Epidural Anesthesia, Hypotension, and Changes in Intravascular Volume

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Background: The most common side effect of epidural or spinal anesthesia is hypotension with functional hypovolemia prompting fluid infusions or administration of vasopressors. Short-term studies (20 min) in patients undergoing lumbar epidural anesthesia suggest that plasma volume may increase when hypotension is present, which may have implications for the choice of treatment of hypotension. However, no long-term information or measurements of plasma volumes with or without hypotension after epidural anesthesia are available.

Methods: In 12 healthy volunteers, the authors assessed plasma (^{125}I-albumin) and erythrocyte (^{51}Cr-EDTA) volumes before and 90 min after administration of 10 ml bupivacaine, 0.5%, *via* a thoracic epidural catheter (T7–T10). After 90 min (t = 90), subjects were randomized to administration of fluid (7 ml/kg hydroxyethyl starch) or a vasopressor (0.2 mg/kg ephedrine), and 40 min later (t = 130), plasma and erythrocyte volumes were measured. At the same time points, mean corpuscular volume and hematocrit were measured. Systolic and diastolic blood pressure, heart rate, and hemoglobin were measured every 5 min throughout the study. Volume kinetic analysis was performed for the volunteers receiving hydroxyethyl starch.

Results: Plasma volume did not change *per se* after thoracic epidural anesthesia despite a decrease in blood pressure. Plasma volume increased with fluid administration but remained unchanged with vasopressors despite that both treatments had similar hemodynamic effects. Hemoglobin concentrations were not significantly altered by the epidural blockade or ephedrine administration but decreased significantly after hydroxyethyl starch administration. Volume kinetic analysis showed that the infused fluid expanded a rather small volume, approximately 1.5 l. The elimination constant was 56 ml/min.

Conclusions: Thoracic epidural anesthesia *per se* does not lead to changes in blood volumes despite a reduction in blood pressure. When fluid is infused, there is a dilution, and the fluid initially seems to be located centrally. Because administration of hydroxyethyl starch and ephedrine has similar hemodynamic effects, the latter may be preferred in patients with cardiopulmonary diseases in which perioperative fluid overload is undesirable.

A COMMON physiologic effect of epidural and spinal anesthesia is hypotension, primarily due to blockade of the sympathetic nervous system causing arterial and venous vasodilation with subsequent "functional" hypovolemia. Previous short-term (20-min) observations without concomitant fluid administration have suggested a movement of fluid from the interstitial to the intravascular space after epidural anesthesia with hypotension based on hemoglobin measurements,[1] and the same observation has been made in volunteers with induced "functional" hypovolemia after application of lower body negative pressure.[2] However, no long-term measurements or measurements of actual fluid volumes after hypotension with spinal or epidural anesthesia are available. Because hypotension normally develops within the initial 30 min after epidural anesthesia and allows time for capillary refill to occur, measurements made approximately 90 min after the induction of epidural anesthesia may be considered an appropriate time point to study long-term effects. Because postoperative fluid excess may have undesirable effects on various organ functions,[3] a potential endogenous increase in plasma volume after neuraxial blockade may have implications for choosing the optimal regimen to treat hypotension (*i.e.*, fluid or vasopressors). Therefore, we investigated in detail changes in intravascular volume and fluid kinetics after application of thoracic epidural anesthesia and with subsequent administration of vasopressors or plasma expanders.

Materials and Methods

General Procedure

We studied 12 healthy volunteers, 3 women and 9 men, with a median age of 27.5 yr (range, 22–29 yr), a median height of 181.5 cm (range, 168–88 cm) and a median weight of 75.5 kg (range, 57.2–85.8 kg), in a prospective, randomized study. No subjects were medicated, and none showed abnormal findings in their medical history or objective examination. The women were included after a negative pregnancy test result on the morning of the study. The regional ethics committee (Hvidovre, Denmark) approved the study, and subjects gave written, informed consent before inclusion. The subjects fasted from midnight the day before the study. An epidural catheter was inserted in the T7–T10 interspace *via* standard loss-of-resistance technique by an experienced anesthesiologist (C. L.). Appropriate catheter placement was tested with 3 ml lidocaine, 2%, with 1:200,000 epinephrine (t = 0). Then 5 + 5 ml bupivacaine, 0.5%, was injected (t = 5). The sensory upper level of the blockade (determined by pin prick) was aimed at T4. If the sensory blockade did not reach T4 after 20 min, an additional 5 ml bupivacaine, 0.5%, was administered. After 90 min, subjects were randomized by the closed-envelope method to receive either 0.2 mg/kg intravenous ephedrine or 7 ml/kg hydroxyethyl starch

(HES; Voluven®, 6% HES, 130/0.4; Fresenius Kabi, Bad Homburg, Germany). No fluids or vasopressors were given up to that point. HES was infused over 5 min through a peripheral vein. Plasma volume, erythrocyte volume, hematocrit, and mean corpuscular volume (MCV) were measured before the epidural blockade, at t = 90, and at t = 130 (see following sections). The study was terminated 60 min after completion of the HES infusion (t = 155). Subjects were monitored with electrocardiography and blood pressure monitoring (arm cuff) every 5 min throughout the study by an anesthesiologist. The baseline values of systolic and diastolic blood pressure and heart rate were calculated as the mean of two preinfusion measurements. Sensory blockade was monitored (by pin prick) every 20 min. Subjects with a maximal decrease in systolic blood pressure of greater than 20% from the baseline value within 80 min after induction of epidural anesthesia were considered hypotensive, and subjects with a decrease in systolic blood pressure of 20% or less from the baseline value were considered normotensive.

Plasma and Erythrocyte Volumes

Plasma and erythrocyte volumes were determined by standard tracer dilution technique[4] after triple injection of 200 kBq ^{125}I-labeled human albumin and single injection of 2 MBq ^{51}Cr sodium chromate *in vivo*–labeled erythrocytes, respectively. In detail, plasma volume was determined by injection of 200 kBq ^{125}I-labeled human albumin at each time point (subtracting any residual activity from the previous sample), obtaining blood samples after 10 min and determining plasma volume from these.[5] Because the method of obtaining multiple blood samples and calculating plasma volume by regression to zero values requires unchanged capillary permeability, hematocrit, and plasma protein concentration (all of which may change after epidural anesthesia), we chose the single-sample technique, which furthermore has the advantage of minimizing blood loss due to sampling.

Hematocrit and Mean Corpuscular Volume

Body hematocrit was calculated as the ratio between erythrocyte and plasma volume measurements at t = −10, t = 90, and t = 130 min. At the same time points, peripheral hematocrit (sampling from a peripheral vein) and MCV (separate sampling from a peripheral vein [9 ml blood drawn per subject] after reinjection of the initially drawn 2 ml blood) were determined.

Hemoglobin Sampling

Samples for measuring blood hemoglobin were drawn from the venous cannula in the arm not used for infusion every 5 min throughout the study. The first sample (baseline) was drawn in triplicate, and the mean value was used in the calculation of the baseline value. Before each sample, 2 ml blood was drawn to clear the sampling line. This amount was reinjected after the sam-

pling. A total of 14.0 ml blood was drawn for the analysis throughout the study (mean, 0.43 ml [14 ml/32] per sample) and replaced after each sampling by a total of 14.0 ml isotonic saline. The hemoglobin measurements were analyzed using an ABL510 Blood Gas Analyzer (Radiometer, Copenhagen, Denmark; coefficient of variation 1–3%, manufacturer's data).

Volume Kinetic Analysis

The distribution of the fluid given by infusion of HES was analyzed using a one-volume kinetic model.[6] In this model, the fluid is given at a rate k_i and is distributed in an expandable space having a volume (v), which the body strives to maintain at a target volume (V). Elimination occurs at a rate proportional by a constant (k_r) to the deviation from the target volume, V. In the current study, the base elimination constant (k_b), usually used to describe non–dilution-dependent elimination, was used by the analysis program to quantify the flow of fluid from more remotely located spaces back into the fluid space expanded by the infusion. The following differential equation describes the dilution changes in v:

$$\frac{dv}{dt} = K_i - k_b - k_r \frac{(v - V)}{V} \tag{1}$$

Because plasma volume is a part of v, dilution of arterial plasma was used to indicate $(v - V)/V$. Therefore:

$$(v - V)/V = [[(Hb_0 - Hb_n)/Hb_n](1 - Hct)] \tag{2}$$

Kinetic analysis was performed on all individual infusion experiments. The best estimates of the model parameters V, k_r, k_b, and their associated SEs were obtained by fitting the mathematical solutions to equation 2, which have been presented previously,[6] to the experimental data by using a nonlinear least-squares regression routine programmed in MATLAB version 4.2 (MathWorks Inc., Natick, MA). The result was presented as a one-volume model with parameters V, k_r, and k_b.

Statistical Analysis

Data were analyzed using nonparametric statistical methods. The Wilcoxon signed-rank test for paired observations was used to describe differences before *versus* after epidural anesthesia. For comparing data between the groups (fluid *vs.* ephedrine), the Mann-Whitney test was used. For correlations between two parameters, the Spearman ρ was applied. Categorical data were analyzed using the Fisher exact test. $P < 0.05$ was considered significant. Continuous data (systolic and diastolic blood pressure, heart rate, and hemoglobin values) were analyzed with the Friedman analysis of variance. Volume kinetic parameter estimates are given as medians and 25th–75th percentiles. These parameters are the results from nonlinear regression analyses and contain SEs.

Sample Size Estimation

The coefficient of variation of plasma volume measurements with the applied technique is known to be approximately 2%. We considered an increase in plasma volume of 150 ml after epidural anesthesia to be clinically relevant (initial plasma volume assumed to be 3,500 ml, estimated SD of difference 101). With a power to detect a minimal relevant difference of 80% and a level of significance of 0.05, eight subjects were needed. To account for variable subject responses, we included 12 subjects in the study.

Results

All subjects completed the study and followed the study protocol. Two subjects received supplemental bupivacaine (25 mg) because of insufficient sensory blockade. A median of 500 ml HES (range, 500–625 ml) and a median of 16 mg ephedrine (range, 10–17 mg) were administered in the respective groups at t = 90.

Systolic and Diastolic Arterial Pressure and Heart Rate

Both systolic and diastolic blood pressure and heart rate decreased significantly after administration of epidural anesthesia from t = 0 to t = 90 (fig. 1). Systolic blood pressure increased significantly after administration of both HES and ephedrine (from t = 90 to t = 130) without a difference between the groups, whereas neither diastolic blood pressure nor heart rate changed significantly after administration of either HES or ephedrine (fig. 1).

Plasma Volume

Plasma volume did not change 90 min after epidural anesthesia compared with baseline (all subjects) or when subdivided into normotensive or hypotensive subjects (table 1 and fig. 2). Changes in plasma volume did not correlate to the degree of hypotension (Spearman $\rho = 0.26$; $P = 0.41$). Forty minutes after administration of HES, plasma volume was significantly increased by a median of 324 ml, whereas no significant changes in plasma volume were observed after ephedrine administration (table 1).

Erythrocyte Volume

Erythrocyte volume did not change significantly during the study (table 1 and fig. 2).

Hematocrit

Peripheral hematocrit decreased significantly (from 0.41 to 0.40) at t = 90 compared with baseline and decreased significantly after HES administration (from 0.40 to 0.38) (table 1). Body hematocrit did not change during the study (table 1).

Mean Corpuscular Volume

Mean corpuscular volume data were only available from six subjects and did not change during the study (table 1).

Hemoglobin Concentration

Hemoglobin concentrations did not change significantly from t = 0 to t = 90 in either normotensive or hypotensive subjects. A significant decrease was seen after administration of HES (t = 90 to t = 130), whereas ephedrine administration did not change hemoglobin concentrations (data not shown).

Volume Kinetic Analysis

The administration of epidural anesthesia created a small dilution, approximately 10%, followed by a dilution after HES administration (fig. 3). On average, HES expanded a central volume of 1,482 ml (range, 825–1,759 ml) and was eliminated from the system by a constant k_r, 56 ml/min (range, 36–72 ml/min) (table 2). k_b, in this model reflecting the rate of fluid *recruited* into V, was estimated to be −3.7 ml/min (range, −5.3 to −1.6 ml/min).

Discussion

This study was mainly undertaken to investigate the changes in blood volume after epidural anesthesia *per se* and to capture the behavior of fluid given intravenously during epidural anesthesia in a situation in which volume loading is controversial. We found that plasma volume did not change *per se* after thoracic epidural anesthesia despite a decrease in blood pressure. Plasma volume was increased with fluid administration but was unchanged with vasopressors, whereas both treatments had similar hemodynamic effects. Hemoglobin concentrations were not significantly altered by either epidural blockade or ephedrine administration but were significantly decreased after HES administration.

The observed decrease in systolic and diastolic blood pressure and heart rate after epidural anesthesia corresponds with previous observations in healthy volunteers,[7] and the time frame of these circulatory effects are also well known.[7] To allow for a possible redistribution of fluid from the interstitial phase to the intravascular space, we chose 90 min as the appropriate time to evaluate the intravascular volume parameters. Previous studies during experimental hypovolemia have found a capillary refill to occur within 5 min,[2,8] and short-term studies (20–30 min) with and without concomitant fluid administration after lumbar epidural anesthesia with hypotension have also suggested a capillary refill to occur based on hemoglobin measurements.[1,9] However, these suggestions have not been documented by actual blood/plasma volume measurements. In several series of pa-
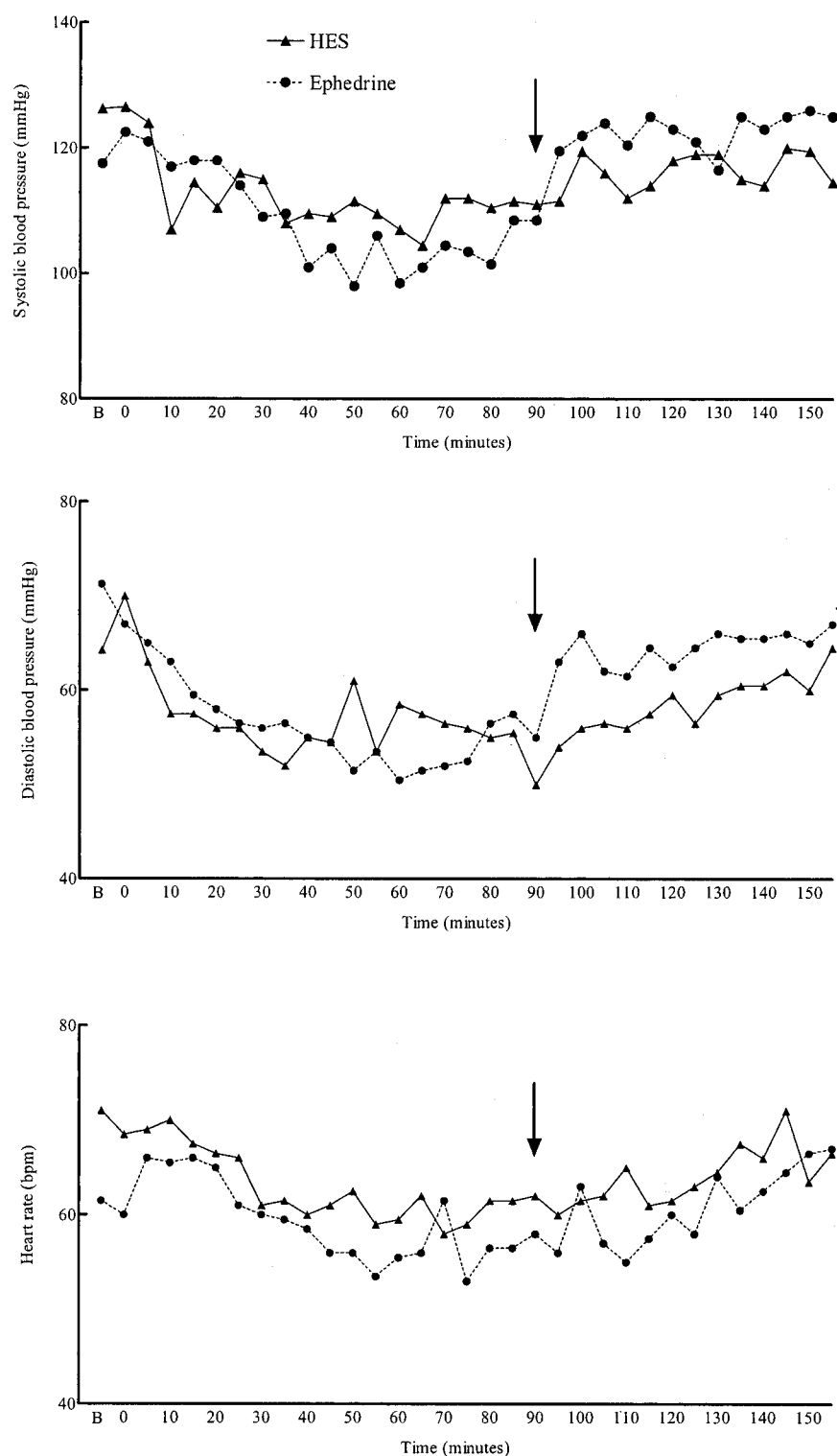
Fig. 1. Systolic and diastolic blood pressure and heart rate after administration of epidural anesthesia (t = 0) and hydroxyethyl starch (HES)–ephedrine (*arrows*). Median values are shown. B = baseline value.

tients undergoing lumbar epidural anesthesia, a larger percentage of an infused amount of fluid was retained intravascularly in hypotensive compared with normotensive patients (only indirectly measured by decrease in hemoglobin concentration, however).[1,10] The reasons behind a possible intravascular fluid retention in hypotensive compared with normotensive subjects during

experimental conditions have not been fully clarified, but mostly, they have been attributed to changing Starling effects.[10] Transcapillary fluid flux is governed by differences in the colloid and hydrostatic pressures between the plasma and the interstitial space. Initially, when a fluid load is given, most of the infused fluid shifts from the circulation to the interstitial compartment,

Table 1. Blood Volumes after Epidural Anesthesia

	Baseline (n = 12)	t = 90 (n = 12)	t = 130 Ephedrine Group (n = 6)	t = 130 HES Group (n = 6)
Plasma volume, ml	3,360 (2,601–3,754)	3,422 (2,482–3,984)	3,483 (2,679–4,144)	3,746† (3,378–4,044)
Erythrocyte volume, ml	1,983 (1,398–2,267)	1,980 (1,332–2,361)	1,948 (1,770–2,320)	2,113 (1,355–2,411)
Peripheral hematocrit	0.41 (0.37–0.47)	0.40* (0.35–0.46)	0.40† (0.37–0.44)	0.38† (0.33–0.47)
Body hematocrit (fraction by isotope ratios)	0.37 (0.31–0.40)	0.37 (0.30–0.42)	0.37 (0.30–0.39)	0.35 (0.28–0.42)
MCV, fl	89 (n = 6) (85–93)	89 (n = 7) (85–94)	86 (n = 3) (85–93)	90 (n = 4) (89–92)

Plasma volume, erythrocyte volume, hematocrit, and mean corpuscular volume (MCV) before and after epidural bupivacaine. Data are median and range (in parentheses).

* Significant compared with baseline.   † significant compared with t = 90.

fl = femtoliter; HES = hydroxyethyl starch.

thereby increasing its hydrostatic pressure. When the arterial pressure decreases after 15–20 min, there is a fluid flux causing intravascular hemodilution. However, significant hemodilution 20 min after the onset of lumbar epidural anesthesia has only been observed when epidural anesthesia was accompanied by fluid administration.[1] These findings were confirmed by this study because blood and plasma volumes were similar both at the beginning of the experiment and before interventions at t = 90 (table 1). However, when fluid was administered, there was a profound dilution and increased blood volume (table 1), which shows that epidural anesthesia *per se* had no effect on blood volume.[1]

To more precisely describe the changes in intravascular volume, we measured hematocrit, erythrocyte volume, and MCV. Erythrocyte volume did not change significantly during the study but tended to increase with fluid administration (table 1). The reasons for this are unclear because no changes in individual erythrocyte cell volumes occurred (measured by MCVs). However, to be accurate, the indicator dilution techniques required uniform distribution of the tracer. Previous findings have suggested that this is in fact not true during epidural anesthesia because ^{99}Tc-labeled erythrocytes sequester within the denervated area after epidural anesthesia (assessed by gamma camera scan and plethysmography).[11] However, these effects were studied only during the initial hemodynamic changes (until 25 min after epidural anesthesia). During the later measurements in the current study (t = 90 min) when all subjects were hemodynamically stable and systolic pressure was back at baseline value, we considered distribution of the tracer to be uniform. Blood and plasma volumes are traditionally estimated by indicator dilution and mass balance techniques,[12,13] and in recent years, they have been supplemented by volume kinetic analyses,[14,15] a pharma-
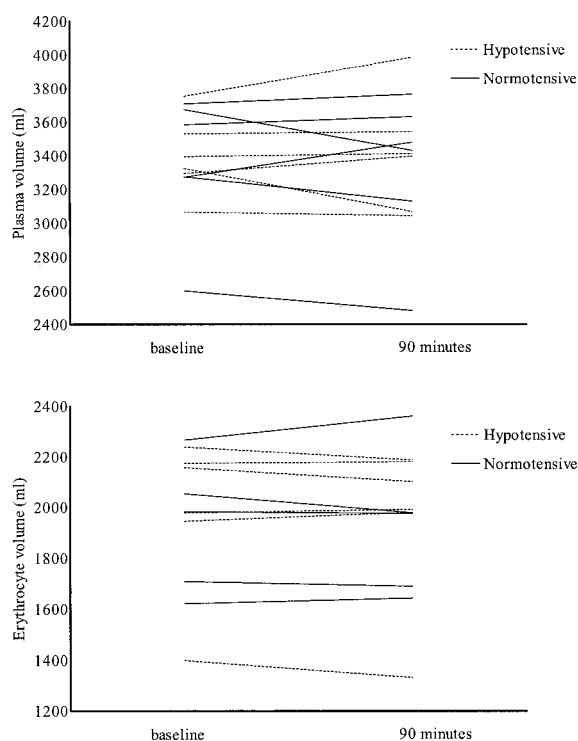

Fig. 2. Plasma volume (n = 12) and erythrocyte volume (n = 11) after epidural anesthesia in normotensive (maximal decrease in systolic blood pressure ≤ 20% from the baseline value) *versus* hypotensive subjects (maximal decrease in systolic blood pressure > 20% from the baseline value), both within 80 min after induction of epidural anesthesia.
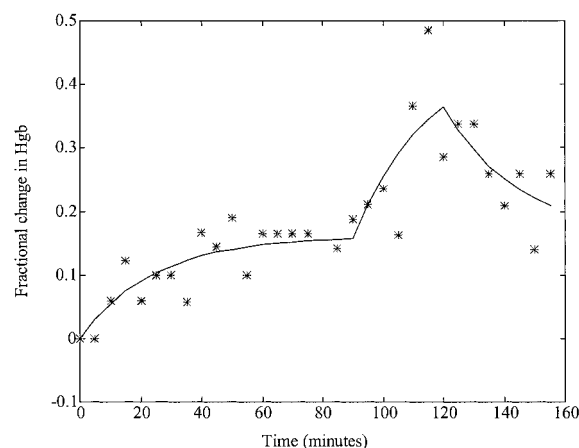

Fig. 3. Final fit, one-volume model. Volume kinetic analysis of one subject receiving 7 ml/kg hydroxyethyl starch over 5 min during epidural anesthesia. The epidural is placed at 0 min, and infusion is started at 90 min. The experiment ends at 155 min. Hgb = hemoglobin.

Table 2. Volume Kinetic Analysis of Hydroxyethyl Starch after Epidural Anesthesia

	Best Estimate	SE
V, ml	1,482 (825–1,759)	550 (324–840)
k_r, ml/min	56 (36–72)	19 (11–24)
k_b, ml/min	−3.7 (−5.3 to −1.6)*	2 (2–3.5)

Volume kinetic parameter estimates for the experiments with intravenous infusions of hydroxyethyl starch after administration of epidural anesthesia. Data are the median (25%–75% percentiles) for individual analyses of all experiments.

* The negative base elimination constant (k_b) reflects flow back into the expanded fluid space.

k_r = elimination rate proportional by a constant; V = target volume.

cokinetic tool used to study more closely the time course of fluid shifts in various settings.[6,16] This method has many similarities to pharmacokinetics but is based on the dilution of the venous plasma caused by the infused fluid instead of measuring the concentration of a drug in the blood. To look more closely at the fluid behavior during infusion, indicator dilution techniques in this study were supplemented by volume kinetic calculations. Hemoglobin analysis showed that when epidural anesthesia was applied, there was a very small dilution (fig. 3). When HES was administered, volume kinetic analysis showed a dilution of the plasma volume (fig. 3) in accordance with the findings when the indicator dilution technique was used (table 1). The volume kinetic data delineate the time course of HES distribution, which cannot be assessed by tracer dilution technique. The administration of HES expanded a central volume, V, that seemed to be quite small, approximately 1.5 l (table 2), which is approximately half of the measured plasma volume (table 1). Therefore, the effect of HES may be seen as a rapid expansion of central volume with an increase in preload to prevent hypotension. The elimination rate constant k_r further indicated a rapid elimination (table 2), being on the average 56 ml/min, which is a value closer to what has been obtained for crystalloid fluid boluses.[6,15] As a comparison, k_r for dextran 70 in healthy normotensive volunteers was 10 ml/min.[6] It could be hypothesized that the rapid reduction of the dilution after the end of infusion is due to redistribution between the small central fluid space (1.5 l) and the remainder of the plasma volume. This would indicate a step-by-step fluid distribution during infusion from centrally located spaces to more peripherally perfused parts during the administration of regional anesthesia. The preferential distribution of infused fluid to the central plasma volume, together with a slower transport of fluid to a more remote body fluid space, is a meaningful adaptation because infused fluid then restores cardiac

preload more effectively. Another interesting finding is that the kinetic evaluation allowed quantification of the recruitment of fluid from the periphery to the central fluid space (in which hemoglobin is readily equilibrated) at a rate of approximately 4 ml/min (table 2). This quantifies the transcapillary flux that occurs during fluid loading under epidural anesthesia. On the contrary, ephedrine did not have these volume shifts.

In conclusion, we have demonstrated that epidural anesthesia *per se* does not lead to any changes in intravascular volume and that both ephedrine and fluids have comparable hemodynamic effects when applied 90 min after establishing an epidural blockade. Furthermore, an infused fluid causes a profound dilution and seems to be more centrally located under epidural anesthesia. Because both ephedrine and fluids have similar hemodynamic effects, vasopressors may be preferred in the treatment of hypotension after epidural anesthesia, especially for patients with cardiopulmonary diseases in which perioperative fluid overload is undesirable.[3]

References

1. Hahn RG: Haemoglobin dilution from epidural-induced hypotension with and without fluid loading. Acta Anaesthesiol Scand 1992; 36:241–4
2. Lanne T, Lundvall J: Very rapid net transcapillary fluid absorption from skeletal muscle and skin in man during pronounced hypovolaemic circulatory stress. Acta Physiol Scand 1989; 136:1–6
3. Holte K, Sharrock NE, Kehlet H: Pathophysiology and clinical implications of perioperative fluid excess. Br J Anaesth 2002; 89:622–32
4. Moore FD: Body composition and its measurement in vivo. Br J Surg 1967; 54(suppl):431–5
5. Henriksen JH, Bendtsen F, Sørensen TIA, Stadeager C, Ring-Larsen H: Reduced central blood volume in cirrhosis. Gastroenterology 1989; 97:1506–13
6. Svensen C, Hahn RG: Volume kinetics of Ringer solution, dextran 70, and hypertonic saline in male volunteers. ANESTHESIOLOGY 1997; 87:204–12
7. Stanton-Hicks MA: Cardiovascular effects of extradural anaesthesia. Br J Anaesth 1975; 47:253–61
8. Lundvall J, Lanne T: Large capacity in man for effective plasma volume control in hypovolaemia via fluid transfer from tissue to blood. Acta Physiol Scand 1989; 137:513–20
9. Drobin D, Hahn RG: Time course of increased haemodilution in hypotension induced by extradural anaesthesia. Br J Anaesth 1996; 77:223–6
10. Hahn RG: Increased haemodilution in hypotension induced by epidural anaesthesia. Acta Anaesthesiol Scand 1993; 37:357–60
11. Arndt JO, Hock A, Stanton-Hicks M, Stuhmeier KD: Peridural anesthesia and the distribution of blood in supine humans. ANESTHESIOLOGY 1985; 63:616–23
12. International Committee for Standardization in Haematology: Recommended methods for measurement of red-cell and plasma volume. J Nucl Med 1980; 21:793–800
13. Jones JG, Wardrop CA: Measurement of blood volume in surgical and intensive care practice. Br J Anaesth 2000; 84:138–42
14. Brauer LP, Svensen CH, Hahn RG, Kilicturgay S, Kramer GC, Prough DS: Influence of rate and volume of infusion on the kinetics of 0.9% saline and 7.5% saline/6.0% dextran 70 in sheep. Anesth Analg 2002; 95:1547–56
15. Connolly CM, Kramer GC, Hahn RG, Chaisson NF, Svensen CH, Kirschner RA, Hastings DA, Chinkes DL, Prough DS: Isoflurane but not mechanical ventilation promotes extravascular fluid accumulation during crystalloid volume loading. ANESTHESIOLOGY 2003; 98:670–81
16. Drobin D, Hahn RG: Kinetics of isotonic and hypertonic plasma volume expanders. ANESTHESIOLOGY 2002; 96:1371–80