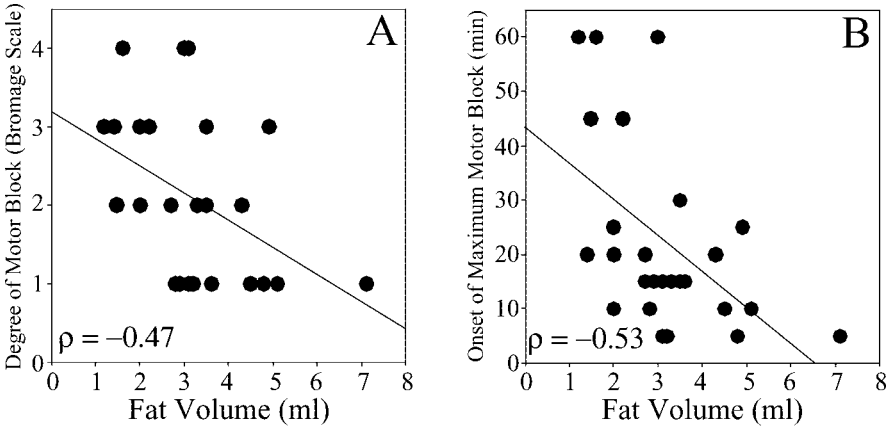

Fig. 4. (*A*) Inverse correlation between posterior epidural fat volume and the degree of motor block level ($\rho = -0.47$, $P = 0.018$). (*B*) Inverse correlation between posterior epidural fat volume and the onset of maximum motor block ($\rho = -0.53$, $P = 0.008$). Although the correlation coefficients (ρ) and P values were calculated using the Spearman rank correlation, the linear regression lines are presented in these graphs.

primary determinant of the spread of epidural anesthesia with ropivacaine. To the best of our knowledge, this is the first study to demonstrate a critical intrinsic factor that influences the spread of epidural anesthesia. In addition, the results of the current study demonstrate that the posterior epidural fat volume might influence the intensity of the motor block and the duration of the sensory block after epidural anesthesia with ropivacaine. They also suggest that EVPV influences the duration of epidural anesthesia with ropivacaine.

A number of factors influence the spread of local anesthetic solutions in the epidural space.[1,2] In the current study, these extrinsic factors were standardized. We injected an identical dose of ropivacaine epidurally with the needle aperture directed cephalad at the same rate and site of injection. A single injection technique without catheter placement was selected to minimize technical variations, which are more likely to occur with catheter techniques. Although many studies report that age, height, pregnancy, and arteriosclerosis are intrinsic factors,[1,2,4] we limited our study to healthy patients within a narrow age range. In addition, our patients were injected epidurally at the same time (1:00 PM) to avoid chronobiologic variations in epidural anesthesia. Debon *et al.*[11] reported a circadian variation of analgesia duration after epidural ropivacaine injection in laboring women.

The epidural space contents are discontinuous circumferentially and repeat metamerically. The anterior epidural space is isolated from the rest of the epidural space and is nearly filled with veins except caudal to the L4–L5 disk, where a fat-filled anterior epidural space develops.[9] The lateral epidural compartments contain nerves and fat, which is lobulated by septae. The posterior fat-filled epidural compartment is enclosed and not continuous with the lateral compartment. This fat is homogeneous and without any apparent fibrous septation.[9] In the current study, we measured only the posterior epidural fat volume because the posterior epidural space contains mostly fat and this triangular posterior fat is easily discriminated in T2-weighted MR images (fig. 1A).[18] Further, it is assumed that local anesthetic solutions are likely injected into or near the posterior epidural fat, not into the lateral or anterior space, when a single injection with a medial approach is used.

The spread of local anesthetic solutions in the epidural

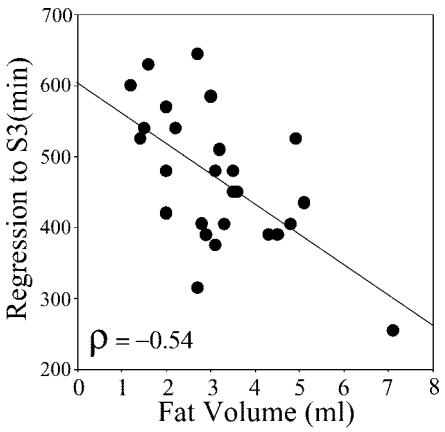

Fig. 5. Inverse correlation between posterior epidural fat volume and the time of regression to S3 ($\rho = -0.54$, $P = 0.007$). Although the correlation coefficient (ρ) and P value were calculated using the Spearman rank correlation, the linear regression line is presented in this graph.

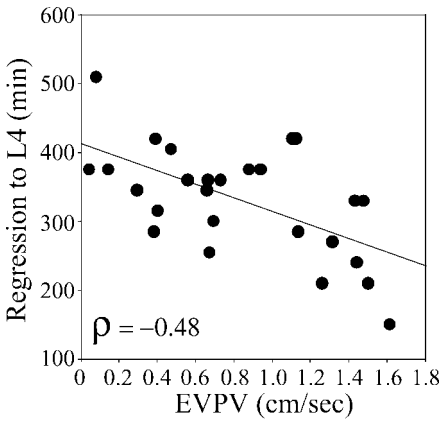

Fig. 6. Inverse correlation between epidural venous plexus velocity (EVPV) and the time of regression to L4 ($\rho = -0.48$, $P = 0.017$). Although the correlation coefficient (ρ) and P value were calculated using the Spearman rank correlation, the linear regression line is presented in this graph.

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, 0–14†	0.61	< 0.0001					
			22.04			2.48	
				Surface Area, cm^2	−1.35	0.22	−0.79
Onset time of peak caudal sensory block level, min	0.38	0.0005					
			−11.06			7.25	
				Surface Area, cm^2	2.55	0.63	0.64
Onset time of peak cephalad block level, min	0.46	< 0.0001					
			86.96			11.31	
				CSF Volume, ml	−1.33	0.28	−0.69
Time to regression to L3, min	0.34	0.003					
			3.71			130.69	
				EVPV, cm/s	−92.48	29.45	−0.52
				BMI, kg/m^2	15.79	5.80	0.45
Time to regression to L4, min	0.27	0.004					
			408.58			25.61	
				EVPV, cm/s	−85.73	27.03	−0.54
Time to regression to L5, min	0.28	0.003					
			497.5			32.90	
				Fat Volume, ml	−31.28	9.58	−0.56
Time to regression to S1, min	0.27	0.004					
			539.55			37.35	
				Fat Volume, ml	−34.71	10.87	−0.55
Time to regression to S2, min	0.33	0.001					
			592.09			40.50	
				Fat Volume, ml	−42.57	11.79	−0.59
Time to regression to S3, min	0.34	0.010					
			603.46			39.01	
				Fat Volume, ml	−42.52	11.36	−0.61
Maximum degree of motor block, 0–4‡	0.26	0.005					
			3.16			0.38	
				Peak $CSFV_{diastolic}$, cm/s	−1.79	0.57	−0.54
Onset time of maximum motor block, min	0.24	0.006					
			42.24			7.57	
				Fat Volume, ml	−6.62	2.20	−0.52
Time to spontaneous voiding, min	0.12	0.046					
			30.43			189.73	
				BMI, kg/m^2	17.51	8.34	0.39

* Only the statistically significant correlations are presented. † Level: L3 = 0, T1 = 14. ‡ Modified Bromage scale (0 = no block, 4 = complete motor block); see text for details.

BMI = body mass index; CSF = cerebrospinal fluid; CSFV = cerebrospinal fluid velocity; EVPV = epidural venous plexus velocity.

space and their principal sites of action are complicated and subject to debate. It was demonstrated in the study by Hogan,[5,6] using epidurography with computerized tomographic imaging and cryomicrotome imaging, that the passage of solution injected into the epidural space is almost completely circumferential, encircling anterior to the dura, as well as posterior. However, patterns of distribution exhibit great variability, including outlining of posterior fat, at least on one side, or preferential accumulation in the anterior or posterolateral areas, as well as variable amounts passing through the foramina.[5,6] Suggested sites of action of local anesthetic solutions after epidural injection are the spinal nerves intradurally, the mixed nerves in the paravertebral spaces, and the spinal cord.[1,2] By diffusing thorough the dural sleeves, local anesthetics block the spinal nerves intradurally. In the current study, dural SA was inversely correlated with the peak sensory block level and the onset of peak caudad spread, whereas it was positively correlated with the onset of peak cephalad spread (figs. 1, 2A, and 2B). These results indicate that dural SA variability among patients accounts for the interindividual variability in the spread of epidural anesthesia, supporting the hypothesis of the cylindrical reservoir as proposed by Bromage.[1,2] Although the exact mechanism for this relation remains to be elucidated, the results of the current study suggest that the dural SA is the primary determinant of epidural longitudinal distribution of local anesthetics. Also, this mechanism might explain the more extensive epidural anesthesia in patients with in-

creased abdominal pressure, which occurs with obesity or pregnancy, because of compression of the dural sac, resulting in a decrease in the dural SA.[1,2,19] However, it is also possible that the opposite is true. The greater block extent that results from a thoracic epidural local anesthetic dose as compared with lumbar administration might be due, at least in part, to a reduced posterior epidural space.[2] In analogy, therefore, it is possible that a greater dural SA results in greater block extent because a large thecal sac should result in less epidural space if the size of the spinal canal is the same. However, it is unlikely that greater dural SA results in less epidural space, because the area of the sac significantly correlated with that of the spinal canal at the lamina of L3 ($r = 0.76$ by linear regression analysis, $P < 0.001$), *i.e.*, a larger thecal sac was associated with a larger spinal canal.

Diffusion of local anesthetics through the dura also results in the appearance of local anesthetics in the CSF, with peak concentrations occurring 5–45 min after epidural injection in human.[1,2,20] As mentioned earlier, the lumbosacral CSF volume is the main/primary determinant of sensory block spread of spinal anesthesia.[7,8] Analogous to spinal anesthesia, therefore, one might argue that CSF volume is the main determinant of sensory block spread of epidural anesthesia because local anesthetics in the CSF through the dura are diluted by CSF. CSF volume is significantly correlated with the peak sensory block level and the onset of peak caudad and cephalad spread, similar to dural SA. In addition, multiple regression analysis revealed that CSF volume was the only significant predictive variable for the onset of cephalad spread. Considering the calculation methods, however, these correlations were inevitable: CSF volume was calculated by multiplying the dural sac area by length, whereas SA was calculated by multiplying the perimeter of dural sac by length. Although the exact contribution of the subarachnoid site of action of local anesthetics to establish initial neural blockade after an epidural loading dose is unclear, it is generally assumed that this process has a minor role.[1,2] One of the reasons for its minor role is the dissociation of epidural anesthesia and concentration of local anesthetics in CSF.[1]

Rosenberg *et al.*[10] investigated the absorption of amide local anesthetics *in vitro* and speculated that interindividual variability in the amount of extraneural fatty tissue might be a reason for the varying spread and intensity of regional anesthesia. In the current study, fat volume correlated with the degree of motor block and onset time of maximum motor block, supporting the suggestion of Rosenberg *et al.*[10] On the other hand, we did not demonstrate a significant correlation between the posterior fat volume and the peak sensory block level and between the posterior fat volume and the onset time of peak caudal block level. One possible explanation for the lack of a statistical correlation might be related to the molecular size and the lipid solubility of ropivacaine, both of which are intermediate to bupivacaine and lidocaine.[10] The smaller molecular size with less lipid solubility of local anesthetics favors penetration into the nerve sodium channels.[10] Consequently, the absorption of ropivacaine into the epidural fat might be slower than epidural longitudinal distribution. Another explanation might be that we did not investigate the intensity of sensory block because we measured sensory block only by pinprick, whereas the degree of the motor block was evaluated by the modified Bromage scale. Investigating the intensity of sensory block combining it with a different measurement of sensory block, such as transcutaneous electric stimulation, might account for the differential effect in sensory and motor block in the current study. In addition, the number of patients included in the current study might be insufficient to identify a correlation between fat volume and the peak sensory block level ($\rho = -0.38$, $P = 0.058$).

Emanuelsson *et al.*[3] reported that the duration of the sensory block after epidural injection of ropivacaine correlated with the slow systemic absorption half-life and that the differences in the rate of absorption of ropivacaine from the epidural space might be one factor responsible for the variability in duration. In the current study, there was a significant correlation between posterior epidural fat volume and regression to L5–S3 (table 3 and fig. 3), supporting our hypothesis. This correlation is consistent with the findings obtained by Emanuelsson *et al.*[3] in that slow absorption from the epidural space reflects the duration of epidural block using ropivacaine. Although it is unclear whether the posterior epidural fat volume correlates with the slow systemic absorption half-life, which is measured by pharmacokinetic calculation, the longer disposition with the greater amount of epidural fat might influence the larger absorption half-life. Further, the correlation between the posterior epidural fat volume and the duration of epidural anesthesia with ropivacaine might also be consistent with the fact that the bioavailability of opioids in the epidural space is determined by their hydrophobicity, with less hydrophobic drugs having greater bioavailability.[21] In addition, the correlation is consistent with a case reported by Lang *et al.*,[22] in which a patient experienced repeated failed epidural analgesia (quick fade of analgesia) associated with an unusually large amount of posterior epidural fat.

To our knowledge, there is no published study in which the lumbar EVP flow was quantitatively measured, although there are a few studies that investigated cervical EVP flow, which had conflicting results.[14,15] Levy and Di Chiro[14] reported that cervical EVP flow is closely coupled to CSF flow. In systole, CSF flow became caudal and EVP flow sometimes became cephalad.[14] In contrast, Enzmann and Pelc[15] reported that the flow characteristics of cervical EVP did not have a consistent phase relation with CSF flow. In the current study, the direction of lumbar EVP flow was consistently cephalad,

whereas the CSF flow in the lumbar spine at the L3–L4 level was cephalad and caudal. In general, the cephalad direction increased when CSF flow became caudal, consistent with the findings obtained by Levy and Di Chiro.[14] In the current study, the average EVPV and EVP flow rates, which were calculated for each image by multiplying the average signal intensity of an ROI with its area,[17] were 0.8 cm/s and 3.8 ml/min, respectively. The validity of these values is unclear because there is no information regarding EVPV at the L3–L4 level. In this regard, EBF measured by a local ^{133}Xe clearance technique was 5.0–6.0 ml · min^{-1} · 100 g tissue^{-1}.[13,23]

Mogensen *et al.*[13] reported that changes in EBF during continuous epidural infusion of bupivacaine might be an important factor contributing to differences in the rates of regression of sensory block. Two of seven patients whose EBF remained constant after the initial increase maintained the initial sensory block level, whereas the sensory block level in the other five patients whose EBF significantly increased after epidural bupivacaine decreased five to seven segments.[13] In the current study, there were significant correlations between the regression to L3 and to L4 and EVPV, *i.e.*, increased EVPV was associated with a shorter time for the block to regress to L3 and L4 (fig. 6). In addition, EVPV correlated with the onset of the peak caudal block level. These findings suggest that EVPV influences the spread and duration of epidural anesthesia with ropivacaine. However, the EVPV findings in the current study must be interpreted cautiously. First, EVPV after epidural ropivacaine is unclear. EBF decreases after epidural ropivacaine because ropivacaine has a vasoconstrictor effect.[24] Accordingly, EVPV might be expected to decrease with great variability in the extent of decrease after epidural ropivacaine. Further, there are several disadvantages to the cardiac gating phase-contrast technique, which was discussed in our previous report.[8] Further study is required before making conclusions regarding the influence of EVPV, EBF, or both on the extent and duration of epidural anesthesia with ropivacaine.

Other potential study limitations include the following: Although the mean values of peak $CSFV_{systolic}$, peak $CSFV_{diastolic}$, and average CSFV in this study were in accord with those obtained in our previous study,[8] peak $CSFV_{diastolic}$ correlated with weight and body mass index in the current study, contrary to the previous study. The reason for this discrepancy is unclear, because it is unlikely that the difference in the definition of ROI between the previous and current studies explains this discrepancy. Similarly, it is also difficult to explain the significant correlations between peak $CSFV_{diastolic}$ and measures of motor block. The correlations between peak $CSFV_{diastolic}$ and measures of motor block might be statistically significant because of the significant correlation between fat volume and peak $CSFV_{diastolic}$. Therefore, as mentioned above, there are several methodologic inaccuracies in the measurement of CSF flow using phase-contrast MR imaging. In addition, we did not measure the anterior or lateral fat volume because they were not as easy to measure as compared with the posterior fat volume. However, solution injected into the epidural space usually spreads circumferentially.[5,6] Improved resolution with new MR imaging technology will reveal the role of epidural fat in the spread, intensity, and duration of epidural anesthesia. Further, we must comment on the multiple regression analysis. Although all selected predictive values must ideally be uncorrelated,[25] there were significant correlations among the selected variables in the current study. In our previous study, we used forward and backward stepwise selection because we believed that it was important to select parameters that make R^2 close to 1.0, being careful to detect multicollinearity.[8] However, almost all the variables would have been selected if backward stepwise selection was used in the current study. This means that there was multicollinearity.[25] As a consequence, we used forward stepwise selection to identify the most useful variables for predicting the extent and duration of epidural anesthesia with ropivacaine. In addition, this study was performed in a limited situation. Ropivacaine was injected epidurally with a single injection technique in small Japanese patients aged younger than 46 yr. It is therefore possible that there would be different results in different populations using the catheter technique. Finally, we must consider the possible influence of the injection site. This issue has been discussed previously.[26,27]

Our findings provide valuable insight into the mechanism and a better explanation of the unpredictability of spread and duration of epidural anesthesia with ropivacaine. However, the findings will not be helpful for guiding clinical practice. Although the dural SA is reliably predictive of the peak sensory block level, our results cannot be expected to improve the ability to predict the spread of epidural anesthesia with ropivacaine in clinical practice, because MR imaging is not always obtained before anesthesia.

In summary, the current study indicates that the dural SA is the primary determinant for the peak sensory block of epidural anesthesia with ropivacaine and the main factor that influences the onset time of the peak block level. The current study also indicates that posterior epidural fat volume is associated with the degree of the motor block and with the duration of the sensory block. The results of the current study also suggest that EVPV at the L3–L4 level influences the onset time of the peak caudal block level and the regression to L3 and L4.

The authors thank the surgeons and nurses in the operating room and orthopedic wards and the workers in the Department of Radiology of Self Defense Force Hanshin Hospital (Kawanishi, Hyogo, Japan) for their cooperation.

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