

# Blood Pressure, but Not Cerebrospinal Fluid Fentanyl Concentration, Predicts Duration of Labor Analgesia from Spinal Fentanyl

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## ABSTRACT

**Background:** There is a wide variability in dilution of drugs in cerebrospinal fluid after spinal injection, as measured near the site of injection. With local anesthetics, there is a wide variability in speed of onset, which correlates with block duration. The authors tested whether local cerebrospinal fluid drug concentrations and onset time would predict duration of analgesia from spinal fentanyl in laboring women.

**Methods:** After written informed consent, fentanyl (50  $\mu$ g) was injected using the combined spinal epidural method in 56 women requesting analgesia for labor. The stylet was reinserted in the spinal needle, and 60 s later, the cerebrospinal fluid was aspirated for fentanyl assay. Time to analgesia and duration of analgesia were recorded, and data were analyzed by linear regression.

**Results:** Fifty-two women were included for data analysis. The cerebrospinal fluid fentanyl concentrations were  $3.1 \pm 5.9$   $\mu$ g/ml, with a 7-fold range (0.9–5.9  $\mu$ g/ml). Fentanyl concentration did not correlate with onset, initial sensory level at 5 and 10 min, or duration of analgesia. Decreased diastolic and increased systolic blood pressure and lower parity, but not fentanyl concentrations, correlated with longer labor analgesia. The resultant model was predictive when applied to data from four previous studies of spinal opioid analgesia duration.

**Conclusions:** Contrary to our hypothesis, the local concentration of fentanyl in the cerebrospinal fluid 1 min after injection was not correlated with onset or duration of labor analgesia. The unexpected but consistent relationship between blood pressure and combined spinal epidural analgesia duration suggests that resting hemodynamic state affects the distribution and/or clearance of intrathecally administered opioids.

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## What We Already Know about This Topic

- ❖ Duration of analgesia from intrathecal fentanyl in labor is variable
- ❖ Distribution of fentanyl in spinal fluid could explain part of this variability

## What This Article Tells Us That Is New

- ❖ Concentration of fentanyl in spinal fluid 1 min after injection did not predict duration of labor analgesia
- ❖ Systolic and diastolic blood pressure were related to duration in this study and in four other studies from this institution

A HALLMARK of intrathecally administered drugs is the large interindividual variability in effect. Given this large variability with a single-shot technique, clinicians use a relatively large dose of drug to diminish the risk of therapeutic failure. Such large doses may increase the incidence of side effects, primarily hypotension with local anesthetics and respiratory depression from opioids, and less worrisome but still bothersome problems such as prolonged stay in the recovery room from residual motor block from local anesthetics or prolonged nausea after intrathecal opioids. A better understanding of patient or injection factors that determine the block characteristics would help clinicians individualize drug dose, potentially reducing these side effects.

Multiple factors have been examined to explain the large variability in onset, extent of cephalad spread, and duration of block after lumbar intrathecal injection of local anesthetics and opioids. Patient height and weight have little influence on duration of spinal anesthesia,<sup>1</sup> whereas the interaction between patient position and baricity of injectate does.<sup>2</sup> Some studies suggest that the volume of cerebrospinal fluid (CSF) in the lumbosacral space, as determined by magnetic resonance imaging, is negatively correlated with the extent of cephalad spread and block duration,<sup>3</sup> although this correlation is weak and clinically impractical.

We recently examined the pharmacokinetics of morphine and fentanyl in healthy, nonpregnant volunteers by injection through a needle in a lower lumbar interspace and sampling repeatedly at an upper lumbar interspace more than 2 h.<sup>4</sup> There was a remarkable difference in the shape of CSF drug concentration *versus* time curves among individuals at this

sampling site cephalad to injection. Some injections resulted in initially high concentrations with a steady decrease, others resulted in nearly constant concentrations, and yet others resulted in slowly increasing concentrations. Most interestingly, drug concentrations converged at approximately 30–60 min to a narrow range. We generated a pharmacokinetic model of this unusual phenomenon by using a mixing parameter and suggested that injections with initially high concentrations at the cephalad site had rapid initial mixing, whereas those with slowly increasing concentrations had slow initial mixing. This pharmacokinetic model accurately predicted drug concentrations within individuals.

The primary purpose of this study was to determine whether the variability of acute mixing of fentanyl in CSF, as determined by sampling 60 s after injection, was correlated with block characteristics of intrathecal injection during combined spinal epidural (CSE) for labor. We specifically hypothesized that greater fentanyl concentrations 1 min after injection would be an evidence of less immediate dilution, implying slower cephalad movement of fentanyl. Because fentanyl must ascend to the T10 dermatome of the spinal cord itself to provide pain relief in the first stage of labor, we further hypothesized that less mixing (higher concentrations at the site of injection) would be correlated with a slower onset of analgesia, less extensive cephalad spread of hypesthesia to pinprick 5 and 15 min after injection, and shorter duration of analgesia.

A secondary purpose of this study was to determine the influence of blood pressure and heart rate on acute dilution of fentanyl after intrathecal injection. Movement of CSF in the spinal canal occurs in a pulsatile manner coinciding with cardiac cycle.<sup>5</sup> We reasoned that individuals with evidence for a hyperdynamic state, such as increased blood pressure, pulse pressure, or heart rate, might have a greater magnitude of CSF oscillations and hence more rapid mixing of fentanyl after spinal injection.

## Materials and Methods

### Primary Study of CSE Fentanyl

After obtaining written informed consent and Institutional Review Board approval from Wake Forest University School of Medicine, Winston-Salem, North Carolina, we studied 56 healthy, laboring women at term with a singleton pregnancy requesting analgesia between June 23, 2004, and August 3, 2005. Both primiparous and multiparous women were included, both with and without exogenous oxytocin administration to augment labor. Inclusion criteria included cervical dilatation less than 6 cm when the CSE analgesic was placed. We excluded patients with weight more than 115 kg, patients unable to understand English, patients receiving intravenous analgesics within 60 min before the time of study, and those allergic to fentanyl. A verbal pain score (0–10) was obtained just before beginning the CSE procedure, asking the patient to rate the average pain of her last three contractions. Blood pressure and heart rate were measured using an

automated oscillometric cuff on the arm with the patient in the supine position with left uterine displacement just before sitting for CSE placement.

A CSE technique was performed, according to our standard practice, using an 18-gauge epidural needle inserted by loss of resistance to less than 3 ml saline at a mid-to-low lumbar interspace and a 27-gauge pencil-point spinal needle inserted through the epidural needle with clear CSF obtained. Fentanyl (50  $\mu$ g) diluted to a total volume of 3 ml with sterile saline was injected over 10 s while observing the clock. The stylet was then reinserted in the needle. One minute later, the stylet was removed, any fluid in the hub was quickly aspirated and discarded, and 0.5 ml was removed for fentanyl assay. The spinal needle was then withdrawn, a 20-gauge epidural catheter was inserted through the epidural needle, the epidural needle was withdrawn, and the catheter was secured with clear tape. All procedures were performed by one investigator (K.E.N.) with patients in the sitting position. Women were placed in the supine position with head of the bed elevated less than 30° and left uterine displacement within 5 min of intrathecal injection. Women who reached complete cervical dilatation or who delivered within 60 min of injection were excluded from data analysis.

The primary outcome measure was duration of analgesia, defined as the time from CSE injection until request for additional analgesia. A group size of 52 was determined to be able to see a Pearson correlation between fentanyl concentration and duration of analgesia of  $\pm 0.38$  (two-sided  $\alpha = 0.05$ ,  $1 - \beta = 0.80$ ). The major secondary outcome measure was onset of analgesia, defined as the time from intrathecal injection until pain with uterine contraction decreased to a verbal report 3 or less on a 0–10 scale. The most cephalad level of hypesthesia to pinprick was determined at 5 and 10 min after spinal injection. Testing was performed bilaterally. If there was a discrepancy, the dermatome midway between the two was recorded.

CSF samples were placed immediately on ice. All samples were clear to visual inspection but were nonetheless centrifuged before freezing at  $-80^{\circ}\text{C}$  until analysis. Fentanyl was measured in the unextracted samples by high pressure liquid chromatography with ultraviolet detection as previously described.<sup>6</sup> The limit of detection was 50 ng/ml.

### Statistical Analyses

All statistical analyses were conducted using SPSS 13.0 (SPSS, Inc., Chicago, IL). Before undertaking the primary and secondary analyses, the distributions of each variable were examined for suitability in regression/correlation analysis, and the existence of outliers was evaluated. There were no missing data. The primary analysis identified factors predictive of block duration using partial correlations, after controlling for previous delivery (first delivery *vs.* second or later delivery). For these analyses, the correlation between dermatome level and duration of analgesia was indexed using a Spearman correlation after residualizing duration by previous birth status (*i.e.*, controlling for previous birth). The

**Table 1.** Descriptive Statistics and Independent Correlations with Block Duration after Controlling for Previous Birth Number (0 vs.  $\geq 1$ )

Prediction Variable	n	Mean	SD	Correlation with Duration
Systolic BP (mmHg)	52	126.0	14.3	-0.03
Diastolic BP (mmHg)	52	73.2	10.2	-0.33*
Heart rate (beats/min)	52	82.4	12.6	0.20
Verbal pain (0–10)†	52	7.8	1.3	0.07
Sampling time (min)	52	72.0	3.5	0.11
Onset of relief (min)	52	5.0	2.0	-0.21
Dermatome at 5 min‡	52	T6	3.2	-0.18
Dermatome at 10 min‡	52	T4	3.2	-0.24
Cerebrospinal fluid Fentanyl ( $\mu\text{g/ml}$ )	52	3.1	1.0	-0.07
Cervical dilation (cm)	52	3.5	1.3	-0.17
Block duration (min)	52	99.2	41.0	
Nulliparous	30	109.6	39.5	
Multiparous	22	84.9	39.5	

\*  $P < 0.05$ . † Pain rating with contractions before intrathecal injection. ‡ Spearman correlation with residualized duration. BP = blood pressure.

primary analysis identified factors predictive of analgesic duration by calculating the Spearman correlation between predictors (e.g., CSF fentanyl concentration and blood pressure) and block duration (table 1). After calculating the correlations of each independent variable considered, we built a multivariate model that included parity, diastolic blood pressure, systolic blood pressure, and the interactions among the three. We did not undertake an automated approach to build the model (e.g., generalized additive models) but settled on the final model through trial and error and physiologic plausibility.

The predictive utility of the final multivariate model cannot be evaluated on the original data, because the model was the result of many data-driven inferences. Therefore, we tested the predictive utility of the final model using two different strategies: (1) a bootstrap analysis using repeated random draws from the collected sample to examine the consistency of the estimates, and (2) external validation of the model through a retrospective reanalysis of several previously published datasets. The bootstrapping analysis was conducted using SAS (SAS, Inc., Cary, NC), with 100 novel replications of the actual dataset, using unrestricted random sampling with replacement and reestimation of the model parameters.

For the external validation, we examined the block duration of CSE opioid in four previous studies at our institution. Each of these examined different solutions (sufentanil plus bupivacaine with or without clonidine,<sup>7</sup> sufentanil with or without neostigmine,<sup>8</sup> or fentanyl or sufentanil<sup>9</sup>), but in each case blood pressure and heart rate were measured just before CSE injection, and the duration of analgesia was determined in the same manner as this study. These datasets were aggregated into a pooled regression model by including several

terms to control for study and treatment effect within study in the first step. Next, the effects of systolic and diastolic blood pressure were entered into the equation in the second step with the change in  $R^2$  evaluated for significance. For all models, statistical significance was evaluated at  $\alpha = 0.05$ .

## Results

Four patients were excluded because of protocol violations (did not aspirate needle hub or had received butorphanol intravenously before study) or missing data (did not obtain sensory level at 5 min after injection or delivered before need for analgesia), leaving 52 evaluable patients. Patients included for data analysis were on average 26-yr old (SD = 5.5; range, 18–38), 164 cm tall (SD = 6.1; range: 152–178), and 81 kg in weight (SD = 11; range, 60–103), and 58% of subjects were nulliparous. Pain score on entry was  $7.8 \pm 0.2$  on a 0–10 verbal scale. CSF sampling, which began 60 s after injection in all patients, was completed at  $72 \pm 0.5$  s after injection, with a range of 67–81 s.

### Primary Analysis: Predictive Value of CSF Fentanyl Concentration

CSF fentanyl concentrations were  $3.1 \pm 5.9 \mu\text{g/ml}$ , with a 7-fold range (0.9–5.9  $\mu\text{g/ml}$ ). There was no significant relationship between the time CSF sampling was completed and CSF fentanyl concentration. CSF fentanyl did not correlate with onset, initial sensory level at 5 or 10 min, or with duration of analgesia. In addition, CSF fentanyl was not related to blood pressure (systolic, diastolic, or mean), pulse pressure, heart rate, or the sum or product of the mean blood pressure and heart rate or pulse pressure and heart rate.

### Correlations Between Block Duration and Predictor Variables

Increasing parity was associated with a sizeable reduction in block duration,  $t(50) = 2.2$ ,  $P = 0.03$ ; Cohen's  $d = 0.63$ . Several predictors had a modest ( $|r| \geq 0.20$ ) relationship with block duration (table 1). Diastolic blood pressure was the only predictor with a statistically significant association, exhibiting a modest inverse relationship,  $r(49) = -0.33$ , with block duration.

### Construction of a Multivariate Prediction Model

The multivariate predictive model was built in three steps. Table 2 displays the regression weights for each step along with their 95% confidence intervals and  $P$  values, which must be interpreted with skepticism because of the many confounding variables not considered in the model.<sup>10</sup> As expected in the first step, previous birth number was found to account for a sizeable (9%) portion of the variance in block duration,  $R^2 = 0.09$ . In step 2, systolic and diastolic blood pressure added an additional 12% of variance. In step 3, previous birth number was found to moderate the effect of systolic blood pressure on analgesic duration, requiring the addition of interaction terms accounting for 15% of the vari-

**Table 2.** *Post hoc* Regression Model Examining the Influence of Blood Pressure and Pregnancy on Block Duration

Step	Variable	B	95% CI	P Value	R <sup>2</sup>	Adjusted R <sup>2</sup>
1	Constant	109.6			0.09*	0.07
2	Pregnancy number	-24.7	-46.9 to -2.45	0.03*	0.16	0.12*
3	Constant	165.7		0.21*		
	Pregnancy number	-24.0	-45.3 to -2.6	0.03*		
	Systolic BP	0.46	-0.39 to 1.3	0.28		
	Diastolic BP	-1.6	-2.7 to -0.4	0.01*		
	Constant	0.99		0.35†	0.28	0.15‡
	Pregnancy number	225.2	27.0 to 423.5	0.027*		
	Systolic BP	2.1	0.79 to 3.4	0.002†		
	Diastolic BP	-2.1	-3.4 to -0.78	0.003†		
	Systolic BP × pregnancy number	-2.5	-4.2 to -0.90	0.003†		
	Diastolic BP × pregnancy number	0.96	-1.5 to 3.4	0.43		

From these data, duration of analgesia (min) =  $0.99 + 225.2 \times (\text{parity}) - 2.1 \times (\text{diastolic BP}) + 2.1 \times (\text{systolic BP}) + 0.96 \times (\text{diastolic BP} \times \text{parity}) - 2.5 \times (\text{systolic BP} \times \text{Parity})$ , where BP are in mm Hg and parity is 0 or 1.

\*  $P < 0.05$ ; †  $P < 0.001$ ; ‡  $P < 0.01$ .

BP = blood pressure; CI = confidence interval.

ance. Figure 1 displays the effect of previous birth number on the relationship between diastolic (fig. 1A) and systolic (fig. 1B) blood pressure and block duration. Figure 1C displays the scatter of the actual block duration with predicted block duration calculated by taking the linear composite of variables from step 3 of the regression model.

The final model appears in table 2. This model structure is parsimonious, consisting of only three of the primary predictor variables, and accounts for 35% of the variance of block duration ( $R^2 = 0.35$ ). Further, the multivariate model remained significant when adjusted for likelihood of replica-

tion in the four prior datasets from our institution, adjusted  $R^2 = 0.28$ .

#### Internal Validation of the Multivariate Model

The multivariate prediction model was estimated on each of the 100 bootstrapped datasets sampled from the original data. The model demonstrated adequate stability, with each of the coefficients exhibiting consistent effects across the range of datasets. For example, the diastolic blood pressure coefficients were statistically significant in 89% (89/100) of the replications, the systolic blood pressure in 94% of the

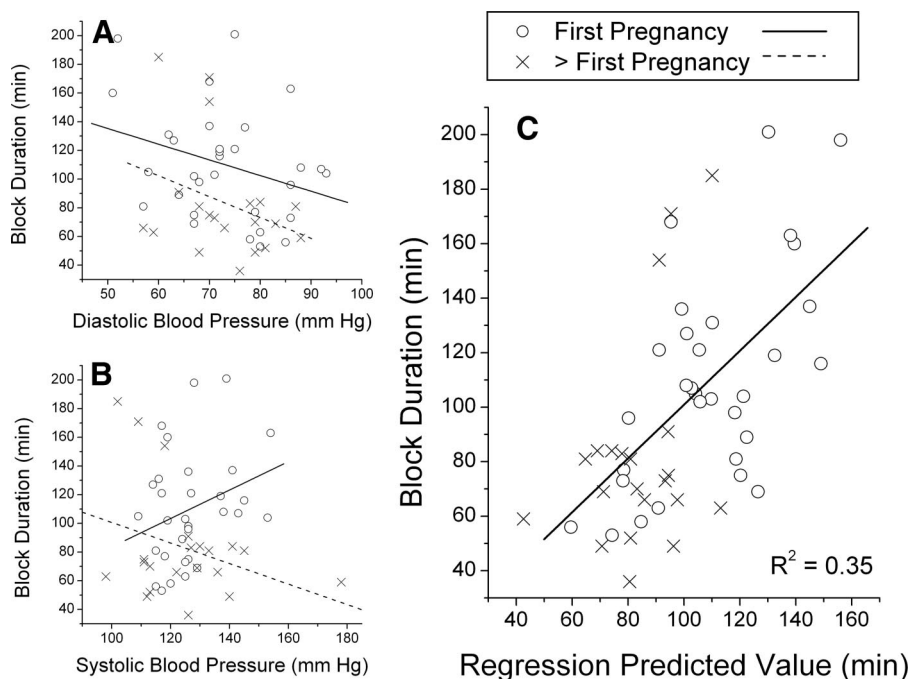


Fig. 1. Scatter plots of the relationship between block duration and diastolic blood pressure (A), systolic blood pressure (B), and the prediction model from table 2 (C). The significant interaction between pregnancy number and systolic blood pressure can be observed in (B) with different relationships between systolic blood pressure and duration observed by pregnancy number,  $P = 0.003$ . The overall prediction model accounted for 35% of the variance in block duration.



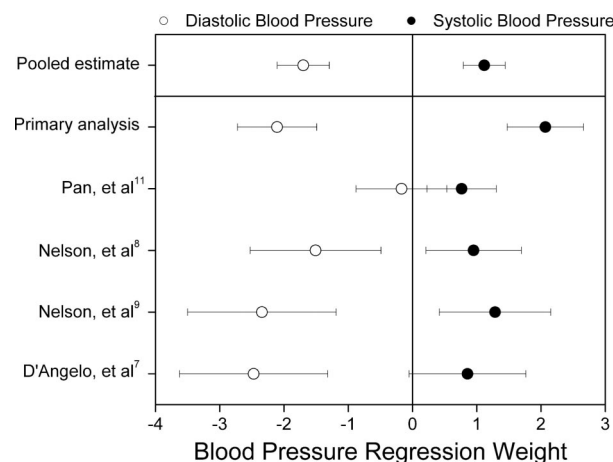


Fig. 2. Examination of the regression weights from the regression models. Diastolic blood pressure added significantly to prediction in 3 of 5 studies examined. Systolic blood pressure added significantly to prediction in 2 of 5. Both coefficients showed remarkable consistency in their direction but variability in their magnitude. When aggregated across studies, both systolic and diastolic blood pressure added significantly to prediction. Data are presented as mean and 95% confidence limits (7.8% of variance  $F(2, 126) = 9.7, P < 0.001$ ; systolic 1.12 [0.326],  $P = 0.001$ ; diastolic  $-1.70$  [0.406],  $P < 0.001$ ).

replications, and systolic blood pressure  $\times$  parity association was statistically significant in 90% of the replications. In contrast, the diastolic blood pressure  $\times$  parity interaction was only statistically significant in 9% of the replications, which was expected given that it was statistically nonsignificant in the original model.

In response to reviewer concerns, we added cervical dilatation to the model to examine the robustness of the blood pressure effects after considering degree of dilatation. Although dilatation slightly affected the duration of analgesia, the effect was not significant and did not account for the influence of blood pressure on analgesic duration.

### External Validation of the Multivariate Model

The multivariate prediction model was tested on four datasets of nulliparous parturients.<sup>7-9,11</sup> To control for the potential effects of the different studies and intrathecal drugs on the blood pressure relationships, we first modeled block duration as a function of study and intrathecal drug and study  $\times$  drug interaction, and then examined the unique contribution of blood pressure on duration.

Figure 2 displays the final regression weights for each study and the aggregated (pooled) estimate. Although the small sample size in most of the studies precluded definitive individual statistical evaluation, each of the studies exhibited the same directional relationship between blood pressure and block duration. Specifically, increasing diastolic blood pressure was associated with shorter block durations. Conversely, higher systolic blood pressure was associated with longer block duration. When the individual studies were pooled, this consistency in observed effects led to statistically significant prediction, with systolic and diastolic blood pressure accounting for 7.8% of residual in block duration,  $F(2,$

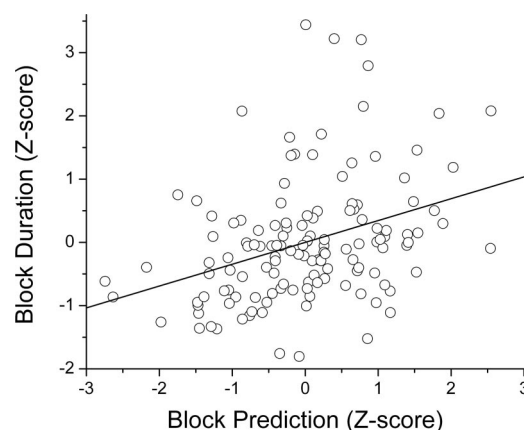


Fig. 3. Scatter plot examining the relationship between blood pressure (systolic and diastolic) and block duration aggregated across studies. Blood pressure accounted for 7.8% of the overall variance in block duration ( $n = 135$ ).

126) = 9.7,  $P < 0.001$ . Figure 3 displays the scatter of the predicted block duration with actual block duration by using the pooled estimates from all studies, including this study.

Finally, we calculated the accuracy of using preinjection systolic and diastolic blood pressure and patient parity to predict analgesia of short duration from spinal opioids. The prediction model could only achieve 64% sensitivity and 10% specificity in identifying patients at risk for low-duration blocks, defined as the 8.1% of patients whose blocks were 1 SD below the mean ( $\leq 56$  min).

### Discussion

Duration of labor analgesia from spinally administered opioids is remarkably variable, even at the same dose, volume, and baricity, and when injected at similar time points during the progress of labor. Genetic polymorphisms in opioid receptor expression have been demonstrated to play a role in the potency of spinally administered opioids, but this accounts for a small part of the interindividual variability.<sup>12</sup> Similarly, large variability in duration of spinal anesthesia has been partially explained by individual variations in lumbosacral CSF volumes.<sup>13</sup> Speed of drug movement and mixing in CSF is also important, because rapid onset correlates with more cephalad spread of anesthesia, which also correlates with longer duration.<sup>3</sup> We anticipated that rapid mixing in CSF, as indicated by lower local residual fentanyl concentrations after injection and more rapid onset of analgesia, would correlate with duration of labor analgesia from spinal fentanyl. We failed to observe such a correlation.

As expected, dilution of fentanyl in CSF after bolus spinal delivery, as measured by drug concentrations 60 s later, varied considerably among individuals. Indeed, the time course of CSF drug concentrations after bolus delivery could only be described with application of an individual mixing kinetic component.<sup>4</sup> The large range of CSF fentanyl concentrations observed in this study in women in labor is similar to that observed in healthy resting men and women volunteers in the

absence of pain.<sup>4</sup> Further pharmacodynamic modeling could not be performed because we sampled CSF only once, and this was before our first reliable measure of analgesia because of the inconsistent timing of labor contractions.

Further analysis revealed an effect of parity on duration of analgesia, with longer duration of analgesia in nulliparous women. This likely reflects the slower progress of labor in nulliparous women, because analgesic efficacy of spinal opioids decreases as labor progressed and women approached the second stage of labor.<sup>14</sup>

We unexpectedly found a relationship between blood pressure and duration of spinal fentanyl analgesia in this study, which we incorporated into a multivariate model. We validated the structure of this model using data from four previous studies in laboring nulliparous parturients. Although the studies were performed with different opioids (fentanyl and sufentanil) and different injection volumes, the model consistently identified a negative correlation between diastolic blood pressure and analgesia duration and a positive correlation between systolic blood pressure and analgesia duration.

How might we explain this unexpected but consistent observation? Our original prediction regarding mixing of fentanyl in CSF was based on recent observations regarding CSF volume and flow patterns in humans, mostly obtained by high resolution magnetic resonance imaging gated to the cardiac cycle. As opposed to the classic teaching that CSF exits the fourth ventricle and circulates caudad in the spinal intrathecal space to the sacrum, with a return flow cephalad, there is virtually no net flow of CSF in the spinal intrathecal space. Rather, with each cardiac cycle, brain blood volume increases, leading to a jet of CSF into the cervical intrathecal space to maintain intracranial pressure constant.<sup>3,5,15–17</sup> This high velocity jet of flow is most typically in the dorsal midline of the cord but meanders laterally and ventrally as a river along the neuraxis. Later in each cardiac cycle, there is a slower velocity return of CSF from the spinal intrathecal space to the cranium, typically along both lateral borders of the cord. Thus, there is an oscillatory movement of fluid in a very nonhomogeneous manner within the spinal canal with each cardiac cycle.

These observations predict that increased cardiac stroke volume, by exaggerating changes in brain blood volume across the cardiac cycle, would increase oscillatory flow magnitude in CSF and promote rapid mixing of drugs in CSF once they reached local areas of oscillations. Decreased diastolic and increased systolic blood pressure, which together would indicate increased pulse pressure, could increase the volume and speed of the CSF oscillatory flow, increasing the duration of analgesia as observed in this study and in data from our previous studies. Confirmation of this hypothesis would require determination of the influence of stroke volume on block duration.

One could argue, based on the hypothesis discussed earlier, that pulse pressure itself provides equivalent information to systolic and diastolic blood pressure for predicting the

duration of analgesia. A model of three variables (pulse pressure, parity, and their interaction,  $R^2 = 0.31$ ) performs nearly as well as the model of five variables (systolic blood pressure, diastolic blood pressure, parity, and their interactions,  $R^2 = 0.36$ ). This pulse pressure model has fewer terms, but applying model information criteria is of limited help to chose between the models because the pulse pressure is derived from the directly measured variables. In addition, pulse pressure is highly correlated with systolic blood pressure ( $r = 0.73$ ), and as a calculated term pulse pressure would be expected to have to include the combined measurement errors of systolic and diastolic pressure. Finally, basing our model on systolic and diastolic blood pressure permits independent estimation of the association of cross relationship of each pressure with parity to analgesic duration.

We did not observe a relationship between local residual CSF fentanyl concentrations and pulse pressure. This might reflect only a small fraction of the injectate reaching sites of rapid oscillation and mixing within the first minute. It would be interesting to test whether increased pulse pressure or stroke volume predicted duration of anesthesia after spinal injection of local anesthetics. In addition, the solution used in this study was likely hypobaric. We do not know whether this observation would be seen with hyperbaric solutions.

In summary, CSF fentanyl concentrations sampled through the injection needle 1 min after a 50- $\mu$ g intrathecal fentanyl injection vary 7-fold and do not correlate with onset or duration of analgesia. Reduced preinjection diastolic blood pressure and increased systolic blood pressure predict increased duration of analgesia, which was validated using previously published data. Although the model is insufficiently accurate for it to be clinically useful in the individual patient, these findings add to our understanding and provide a testable hypothesis regarding the role of pulse pressure, cardiac stroke volume, and CSF oscillations on distribution and block characteristics of spinally administered drugs.

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