BACKGROUND

Spinal anesthesia induces a series of physiological adaptations that include reduction of the systemic vascular resistance and mean arterial pressure (MAP), whereas cardiac output remains relatively unaffected, except in high-level analgesia. These adaptations differ among body regions where the local fluid dynamics is complex and not yet fully understood. Anesthetized areas are characterized by vasodilatation and increased blood flow, whereas a baroreceptor-mediated reflex increase in sympathetic activity in nonanesthetized body regions induces compensatory vasoconstriction. Crystalloid fluid is therefore infused, as the compensatory vasoconstriction is insufficient to maintain an acceptable MAP. However, infusion of fluid is often also insufficient, even when infused very rapidly. Therefore, injection of a vasoconstrictor is required.

Model-predicted capillary leakage in graded hypotension: Extended analysis of experimental spinal anesthesia

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Background: Crystalloid fluid infused during the induction of spinal anesthesia is involved in a complex set of physiological responses, including vasodilatation, reactive vasoconstriction, and changes in mean arterial pressure (MAP). The present evaluation compares the modeled capillary leakage in anesthetized versus nonanesthetized body regions.

Methods: Ten female volunteers (mean age, 29 years) received 25 ml/kg of Ringer’s acetate over 60 min during experimental spinal anesthesia. Blood hemoglobin was measured repeatedly in the radial artery (reference), arm (cubital) vein, and leg (femoral) vein for 240 min. Each pattern of data served as a dependent variable in volume kinetic analyses that used mixed models software and MAP as covariate.

Results: The capillary leakage of fluid from the plasma to the extravascular space peaked at 17 ml/min when MAP was 100 mmHg, and the two venous curves were virtually identical. At MAP 60 mmHg, the rate was reduced to 10-12 ml/min when assessed in arterial blood and leg vein blood, but only 5 mmHg in blood collected from the arm vein. The distribution half-life of infused fluid was then 40 min in the leg and 80 min in the arm. These results suggest that vasoconstriction in nonanesthetized body regions halves the capillary leakage that is observed in vasodilated, anesthetized body regions.

Conclusion: Graded hypotension during spinal anesthesia reduced the capillary filtration of fluid as determined by volume kinetic analysis. The effect was twice as great when venous blood was sampled from a nonanesthetized body region than from an anesthetized body region.
Fluid shifts during anesthesia can be analyzed by volume kinetics using crystalloid fluid as a tracer. This method is based on the close inverse correlation between hemodilution and the blood water, and it might disclose differences in fluid transfer rates depending on whether the sampled body region is anesthetized or nonanesthetized. The results reflect basic physiological mechanisms with regard to the influence of MAP, vasoconstriction, and vasodilatation in fluid filtration and the build-up of tissue edema.

The present study analyzes the transcapillary flow of fluid during spinal anesthesia, with special emphasis on MAP and the difference between anesthetized and nonanesthetized body regions. The data sets have previously been studied using a simpler approach, but recent developments in our mathematical tools now allow an extension of the analysis. These developments include the influence of covariates, which can be used to contrast the transcapillary fluid exchange for different levels of MAP and the spread of analgesia.

Our hypothesis was that an increased blood flow due to vasodilatation in the legs increases the capillary leakage to the extravascular space, and this can help to explain the development of edema and why crystalloid fluid is insufficient to maintain MAP. We used arterial blood as a reference and arm vein blood to contrast the findings from the leg.

2 | METHODS

2.1 | Subjects and approvals

Ten healthy female volunteers aged 21-39 (mean 29) years, with a body weight of 58-67 kg (mean 62.5 kg), participated as an experiment consisting of an infusion of crystalloid fluid during induction of spinal anesthesia. The protocol was approved by the Regional Ethics Committee of Karolinska Institutet (Nr 97/123, officer in charge Paul Hjemdahl, approved on January 19, 1998). The study was not registered in a database due to the retrospective nature of the data. Each volunteer gave her written informed consent after a medical examination. None of the volunteers used daily medication. The protocol originally also contained an experiment with a fluid infusion only, but the data are not reported here.

2.2 | Experimental procedure

The volunteers arrived at the hospital at 8 am. No oral fluid or food was allowed between midnight and completion of the experiment. Instrumentation consisted of cannulas for sampling blood from the radial artery, cubital vein, and femoral vein, and for placement of an indwelling catheter into the bladder. A cannula was also placed in the cubital vein of the opposite arm for the administration of fluid. The volunteers rested in the supine position during an equilibration period of 20 min before the infusion was initiated, and they then remained supine throughout the experiment.

The infusion consisted of an IV infusion of 25 ml/kg acetated Ringer’s solution (Na 130, Cl 110, Ca 2, K 4, acetate 30 mmol/L; osmolality 273 mosmol/kg) provided by an infusion pump (Flo-Guard 6201, Baxter, IL) over 60 min.

After 25 min of the infusion, when almost half of the fluid load had been administered, the volunteer was temporarily placed in a lateral position and received spinal anesthesia with a Whitacre 26-gauge needle (Becton Dickinson) in the lumbar interspace located between the top of the crista iliaca, aiming at L3–L4, using 3.0-ml bupivacaine hydrochloride 5 mg/ml (AstraZeneca AB, Södertälje, Sweden). The spread of the analgesia was tested every 5 min by loss of cold sensation, using an alcohol-drained swab, during the onset of the analgesia. The intervals were extended when the spread of the analgesia had reached steady state. Intravenous ephedrine 5 mg, which could be repeated if necessary, was withheld until arterial hypotension coincided with symptoms (sweating, nausea, or bradycardia).

Blood samples (4 ml) were taken, and the urinary excretion was measured every 5 min during the first 120 min and every 10 min thereafter, for up to 240 min. A discard volume of 3 ml was drawn before each blood collection. This blood was then returned, and the cannula flushed with 3 ml of saline to prevent clotting and to replace the amount of withdrawn plasma.

The hemoglobin (Hb) concentration in whole blood, the red blood cell count, and the mean corpuscular volume were measured with a Technicon H2 (Bayer) using colorimetry at 546 nm for Hb, and light dispersion using a helium neon laser for the other two parameters. Forty duplicate samples drawn at baseline assured a coefficient of variation (CV) of 0.8% for Hb. Plasma dilution was calculated for each time point based on all three erythrocyte indices, given as the mean of the dilution of the Hb and red blood cell counts and corrected for blood sampling as explained in Data S1. Mean corpuscular volume was not included in the calculations as changes were less than 1%.

Heart rate and noninvasive arterial pressure were displayed on an AS 3-monitor (Datex, Finland). Pulse oximetry and electrocardiogram were also monitored. Each experiment was monitored by two anesthesiologists and one anesthesia nurse.
2.3 | Kinetic analysis

The kinetics of the infusion fluid was studied using a two-volume kinetic model (Figure 1A) with rate constants for distribution and redistribution ($k_{12}$ and $k_{21}$), one route of elimination ($k_{10}$), and one scaling factor between the dilution and volume ($V_c$, central volume). This model was fitted to two dependent variables (plasma dilution and urinary excretion) in all experiments on a single occasion, using the Phoenix software for nonlinear mixed effects, version 1.3 (NLME) and the First-Order Conditional Estimation Extended Least Squares (FOCE ELS) as search routine. Every estimate of the plasma dilution and each 30 min portion of urine were used. Separate runs were conducted for arterial blood and for venous blood from the arm and the leg.

This “base model” is intended to reflect normal physiology and has been discussed in several previous publications.4,5 $V_r$ is thought to correspond to the plasma from which distribution and redistribution occurs to the interstitial fluid space, $V_t$. Elimination via $k_{10}$ represents urinary excretion.

All flows are proportional to the value of the rate constant to the volume expansion of a fluid space, as $V_t$ or $V_c$. Hence, the flow of fluid from plasma to the extravascular space (from $V_c$ to $V_t$) was given by the product of $V_c$ and $k_{12}$ and the return flow by the product of $V_t$ and $k_{21}$.

Covariate analysis was then used to examine the possible influence of the individual-specific and time-varying MAP and the spread of analgesia (Th level) on the fixed model parameters ($k_{12}$, $k_{21}$, $k_{10}$, and $V_r$). A new individual measurement was entered on each occasion that plasma dilution was measured.5,7

A covariate was accepted for inclusion if it reduced the residual error of the model, expressed as −2(LL) (log likelihood), by more than 3.8 points ($P < .05$), if the 95% confidence interval (CI) of the parameter estimate did not include zero, and if the between-subject CV was less than 50%. Data S1 shows the differential equations for the kinetic model and explains how the covariates mathematically affect the fixed parameters.

Computer simulations using MATLAB R2019b (Math Works, Inc.) were used to illustrate the influence of the key covariates on the distribution of fluid between plasma ($V_c$), the extravascular fluid space ($V_t$), and the modeled urine flow.

Demographic data were reported as the mean (standard deviation) and the kinetic data were reported as the “best estimate” (95% CI). Changes over time were evaluated by the paired t test and group differences by the unpaired t test. $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Basic data

The four parameters in the base model were successfully fitted to the data on urinary excretion and plasma dilution in arterial blood, in venous blood from the arm, and in venous blood from the leg (Figure 1, Table 1). Each series contained 370 measurement points, with no exclusions. All original data are provided in Data S2.

Only one treatment with ephedrine (10 mg) was provided to one of the volunteers.

MAP varied between 54 and 107 (mean, 83.4) mmHg and the maximum spread of the analgesia from L2 to Th3 (patient mean, Th 5). Both MAP and the spread of the analgesia served as statistically significant covariates to $k_{12}$ (i.e., to the rate constant for the distribution of fluid from the plasma to the extravascular space, from $V_c$ to $V_t$).

3.2 | Capillary filtration

The effect of the covariance of MAP on $k_{12}$ over time was illustrated by the following comparisons between the simulated fluid distribution at MAP 60 and 100 mmHg:

Arterial blood and blood sampled from the femoral vein showed that the modeled absolute flow of infused fluid from the plasma to the extravascular space (from $V_c$ to $V_t$) over time was reduced by approximately 50% at MAP 60 mmHg compared with MAP 100 mmHg (Figure 2A,B). Likewise, the net flow to the extravascular space was lower in the presence of arterial hypotension (i.e., inflow minus outflow) (Figure 2C,D).

By contrast, the net flow obtained by sampling the arm vein was only half as large as the flows indicated by the arterial and leg vein blood (Figure 2B,D). Conversely, the leg vein flow became quite similar to the flow based on arterial blood (“arterialization”) in the

![Figure 1](image-url)

**FIGURE 1** (A) The kinetic model used for analysis and simulation. (B) Measured versus individually predicted urine volume measured every 30 min, based on the data measured in arterial blood. (C) The same plot, but for plasma dilution. (D) The conditional weighted residuals (CWRES) versus the predicted plasma dilution, without considering the individual-specific covariates. Arterial blood data
presence of spinal-induced hypotension, whereas it was virtually identical to the arm vein flow at MAP 100 mmHg.

### 3.3 | Distribution half-lives

The gradual changes in the distribution rate constant ($k_{12}$) with reductions in the MAP, when based on blood sampled from the cubital and femoral veins, are highlighted in Figure 3A. The corresponding distribution half-life (obtained as ln 2/$k_{12}$) was prolonged from 20 to 40 min when MAP decreased from 100 to 60 mmHg and leg vein blood was sampled, and from 20 to 80 min when arm vein blood was sampled (Figure 3B).

### 3.4 | Exploratory analyses

Data S1 contains a kinetic analysis using the spread of analgesia instead of MAP as a covariate in the kinetic model, along with additional illustrations. The elimination half-life is also explored.

### 4 | DISCUSSION

#### 4.1 | Key findings

Our study hypothesis was that fluid filtration in the legs would increase as the vasodilatation accelerates the blood flow, but our results do not support this view. Instead, a large reduction in MAP is more important to the filtration than is the vasodilatation.

Spinal anesthesia causes vasodilatation of preferentially the pre-capillary resistance vessels (arterioles), which increases the capillary hydrostatic pressure and favors capillary filtration. However, the accompanying decrease in MAP, which reduces the capillary hydrostatic pressure, apparently overran the effect of vasodilatation on the capillary filtration. Moreover, the effect of MAP on the capillary

### Table 1

|                 | Arterial | Arm vein | Leg vein |
|-----------------|---------|----------|----------|
| **Base model**  |         |          |          |
| $k_{12}$ ($10^{-3}$ min$^{-1}$) | 49.3 (28.0) | 23.1 (7.8) | 31.5 (13.8) |
| $k_{21}$ ($10^{-3}$ min$^{-1}$) | 12.3 (4.2) | 7.5 (2.4) | 7.6 (6.1) |
| $k_{10}$ ($10^{-3}$ min$^{-1}$) | 30.1 (11.0) | 21.4 (3.7) | 23.9 (5.5) |
| $V_c$ (L)       | 2.76 (0.74) | 4.59 (0.63) | 4.28 (0.98) |
| -(2LL) for base model | -864 | -806 | -889 |
| **Covariate**   |         |          |          |
| MAP on $k_{12}$ | 2.03 (0.94) | 3.15 (0.84) | 1.57 (0.43) |
| -(2LL) with covariate | -878 | -815 | -897 |

Note: The arterial pressure is used as a covariate to the modeled capillary leakage. Data are the best estimate (standard error). The best estimates were used to create both Figures 2 and 3. MAP was applied as a power covariate model. Mean MAP was 83.4 mmHg. Abbreviation: MAP, mean arterial pressure.
filtration was even greater in vasoconstricted than in vasodilated body regions, which is not intuitive.

4.2 | Methodology

The results were obtained by comparing kinetic modeling of the transcapillary exchange of fluid in anesthetized and nonanesthetized body regions when approximately 1.5 L of Ringer’s had been infused before and during onset of spinal anesthesia in volunteers. The respective vascular beds were represented by one leg (vasodilatation) and one arm (vasoconstriction).

The two venous sampling sites indicated virtually identical fluid dynamics when MAP was 100 mmHg. The data used for these estimates are likely to mainly represent the 30 min of fluid loading before spinal anesthesia was induced and, in some cases, also when the anesthesia had subsided.

Arterial blood was analyzed to serve as an integral of the whole body, but it showed a faster flow from the plasma to the extravascular space than was evident from the venous curves. This difference is probably due to sampling of the arterial blood before the infused fluid had passed through the capillaries for the first time.

The hypotension associated with the spinal anesthesia markedly changed this situation. First, the spinal-induced hypotension reduced the capillary leakage of fluid in all three vascular beds. A shift in MAP from 100 to 60 mmHg decreased the capillary leakage by 50%, which probably reflects a decrease in the capillary hydrostatic pressure (cf. Figure 2A vs. Figure 2B). Second, the modeled capillary leakage based on blood sampling from the leg became similar to the arterial curve, which is evidence of widespread vasodilatation and “arterialization” of the venous curve.

4.3 | Vasodilatation versus vasoconstriction

The compensatory vasoconstriction that is likely to have developed in the arm further reduced the capillary leakage to approximately 25% of the baseline value (Figure 3D). This finding implies that more of the infused fluid remains in the bloodstream in response to endogenous vasoconstriction than to vasodilatation. This was an unexpected finding but a logical consequence of the absence of relaxation of the pre-capillary arterioles that is found in vasodilated body regions.

The physiological response to endogenous activation of the sympathetic nervous system consists of arteriolar vasoconstriction (α₁-receptor effect), decreased precapillary resistance (β₂-receptor), and postcapillary venodilatation (β₂-receptor). These changes restrict the precapillary blood flow while reducing the capillary pressure and the postcapillary resistance to flow, which all promote absorption of extravascular fluid. The same changes would also retard capillary leakage of infused crystalloid fluid, which further serves to explain why the capillary filtration is even lower in vasoconstricted than in vasodilated body regions.

The effect of sympathetic activation on the transcapillary exchange of fluid shown here differs from the chemically induced vasoconstriction by exogenous norepinephrine, which is characterized by a reduction in the blood volume rather than by an increase. We hypothesize that exogenous norepinephrine accelerates the capillary filtration mainly by increasing in the capillary hydrostatic pressure, which occurs when MAP increases. The opposite effect by endogenous sympathetic activation found here might then be due to that MAP was decreasing when the measurements were made.
Previous work by our group showed that the blood volume increases in proportion to the reduction of MAP in epidural anesthesia\textsuperscript{11} and general anesthesia.\textsuperscript{12} The changes have been attributed to increased “unstressed volume” due to vasodilatation. However, our present results suggest that the blood volume would increase regardless of dilation or constriction of the vascular system and that the increase would be even greater due to constriction.

4.4 | Splanchnic region

The splanchnic region serves as an important blood reservoir\textsuperscript{13} that also has a high density of adrenergic receptors.\textsuperscript{14} Spinal anesthesia dilates the splanchnic veins except when the analgesic spread is limited to the lumbar region.\textsuperscript{15} Accumulation of infused fluid in the splanchnic region would increase the size of the modeled plasma volume (\(V_p\)) but not affect the fluid distribution, as the latter is based only on the three rate constants and not on \(V_c\). Nevertheless, pooling of blood to the splanchnic region might have contributed to the overall reduction of transcapillary flow rates shown in Figure 2. By contrast, splanchnicus could not have influenced the difference in flow between the arterial and venous systems as splanchnic blood reaches the arterial system before the venous sampling sites we used.

4.5 | Kinetic analysis

The flow curves were not obtained by direct measurement, which would have required intensive pharmacological intervention to maintain the MAP at a constant 100 or 60 mmHg throughout the 4-h experiment. Instead, the flows involved in the disposition of infused Ringer’s acetate solution were quantified by population kinetic analysis, which is an industrial standard for describing the distribution and elimination of drugs.\textsuperscript{7}

The adaptation for fluids that we used operates by detecting a “wall” between a central (\(V_c\)) and a peripheral fluid space (\(V_p\)). The water volume \(V_c\) equilibrates very quickly with the site of infusion and is then said to represent the plasma volume expansion. The flows between these body fluid spaces are indicated by three rate constants (\(k_{12}\), \(k_{21}\), and \(k_{10}\)). The flow from \(V_c\) to \(V_p\), is simply given by the product of \(V_c\) and \(k_{12}\), whereas the return flow is the product of \(V_p\) and \(k_{21}\).

The relationship between transvascular flow and MAP was established by “time-varying covariate analysis” where the flow rate at each of the 37 studied time points of each experiment was matched with the MAP obtained at the same point in time. This approach allowed us to simulate flows at any MAP within the range of arterial pressures measured in the study. This is possible even though the MAP was 60 mmHg during only a limited time period during any experiment. The benefit of our approach is that pharmacological intervention could be avoided, which otherwise would be both an ethical issue and a factor that would cast uncertainty on the results.

4.6 | Limitations

Our study highlights the effect of vasocostrictor and vasodilation on fluid distribution, but the clinical value of the results might be limited due to the increasing focus on vasopressors to prevent hypotension during spinal anesthesia.

Only females were studied because catheterization of the bladder is more traumatic in males.

Half of the fluid load was infused prior to the anesthesia induction, which was done to obtain kinetic data at baseline. The baroreceptor-mediated vasoconstriction in body regions above the upper level of the analgesia was not assessed directly but is a fairly well accepted view based on previous studies.\textsuperscript{1}

No direct evaluation of the role of the splanchnic region to the present findings was made.

Other factors than MAP may affect the transvascular fluid exchange in vasoconstricted and vasodilated body regions, but their roles are unclear. Vasodilation is expected to increase the number of capillaries that are available for fluid exchange, thereby increasing the functional capillary density and the capillary filtration coefficient (CFC). The latter might be relevant to the fluid balance during anesthesia\textsuperscript{15} although animal studies provide conflicting evidence.\textsuperscript{16} By contrast, arterio-venous shunting in the legs increases during spinal anesthesia\textsuperscript{17} and should reduce the endothelial surface available for filtration. Shedding of the endothelial glycocalyx layer might alter the capillary permeability, but the role of this process in the distribution of crystalloid fluid is unclear at present.\textsuperscript{18}

The kinetic analysis operates on the assumption that the body is a single entity, which is only true for the arterial blood after the infusion has ended. Further analysis of this issue, which is given in Data S1, indicates that twice as much of the body volume was subject to vasodilation than to vasoconstriction when the MAP was 60 mmHg, which seems to be reasonable.

Data S1 also discusses the elimination half-life, which averaged 31 min. Hence, nearly all fluid had been excreted after 2 h, but as the last portion of fluid was given at 1 h, the last 5% of the administered volume was eliminated between 3 and 4 h of the study. The quite normal elimination half-life makes hypovolemia and dehydration prior to the study highly unlikely.\textsuperscript{19}

5 | CONCLUSIONS

Arterial hypotension during spinal anesthesia reduced the capillary filtration of infused Ringer’s solution both in anesthetized and non-anesthetized body regions, with the greatest reduction observed in nonanesthetized regions.

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CONFLICT OF INTEREST
None declared.

DATA AVAILABILITY STATEMENT
All data are available in Data S2.

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REFERENCES
1. Liu SS, McDonald SB. Current issues in spinal anesthesia. Anesthesiology. 2001;94:888–906.
2. Ewaldsson CA, Hahn RG. Bolus injection of Ringer’s solution and dextran 1 kD during induction of spinal anesthesia. Acta Anaesthesiol Scand. 2005;49:152–159.
3. Loubert C. Fluid and vasopressor management for Cesarean delivery under spinal anesthesia: continuing professional development. Can J Anaesth. 2012;59:604–619.
4. Hahn RG. Understanding volume kinetics. Acta Anaesthesiol Scand. 2020;64:570–578.
5. Hahn RG. Arterial pressure and the rate of elimination of crystalloid fluid. Anesth Analg. 2017;124:1824–1833.
6. Hahn RG, Lindahl CC, Drobin D. Volume kinetics of acetated Ringer’s solution during experimental spinal anaesthesia. Acta Anaesthesiol Scand. 2011;55:987–994.
7. Owen JS, Fiedler-Kelly J. Introduction to population pharmacokinetic/pharmacodynamic analysis with nonlinear mixed effects models. Hoboken: Wiley & Sons; 2014.
8. Dull RO, Hahn RG. Transcapillary refill: the physiology underlying fluid reabsorption. J Trauma Acute Care Surg. 2021;90:e31–e39.
9. Lister J, McNeill IF, Marshall VC, Plzak Jr. LF, Dagher FJ, Moore FD. Transcapillary refilling after hemorrhage in normal man: basal rates and volumes: effect of norepinephrine. Ann Surg. 1963;158:698–709.
10. Nygren A, Redfors B, Thorén A, Ricksten SE. Norepinephrine causes a pressure-dependent plasma volume decrease in clinical vasodilatory shock. Acta Anaesthesiol Scand. 2010;54:814–820.
11. Drobin D, Hahn RG. Time course of increased haemodilution in hypotension induced by extradural anaesthesia. Br J Anaesth. 1996;77:223–226.
12. Li Y, Zhu S, Hahn RG. The kinetics of Ringer’s solution in young and elderly patients during induction of general anesthesia with propofol and epidural anesthesia with bupivacaine. Acta Anaesthesiol Scand. 2007;51:880–887.
13. Gelman S. Venous function and central venous pressure: a physiologic story. Anesthesiology. 2008;108:735–748.
14. Hogan QH, Stekel TA, Stadnicka A, Bosnjak ZJ, Kampine JP. Region of epidural blockade determines sympathetic and mesenteric capacitance effects in rabbits. Anesthesiology. 1995;83:604–610.
15. Bruegger D, Bauer A, Finsterer U, Bernasconi P, Kreimeier U, Christ F. Microvascular changes during anesthesia: sevoflurane compared with propofol. Acta Anaesthesiol Scand. 2002;46:481–487.
16. Bentzer P, Kongstad L, Grände PO. Capillary filtration coefficient is independent of number of perfused capillaries in cat skeletal muscle. Am J Physiol Heart Circ Physiol. 2001;280:H2627–2706.
17. Sivarajan M, Amory DW, Lindblom LE, Schwettmann RS. Systemic and regional blood-flow changes during spinal anesthesia in the rhesus monkey. Anesthesiology. 1975;43:78–88.
18. Hahn RG, Patel V, Dull RO. Glycocalyx shedding: systematic review and critical appraisal. Acta Anaesthesiol Scand. 2021;65:590–606.
19. Hahn RG, Lyons G. The half-life of infusion fluids: an educational review. Eur J Anaesthesiol. 2016;33:475–482.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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