

# Volume kinetics of Ringer's solution during induction of spinal and general anaesthesia

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The kinetics of an i.v. infusion of 20 ml kg<sup>-1</sup> of Ringer's solution over 60 min was studied in patients undergoing spinal ( $n=10$ ) and general ( $n=10$ ) anaesthesia. The induction resulted in similar changes in volume kinetic parameters in both groups. When a one-volume model was employed ( $n=8$ ), however, the infusion expanded a smaller body fluid space in the four patients who had received preoperative enteric lavage (3.3 vs 8.3 litres), which is consistent with hypovolaemia. When a two-volume model was statistically justified ( $n=12$ ), the induction reduced the rate of fluid equilibration between a fairly small central ( $V_1$ , mean 1.4 litres) and a peripheral body fluid space by about 50% ( $P<0.01$ ). The kinetic analysis suggested that a rapid fluid load of 350 ml given over 2 min just after the induction could possibly prevent arterial hypotension because of central hypovolaemia. This was confirmed in five additional patients.

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The onset of spinal and epidural anaesthesia is often accompanied by acute arterial hypotension. Ringer's solution is usually infused for prophylaxis, although the effectiveness of such a measure has been questioned.<sup>1–4</sup>

The poor preventive effect of fluid is difficult to understand as relative hypovolaemia is believed to be the cause of the hypotension. General anaesthesia also results in arterial hypotension, but its induction is associated with a generalized peripheral vasodilatation rather than a sympathetic block, which might imply that the body handles infused fluid differently than during spinal anaesthesia.

In the present study, we use volume kinetic analysis to compare the distribution and elimination of Ringer's acetate solution during the induction of spinal and general anaesthesia. The purpose of comparing these two situations is to obtain evidence as to whether the approaches for treatment should be the same. Furthermore, we wanted the kinetic analysis to possibly indicate how fluid can be used to prevent the hypotension.

Volume kinetics is based on the assumption that fluid given by i.v. infusion expands either one ( $V$ ) or two ( $V_1$  and  $V_2$ ) fluid spaces in the body. The elimination of fluid from the system and the exchange of infused fluid between  $V_1$  and  $V_2$  are governed by the constants  $k_e$  and  $k_1$ , respectively.<sup>5–11</sup> Repeated measurements of the blood haemoglobin (B-Hb) concentration and urinary excretion were used on a

computer-model to find estimates of the parameters in the volume kinetic models.

## Patients and methods

Twenty patients between 33 and 93 (mean 67) yr of age with a body weight of 43–130 kg (mean 77 kg) undergoing elective surgery requiring general or spinal anaesthesia were studied. The choice of anaesthesia was made on clinical grounds by the anaesthetist (not by the research team). The operations in the spinal anaesthesia group involved inguinal hernia repair ( $n=2$ ), femoro-popliteal vascular bypass surgery ( $n=6$ ), and venous varices ( $n=2$ ). In the general anaesthesia group, the procedures were cholecystectomy ( $n=4$ ), repair of an abdominal aortic aneurysm ( $n=1$ ) and resection of the colon ( $n=5$ ). The male/female ratio in the first group was 5/5 and in the second it was 4/6. Medical conditions requiring chronic medication are presented in Table 1.

The protocol was approved by the Local Ethics Committee and the informed consent of all patients was obtained.

Enteric lavage, consisting of 4 litres of macrogol (Laxabon, Tika, Lund, Sweden) was given on the day before surgery to six patients scheduled for colorectal surgery. After fasting overnight, all patients underwent

**Table 1** Height and body weight, given as mean and SEM, and preoperative medical diseases requiring daily medication in patients scheduled for surgical procedures under spinal or general anaesthesia. Daily medication consisted in: <sup>a</sup>salicylic acid, one patient in each group on  $\beta$ -blockers; <sup>b</sup>furosemide 40 mg

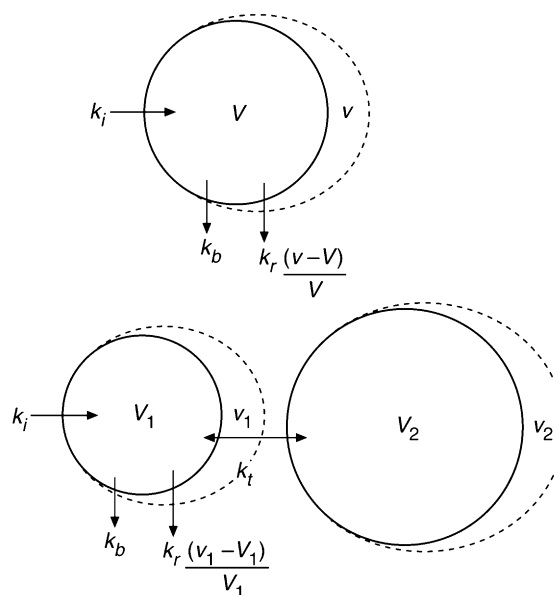
	Spinal anaesthesia (n=10)	General anaesthesia (n=10)
Height (cm)	169 (4)	171 (3)
Weight (kg)	75 (8)	78 (6)
<i>Medical diseases:</i>		
Atherosclerosis <sup>a</sup>	5	3
Mild cardiac failure <sup>b</sup>	0	1
Diabetes, insulin	1	0
Diabetes, diet	1	0
Hypothyroidism	0	1
No disease	3	5

surgery, which started between 08:00 and 12:00. They received 5–7.5 mg of morphine by i.m. injection as premedication approximately 1 h before entering the operating theatre. With the patient in the supine position, a cannula was placed in the cubital vein of each arm for the respective purposes of sampling blood and infusing fluid. Fifteen minutes later, an i.v. fluid load of 20 ml kg<sup>-1</sup> of Ringer acetate solution (Pharmacia, Uppsala, Sweden) was given at a constant rate over 60 min (0.33 ml kg<sup>-1</sup> min<sup>-1</sup>) via an infusion pump (Flo-Gard 6201, Baxter Healthcare, Deerfield, IL, USA). The Ringer solution had the following ionic content: Na 130, K 4, Ca 2, Mg 1, Cl 110 and acetate 30 mmol litre<sup>-1</sup>.

Spinal (n=10) or general (n=10) anaesthesia was induced 20 min after starting the i.v. infusion. When spinal anaesthesia was induced, the patient was turned to a lateral position, and 2–3 ml of isobar bupivacaine 0.5% (Marcaine® spinal, AstraZeneca, Södertälje, Sweden) was injected. Immediately after injection, the patient was turned from the lateral back to the supine position. General anaesthesia was induced with thiopental 5 mg kg<sup>-1</sup> and maintained with fentanyl 0.15 mg (mean dose) and 1–3% sevoflurane in oxygen and ambient air. Endotracheal intubation was facilitated by i.v. injection of rocuronium 0.5 mg kg<sup>-1</sup>.

Monitoring included pulse oximetry and electrocardiography. Non-invasive arterial blood pressure was measured every 3 min in the arm not used for infusion by an automatic device (Datex AS3, Datex, Helsinki, Finland). Ephedrine 5–10 mg was given as an i.v. bolus if the systolic arterial pressure dropped below 60% of baseline. Surgery was not started until the study period was completed.

Venous blood (3.0 ml) was collected every 3 min during the study period of 60 min. A small discard sample was drawn before each blood collection to preclude any admixture of blood from the previous sampling. The cannula was rinsed with 2.0 ml of saline after each sample collection to prevent clotting. The B-Hb concentration was measured by a Technicon H2 device (Bayer, Tarrytown,



**Fig 1** Schematic drawing of the one-volume kinetic model (top) and the two-volume kinetic model (bottom) used to calculate the size of the body fluid space expanded by i.v. infusion of fluid in humans.

NY, USA) with a coefficient of variation of 1%. The first sample was drawn in duplicate and the mean value was used in the calculations. The excreted urine was collected via an indwelling catheter, which had been inserted into the bladder under topical anaesthesia before the study started.

### Additional patients

After the main study had been completed, five additional patients between 55 and 85 (mean 71) yr of age with a body weight of 50–103 kg (mean 77 kg) were studied to examine whether a specific fluid regimen suggested by the volume kinetic analysis of the first 20 patients is able to prevent arterial hypotension during the onset of spinal anaesthesia. The male/female ratio was 3/2 and the operations were similar as in the main study. In these additional patients, no preload was given but 350 ml of Ringer's solution was infused during as little as 2 min just after injecting the bupivacaine. Thereafter, the fluid was given at the 'normal' rate (0.33 ml kg<sup>-1</sup> min<sup>-1</sup>) during 40 min. The same measurements were performed as in the main study.

### Calculations

The distribution of the fluid given by i.v. infusion was analysed using volume-of-fluid-spaces kinetic models, which can be summarised as follows (Fig. 1, top).

In the one-volume model, a fluid volume given by i.v. infusion at a rate  $k_i$  is distributed in an expandable space with a volume ( $v$ ), which the fluid space strives to maintain at a target (baseline) volume ( $V$ ). Fluid leaves the space at a controlled rate proportional with a constant ( $k_r$ ) to the

relative deviation of  $v$  from  $V$ , and also at a fixed basal rate ( $k_b$ ). The increased dilution associated with spinal anaesthesia<sup>12</sup> and possibly also with general anaesthesia was assumed to represent a change in the size of  $V$ , for example, the model determined one size of  $V$  before anaesthesia was induced and another  $V$  for the time after the induction.

In the two-volume model, the primary fluid space ( $v_1$ ) communicates with a remote fluid space ( $v_2$ ). The rate of volume equilibration between the expandable fluid spaces is proportional to the relative difference in deviation from the target values ( $V_1$  and  $V_2$ ) by a constant ( $k_t$ ) (Fig. 1, bottom). Here, the increased dilution associated with anaesthesia was assumed to represent a change in  $k_t$ , for example, the model determined one  $k_t$  before anaesthesia was induced and another for the time after the induction. The differential equations describing the volume changes in the expanded body fluid spaces as well as their matrix solutions are given in the Appendix.

The dilution of the plasma in the cubital vein was used to quantitate the water load as Ringer's solution remains outside the erythrocytes. As the sampled plasma is a part of  $V$ , we obtain the following dilution at time  $t$ :

$$(v(t)-V)/V = [\text{baseline B-Hb/B-Hb}(t) - 1] / (1 - \text{baseline haematocrit})$$

A correction for the loss of erythrocytes during blood sampling was made based on a preoperative blood volume estimated from the patient's height and body weight.<sup>5</sup>

The distribution of the infused i.v. fluid was modelled separately for each subject using Matlab version 5.2 (Math Works Inc., Natick, MA, USA), whereby a non-linear least-squares regression routine based on a modified Gauss-Newton method was repeated until no parameter changed by more than 0.001 (0.1%) in each iteration. The output of the kinetic analysis consisted in the best estimate and the standard error (SE) for  $V$  before and after induction (one-volume model) and for  $V_1$  and  $V_2$  as well as  $k_t$  before and after induction (two-volume model). However, the results of the latter analysis were reported only if an  $F$  test indicated that it was statistically justified.<sup>6</sup>

The following assumptions were made to ensure sufficient stability of the models: (1)  $k_r$  was calculated from the relationship between the integral of the dilution-time curve and the measured urinary excretion, both for the period of time up to when anaesthesia was induced and for the period thereafter.<sup>6</sup> (2)  $k_b$  was set to  $0.8 \text{ ml min}^{-1}$  (700 ml per 24 h) which is a reasonable estimation of the basal fluid loss (insensible water loss and baseline diuresis) from  $V$ . Half of this figure was assumed to appear as urine. (3) In the two-volume model, the individual curves were analysed after using a fixed value of  $V_2$ , assuming that the sum of  $V_1$  and  $V_2$  averages 12.5% of the patient's body weight, which is an average figure found in previous studies.<sup>5-7</sup>

Data are presented as the mean and (SEM) except where noted. Differences within and between the groups were studied using the one-way and repeated-measures ANOVA.

**Table 2** Volume kinetic parameters for loading with Ringer's solution during the onset of spinal ( $n=10$ ) and general anaesthesia ( $n=10$ ). The first line for each parameter in the one-volume and two-volume models gives the parameter estimate and the second line shows the SE associated with this estimate. Data are given as the mean (SEM)

	Spinal anaesthesia	General anaesthesia
<i>Urinary excretion (ml)</i>		
Before induction	58 (16)	57 (21)
After induction	87 (27)	75 (31)
<i><math>k_r</math> (ml min<sup>-1</sup>)</i>		
Before induction	40 (14)	62 (30)
After induction	10 (3)	10 (4)
<i>One-volume space model</i>		
$N$	4	4
$V$ before induction (l)	8.27 (1.45)	3.28 (0.16)
SE	1.91 (0.51)	0.81 (0.35)
$V$ after induction (l)	7.80 (1.06)	3.71 (0.51)
SE	1.17 (0.28)	0.53 (0.14)
Sum of squares ( $10^{-3}$ )	7.9 (1.4)	7.2 (0.4)
<i>Two-volume space model</i>		
$N$	6	6
$V_1$ (l)	1.29 (0.32)	1.56 (0.21)
SE	0.42 (0.13)	0.45 (0.09)
<i><math>k_t</math> (ml min<sup>-1</sup>)</i>		
Before induction	207 (48)	186 (31)
SE	80 (23)	65 (9)
After induction	112 (24)	94 (19)
SE	25 (11)	16 (3)
Sum of squares ( $10^{-3}$ )	4.8 (0.6)	12.7 (5.5)

Correlations between parameters were evaluated by linear regression analysis.  $P < 0.05$  was considered significant.

## Results

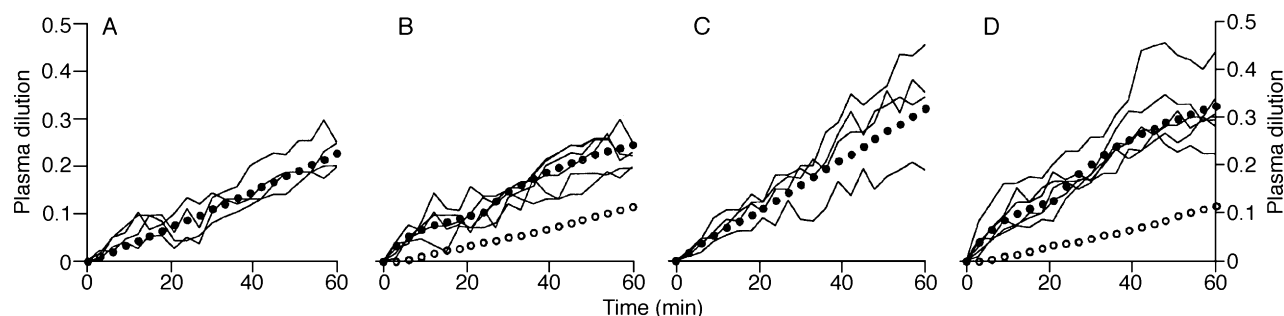
The elimination rate constant ( $k_r$ ) was reduced by the two forms of anaesthesia ( $P < 0.003$ ). After induction,  $k_r$  averaged only  $10 \text{ ml min}^{-1}$  (Table 2).

When the one-volume model was sufficient for an analysis of the data, the induction was not followed by a significant change in the size of  $V$ . However,  $V$  was smaller in the patients undergoing general anaesthesia ( $P < 0.02$ ), which means that the dilution of the plasma increased more in response to the infused fluid (Fig. 2).

The two-volume model was statistically justified in six of the patients in each group. The fairly rapid increase in haemodilution during the onset of anaesthesia (Fig. 2) is reflected in a decrease of  $k_t$  to  $\approx 50\%$  of baseline ( $P < 0.01$ ). In both groups,  $V_1$  was only about 1.4 litres (Table 2).

The mean arterial pressure (MAP) tended to be higher before spinal anaesthesia (121 mm Hg) than before general anaesthesia (111 mm Hg) and the heart rate was lower (74 vs 83 beats  $\text{min}^{-1}$ ), but these differences were not statistically significant (Fig. 3).

Induction of spinal anaesthesia reduced mean (SEM) MAP to 79 (4)% ( $P < 0.004$ ) and general anaesthesia to 70 (3)% of baseline ( $P < 0.001$ ; based on the average MAP recorded



**Fig 2** Dilution-time profiles in individual patients (thin lines) and the modelled dilution based on the mean parameter estimates shown in Table 2 (circles) during a continuous-rate infusion of Ringer's solution during which spinal anaesthesia (subplots A and B) or general anaesthesia (subplots C and D) was induced after 20 min. The one-volume space model was applied to the data in subplots A and C (closed circles=dilution of  $V$ ). The two-volume space model was applied to the data in subplots B and D (closed circles=dilution of  $V_1$ , open circles=dilution of  $V_2$ ).

between 0–18 and 27–60 min). This difference between the groups was statistically significant ( $P < 0.05$ ). Four patients in the general anaesthesia group and two in the spinal group received an i.v. injection of ephedrine to combat hypotension.

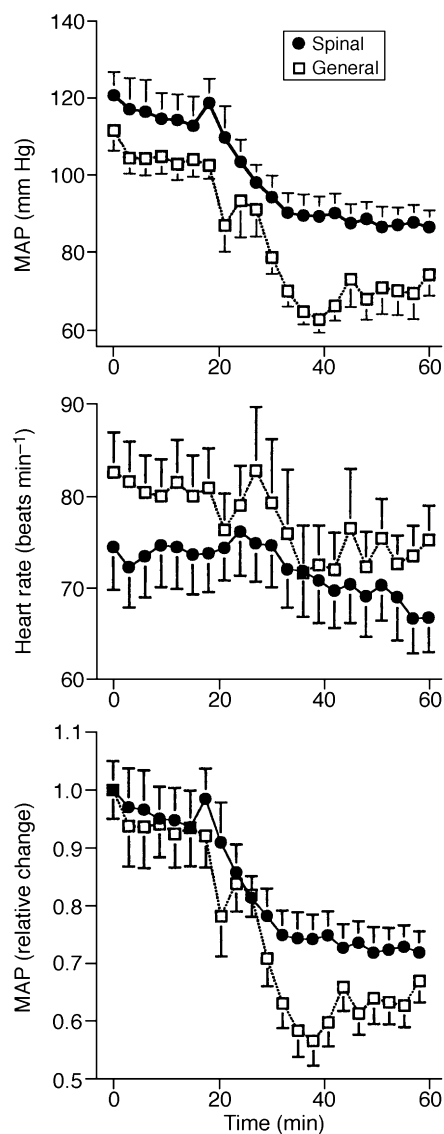
A search was made for factors correlating with the differences in kinetic parameters between individual patients. The decrease in MAP correlated with the size of  $V$  obtained after anaesthesia had been induced (one-volume model) and with the  $k_t$  obtained after anaesthesia had been induced (two-volume model; Fig. 4).

All six patients who underwent enteric lavage before surgery were in the general anaesthesia group. They tended to have a higher heart rate at baseline than the other patients (mean 89 vs 76 beats  $\text{min}^{-1}$ ;  $P < 0.06$ ). Their drop in MAP was more pronounced (down to 63 vs 79% of baseline;  $P < 0.001$ ) and, in the four for whom the one-volume model was statistically justified, the size of  $V$  before anaesthesia was much smaller (3.3 vs 8.3 litre,  $P < 0.02$ ).

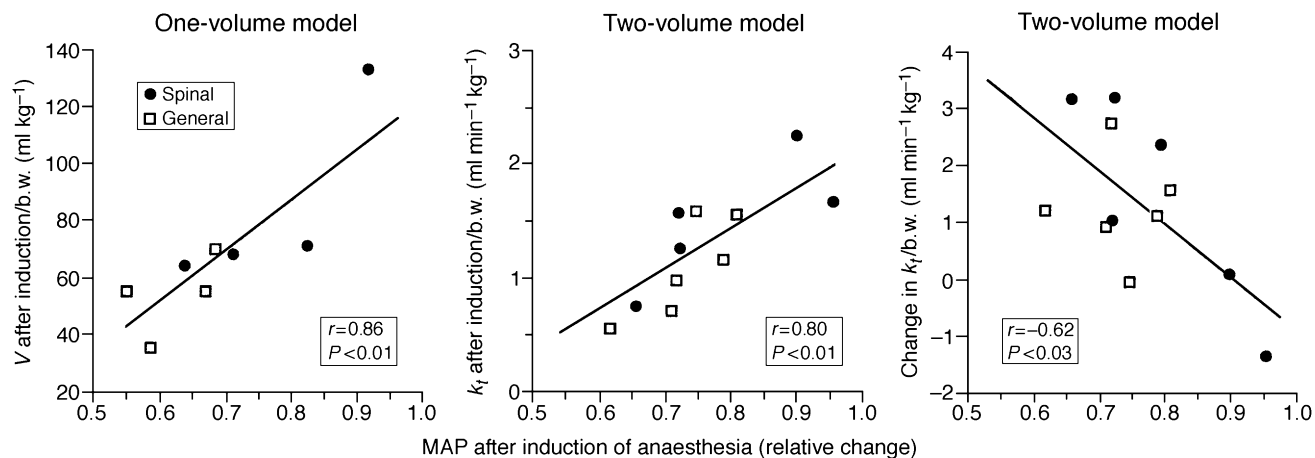
### Simulations and additional patients

Simulations outlined the volume increment representing, in the two-volume model, the 'increased vascular costume' of  $V_1$  associated with anaesthesia (Fig. 5, left). This increased haemodilution required 20 min to develop fully, and averaged only 125–150 ml. We hypothesized that such a volume increment would need to be filled up within a few minutes to prevent relative hypovolaemia in  $V_1$  during the onset of the anaesthesia, but this seemed impossible with the mode of infusion used in the study (Fig. 6). The goal could be reached only with a short rapid infusion, and the infusion rates required to fill  $V_1$  with various amounts of fluid within 2 min are shown in the right panel of Figure 5.

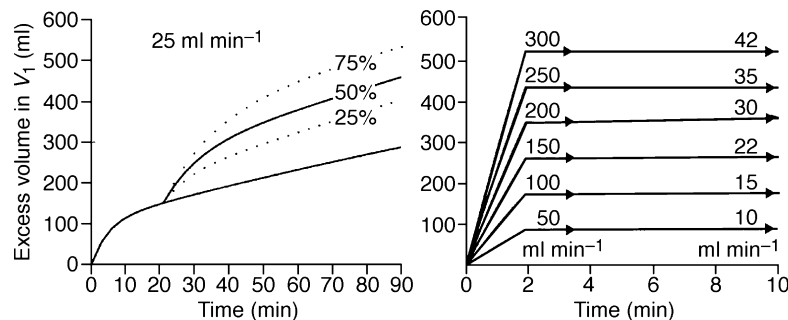
The additional five patients were studied to examine whether the infusion rate suggested to increase  $V_1$  by 125–150 ml within 2 min according to Figure 5 is capable of preventing post-spinal hypotension. None of the additional patients required ephedrine, although their upper level of sensory analgesia was Th 5.6 (1.0) as compared with Th 6.4



**Fig 3** MAP (top) and heart rate (middle) when spinal or general anaesthesia was induced after 20 min of a continuous-rate infusion of 20 ml  $\text{kg}^{-1}$  of Ringer's acetate solution. The relative changes in MAP are also shown (bottom).



**Fig 4** Relationships between the change in MAP during the induction of anaesthesia and the size of  $V$  after it had been induced in the eight patients in whom the one-volume model was statistically justified (left), to  $k_t$  after the induction (two-volume model, middle, one extreme outlier omitted) and to the difference in  $k_t$  from before to after the induction (two-volume model, right). The change in MAP was obtained as the mean of all measurements noted between 0 and 18 min divided by the mean obtained between 27 and 60 min of the study.



**Fig 5** Computer simulations showing left: the excess volume in  $V_1$  before and after the induction of anaesthesia in a subject with a body weight of 75 kg who received an i.v. infusion of 25 ml min<sup>-1</sup> of Ringer's acetate solution. The increment between the solid lines represents, with a 50% probability, the increment in volume resulting from the anaesthesia. (Right) The infusion rates (ml min<sup>-1</sup>) required to obtain, within only 2 min, a predetermined volume increase in  $V_1$  during the onset of anaesthesia. The numbers to the right show the infusion rates required to maintain the volume increase obtained with the first more rapid infusion. Here, the initial phase of volume loading shown in the figure to the left has been omitted.

(0.7) in the other patients receiving spinal anaesthesia. MAP averaged 95 (5)% of baseline during 6 and 39 min after the induction, which a significantly smaller decrease than in the others ( $P<0.01$ ; Fig. 7, top). Urinary excretion was 281 (64) ml ( $P<0.02$  vs the others receiving spinal anaesthesia).

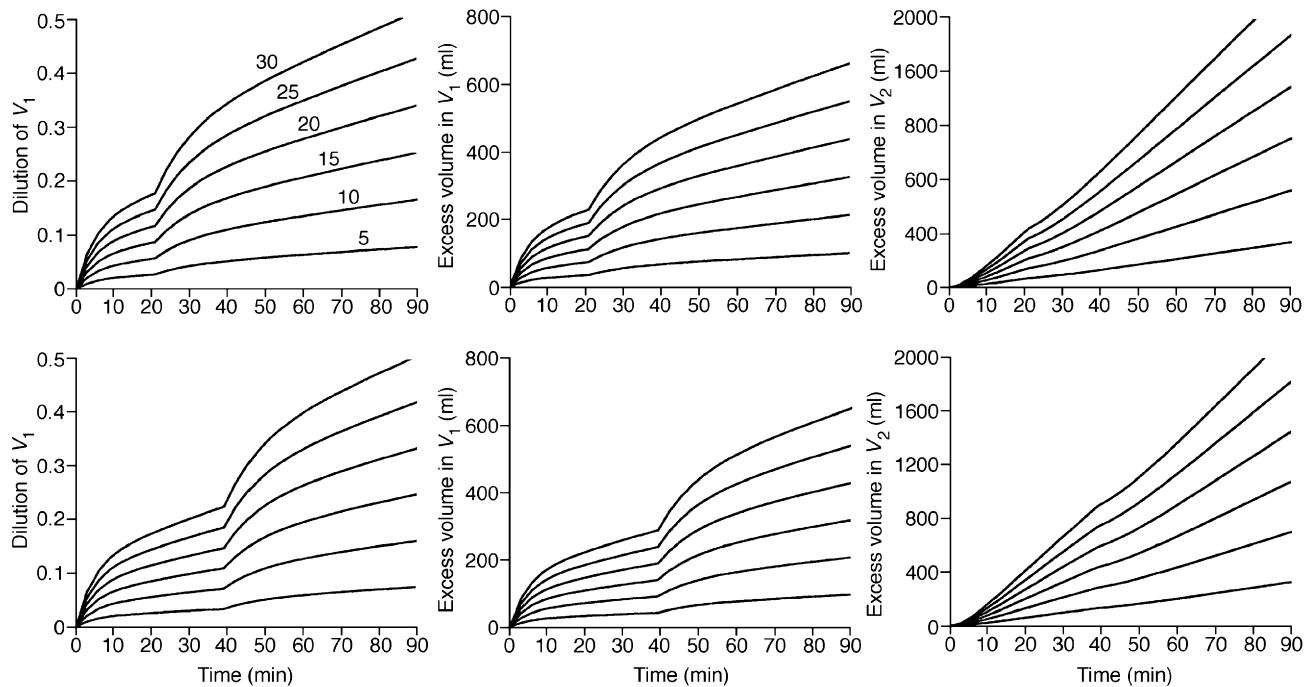
The one-volume model was sufficient to analyse the dilution-time curves in all the additional patients. The size of  $V$  for the 2-min rapid infusion was 4.44 (0.48) litres, while  $V$  for the subsequent slow infusion was 6.70 (0.60) litres (Fig. 7, bottom).

## Discussion

Fluid resuscitation is commonly practiced to combat arterial hypotension during the onset of anaesthesia. The present study illustrates how the body, from a kinetic point of view, handles fluid in such situations. The method used for the study, volume kinetic analysis, has many similarities to pharmacokinetics but is based on the dilution of the venous plasma instead of the concentration of a drug in the blood.

Volume kinetics has served as a tool for describing and simulating the distribution and elimination of Ringer's solution when infused in volunteers,<sup>5-8</sup> trauma patients,<sup>9</sup> and endotoxaemic rabbits.<sup>10</sup> The modification of this mathematical approach employed here is intended to capture the change in volume kinetics from before to after a specific physiological event and has previously been applied to spinal anaesthesia during Caesarean section.<sup>11</sup>

In most patients, the kinetics of the infused fluid was described according to a two-volume model, which means that anaesthesia alters the rate of volume equilibration, expressed by a parameter  $k_t$ , between a central ( $V_1$ ) and a peripheral body fluid space ( $V_2$ ). The overall results indicate that the body handles infused fluid in a similar way during the induction of general and spinal anaesthesia. Both forms of anaesthesia were associated with a reduction  $k_t$  that was also of similar magnitude. Such a decrease of  $k_t$  quantitates an altered relationship in compliance between  $V_1$  and  $V_2$  with regard to volume expansion, which favours fluid accumulation in  $V_1$ .



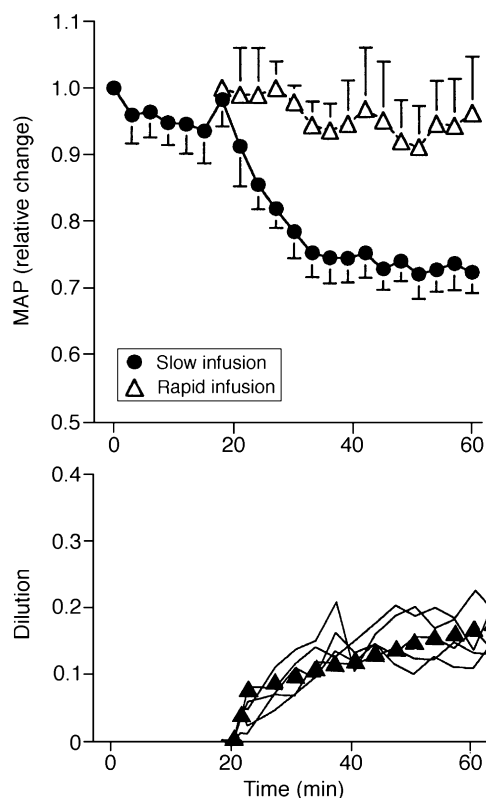
**Fig 6** Computer simulations showing the predicted dilution of  $V_1$  (left) and the excess volume in  $V_1$  (middle) and in  $V_2$  (right) when Ringer's acetate solution was infused at a rate of 5, 10, 15, 20, 25, and 30 ml kg<sup>-1</sup> per 60 min in a subject with a body weight of 75 kg. The upper row shows the situation when anaesthesia was induced after 20 min and the lower one when it was postponed until 40 min. All curves are based on the mean parameter estimates obtained for the 12 infusions for which the two-volume model was applied.

Another finding is that the size of  $V_1$  was very small. In volunteer experiments,  $V_1$  is usually close to the expected size of the plasma volume.<sup>5-7</sup> Most or all of the plasma volume was probably a part of  $V_1$  during the initial 20 min of the present experiments too, but our partial derivative plots showed that the final estimate of  $V_1$  was strongly affected by the increased haemodilution occurring just after the onset of anaesthesia. A problem in the curve-fitting procedure was that  $V_2$  could not be estimated with confidence. Information about the size of  $V_2$  is best obtained from post-infusion data, which were absent this time. The solution to the problem we used, which consisted in assuming a fixed sum of  $V_1$  and  $V_2$  as suggested by other studies, introduces some uncertainty about the pre- and post-infusion estimates of  $k_t$ , although their ratio is not changed.<sup>11</sup> In the present study, however, the estimates of  $k_t$  before the induction are similar to those obtained in volunteers.<sup>5-7</sup> Furthermore, the final estimate of  $V_1$  is only marginally changed by setting different values for  $V_1 + V_2$ .<sup>11</sup>

The combination of a small  $V_1$  and a reduced  $k_t$  indicates that infused fluid circulates primarily in the central blood volume during the onset of anaesthesia. The resulting excessive dilution in  $V_1$  represents an 'enlarged vascular costume', which correlates with the magnitude of the arterial hypotension that develops during the onset of epidural<sup>12 13</sup> and spinal<sup>14</sup> anaesthesia. The maximum dilution during epidural anaesthesia is developed 10–15

min after the drop in arterial pressure<sup>13</sup> and the present study shows that the time lag is the same during induction of spinal anaesthesia. Hypotension developed somewhat later after the induction of general anaesthesia, which is probably a result of the stress associated with the intubation procedure.

Spinal anaesthesia allows relative hypovolaemia to develop in the torso by shifting blood to the legs in healthy volunteers<sup>15</sup> and in patients with cardiac disease.<sup>16</sup> The preferential distribution of infused fluid to the central plasma volume, together with the slower transport of fluid to a more remote body fluid space, is a meaningful adaptation, as infused fluid then restores cardiac preload more effectively. Under these conditions, the vasodilated legs may become part of  $V_2$ . However, the infusion rates normally used for volume loading are simply too low to increase the volume of  $V_1$  by 125–150 ml during the period of time between the injection of bupivacaine and the expected onset of hypotension 5–10 min later. Our data suggest that the strategy having the best chance to fill this increment, and which, therefore, might offer the best chance to prevent a drop in arterial pressure, would be to use a very high infusion rate just after the anaesthetic solution has been injected. Infusing fluid *before* the induction is less efficient as  $k_t$  is higher at that time. In the additional series of five patients, we challenged this hypothesis about preventing hypotension by giving 2-min rapid fluid load just after the



**Fig 7** Spinal hypotension when i.v. fluid is given at different rates. (Top) The relative change in MAP in patients receiving spinal anaesthesia at 20 min. The first group ('slow infusion',  $n=10$ ) were given 20 ml  $\text{kg}^{-1}$  of Ringer's acetate as a continuous infusion over 60 min, and the others ('rapid infusion',  $n=5$ ) had their entire preload given between 20 and 22 min. (Bottom) The dilution-time profiles of the rapid infusion group and the modelled curve (dark triangles) based on the mean values of the volume kinetic parameters.

bupivacaine had been injected. Interestingly, no drop in MAP was observed, despite the fact that the analgesia was even more widespread in the additional patients than in the first 10 patients who received spinal anaesthesia. A follow-up study is planned to evaluate the clinical value of this fluid programme in a larger group of patients.

Another factor promoting central hypovolaemia when fluid is infused at a constant rate over 60 min fluid is that no recruitment of volume seems to occur from  $V_2$  to  $V_1$  during the onset of anaesthesia. Rapid transfer of fluid from muscle to the blood has been described when hypovolaemic stress is induced by a lower negative body pressure,<sup>17</sup> but virtually no haemodilution could be observed when epidural anaesthesia was induced without being accompanied by fluid.<sup>12</sup> Computer simulations based on the volume kinetic data derived here suggest that no such 'backward flow' would occur even if more prolonged volume loading was performed before induction of anaesthesia (Fig. 6, lower). However, the linear relationship between  $k_t$  after the induction and the relative change in MAP (Fig. 3, right) indicates that a transfer of fluid from  $V_2$  to  $V_1$  against a

dilution gradient could occur when MAP falls to below 45% of baseline, as such a drop would theoretically result in a negative  $k_t$ .

Four patients in each anaesthesia group had their dilution-time curves analysed according to a one-volume model. The two-volume model was discarded in these cases as a statistical test indicated that estimating three parameters instead of two did not result in a significantly reduced mean square error of the differences between measured and model-predicted data on dilution.<sup>5</sup> Application of the two-volume model to these curves was possible but resulted in excessive SE for  $k_t$  both before and after the induction. The dilution over time increased in a linear fashion as more fluid was infused, and the plots lack the exponential shape of the two-volume dilution-time curves.

No effect of the induction of anaesthesia became apparent in the one-volume plots. One possible effect would consist in a reduction of  $V$  after the induction, resulting in a more pronounced dilution, as was found before Caesarean section.<sup>11</sup> A small  $V$  means that forces act to keep the infused fluid close to the bloodstream, similar to a low  $k_t$  in the two-volume model, and is associated with anaesthesia-induced hypotension (Fig. 4, left).

Enteric lavage given on the day before the operation seems to have affected the present results. This was not expected when the study was started, but its importance became apparent when we sought an explanation for the difference between spinal and general anaesthesia with respect to the pre-induction size of  $V$  in the one-volume model.  $V$  was small enough to even correspond to the expected size of the plasma volume, which is a sign of hypovolaemia, and we, therefore, believe that the patients were dehydrated by the lavage. This view is supported by the slightly higher baseline heart rate and the more pronounced drop in arterial pressure in these patients. The fact that lavage was employed only in the general anaesthesia group is sufficient to explain the smaller size of  $V$  among these patients as compared with those that received spinal anaesthesia.

Another possible confounder in the study was the occasional use of a small dose of ephedrine to alleviate severe hypotension (systolic pressure <60% of baseline). The doses given are likely to have slightly and transiently reduced the differences in blood pressure response between spinal and general anaesthesia. Ephedrine acts by increasing the cardiac output and, to some degree, by causing vasoconstriction. As argued previously,<sup>11</sup> this drug may have slightly reduced the vasodilatation and the rates of fluid exchange, but no indication of such effects could be obtained from the data. The effect of an i.v. dose of ephedrine is also fairly short. In contrast, the kinetic modelling was based on all data on haemodilution obtained during the 60 min of study.

An important finding is the weak diuretic response to volume loading. Only about 5% of the infused fluid volume of up to 2400 ml was excreted during the study period. The

average half-life of Ringer's acetate, as extrapolated graphically, was between 150 min (one-volume model) and 500 min (two-volume model) before anaesthesia. The induction further inhibited the diuretic response and prolonged the half-life. In comparison, the half-life was approximately 15 min in elderly volunteers.<sup>9</sup> Preoperative stress and the overnight fast probably accounts for most of this difference. Interestingly, the diuretic response was stronger when the fluid therapy was started with a brisk 2-min infusion.

In summary, we found that induction of spinal and general anaesthesia results in similar changes in volume kinetic parameters and usually favoured an accumulation of infused fluid in a relatively small central body fluid space. The kinetic analysis suggests that the arterial pressure is better maintained by infusing fluid very rapidly just after the induction of anaesthesia than to give a preload.

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## Appendix

The one-volume fluid space model is described by the following differential equation:

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

which is solved as a monoexponential solution. Before induction of anaesthesia, it is

$$w(t) = \frac{(k_i - k_b)}{k_r} \cdot (1 - e^{-k_r/V}) \quad 0 \leq t \leq t_1 \quad (2)$$

and after (a) induction

$$w_a(t) = (w_1(t) - \frac{k_i - k_b}{k_r} \cdot e^{-k_r(t-t_1)/(V-\Delta V)} + \frac{k_i - k_b}{k_r} \quad t_1 \leq t \leq \infty \quad (3)$$

where  $w(t)$  is the dilution  $(v(t) - V)/V$  and  $\Delta V$  is the change in baseline (target) volume induced by the anaesthesia.  $k_r$  is calculated from the measured urine excretion and has different values during and after the induction of the anaesthesia.

The following differential equations describes two-volume fluid space model:

$$\begin{aligned} \frac{dv_1}{dt} &= k_i - k_b - k_r \frac{(v_1 - V_1)}{V_1} - \\ &k_t \left[ \frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right] \end{aligned} \quad (4)$$

$$\frac{dv_2}{dt} = k_t \left[ \frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right] \quad (5)$$

As with the one-volume model, the equations have been adapted for the special situation during anaesthesia, and they calculate one  $k_t$  for the period before and another  $k_t$  for the period after the induction. The form used to present the solution of equations 4 and 5 is based on the matrix exponential  $e^{At}$ , which is implemented as a standard function in the mathematical program Matlab. Before anaesthesia, we have

$$\begin{pmatrix} w_1(t) \\ w_2(t) \end{pmatrix} = \frac{k_i - k_b}{k_r} \cdot (I - e^{At}) \cdot \begin{pmatrix} 1 \\ 1 \end{pmatrix} \quad 0 \leq t \leq t_1 \quad (6)$$

and after (a) anaesthesia has been induced, it becomes

$$\begin{pmatrix} w_{1a}(t) \\ w_{2a}(t) \end{pmatrix} = w_1(t) \cdot e^{A \cdot (t-t_1)} + \frac{k_i - k_b}{k_r} \cdot (I - e^{At}) \cdot \begin{pmatrix} 1 \\ 1 \end{pmatrix} \quad t_1 \leq t \leq \infty \quad (7)$$

where the matrix  $A$  is

$$A = \begin{pmatrix} -(k_r + k_t)/V_1 & k_t/V_1 \\ k_t/V_2 & -k_t/V_2 \end{pmatrix} \quad (8)$$

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