Elimination Rate Constant Describing Clearance of Infused Fluid from Plasma Is Independent of Large Infusion Volumes of 0.9% Saline in Sheep

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Background: The purpose of this study was to determine the influence of varying large crystalloid infusion volumes, ranging from a volume that has been safely administered to volunteers to a volume that greatly exceeds a practical volume for studies in normovolemic humans, of rapidly infused 0.9% saline on the elimination rate constant in sheep.

Methods: Six sheep underwent three randomly ordered, 20 min, intravenous infusions of 0.9% saline in volumes of 25 ml/kg, 50 ml/kg, and 100 ml/kg. Repeated measurements of arterial plasma dilution were analyzed using the volume kinetic approach to determine the apparent volumes of the central (V₁) and peripheral (V₂) body fluid spaces, the elimination rate constant (kₑ) describing clearance from the central fluid space and the rate constant (kᵢ) for the diffusion of fluid between the central and the peripheral fluid spaces. The latter constant was split into two constants, one describing flow out from the central fluid space and one describing flow into the central fluid space. Urinary output was measured in all sheep.

Results: kₑ, was comparable at each infused volume (38.3 ± 4.5, 32.2 ± 4.2, and 36.7 ± 7.0 ml/min, respectively, in the 25 ml/kg, 50 ml/kg, and 100 ml/kg protocols). However, for the largest infusion, other kinetic parameters were influenced by the magnitude of the infusion. V₂ was significantly increased (P < 0.05) and the area under the dilution-time curve divided by the infused volume was 20% lower for the largest infusion (P < 0.05). Although urinary output increased as the infusion volume increased, only 59% of the administered volume had been excreted at 180 min after the 100 ml/kg infusion as compared with approximately 90% after the other two infusions (P < 0.01).

Conclusions: Elimination from the central fluid space of large, rapidly infused volumes of saline solution is independent of infused volume. Larger volumes are apparently cleared from the central fluid space (V₁) by expansion of a peripheral volume (V₂) as renal excretion fails to increase in proportion to the volume of infused fluid.

THE kinetic effects of intravenous infusions of sodium-containing crystalloid solutions such as lactated Ringer’s solution or 0.9% saline can be quantified in clinical and animal experiments using techniques similar to those used in pharmacokinetics.1–5 Volume kinetic analysis generates several key parameters: the apparent volumes of a central (V₁) and a peripheral (V₂) body fluid space and an elimination rate constant (kₑ) that quantifies the rate at which fluid exits the expanded central fluid volume as a function of the magnitude of expansion of the central volume according to the equation:

\[
\frac{dv}{dt} = k_i - k_e - \frac{v_i - V_1}{V_2} - \frac{(v_i - V_2)}{V_1} - (v_2 - V_2)
\]

where kᵢ represents the rate of infusion into the central space V₁, the expanded central space is termed vᵢ, the expanded peripheral space is termed V₂, kₑ represents the basal rate of elimination of fluid by insensible and obligatory urinary losses of fluid, and kᵢ is the rate constant for the diffusion of fluid between the central and the peripheral fluid spaces.

In the range of infusion volumes used clinically, the kinetic parameters are similar and can be used to simulate other infusion rates and infusion volumes.6 The kinetic parameters generated by a small, brief infusion (1.2 ml/min for 5 min) of 0.9% saline in sheep were used to simulate accurately the outcome of a larger, more prolonged infusion (1.2 ml/min for 20 min).4 In male volunteers, the kinetic parameters for 2.5% glucose solution adequately predicted the outcome of various infusion rates and volumes of this fluid.6 Various clinically realistic rates of infusion of acetated Ringer’s solution yielded similar model parameters in female volunteers,7 but the size of the expanded body fluid spaces became larger when the solution was infused more rapidly (25 ml/kg over 15 min as compared with 25 ml/kg over 30, 45, and 80 min, respectively),7 suggesting that kinetic parameters might be dependent on the infusion volume of isotonic crystalloids in a high-dose range.

In pharmacokinetic/pharmacodynamic research, there are examples of common drugs in which either very high doses or very high infusion rates alter parameters in comparison to clinically relevant doses or infusion rates.8–11 Therefore, in the current study, our objective was to evaluate in greater detail the kinetic responses to crystalloid infusion volumes that greatly exceed usual clinical practice by infusing 25 ml/kg, 50 ml/kg, and 100 ml/kg of 0.9% saline over 20 min in conscious, normovolemic sheep. We hypothesized that the elimination rate constant kₑ would be similar in each of the three infusions, i.e., that volume elimination from the

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central compartment would remain primarily a function of
the deviation of expanded volume \( (V_e) \) from target
volume \( (V_t) \). As a marker of changes in plasma volume,
the dilution of the blood hemoglobin concentration was
measured repeatedly during and after the infusion, and
the sizes of the expanded body fluid spaces and the rates
for equilibration and elimination were estimated by vol-
ume kinetic analysis.\(^2\) Urinary excretion rates were also
recorded because, in previous studies, urinary output
was proportional to \( k_r \) except under special circum-
stances such as isoflurane anesthesia.\(^3,5\)

Materials and Methods

We studied seven adult splenectomized female merino
sheep with a mean body weight of 36 kg (individually:
34, 34, 35, 38, 39, and 42 kg) in the fasting state. Data
from one animal could not be analyzed using the volume
kinetic computer program and were excluded. The pro-
tocol was reviewed and approved by the Institutional
Animal Care and Use Committee of the University of
Texas Medical Branch at Galveston, Texas.

Surgical preparation, performed under isoflurane anes-
thesia at least 24 h before the first experiment, included
insertion of a pulmonary arterial catheter (Swan-Ganz;
Baxter, Irvine, CA) and bilateral femoral arterial and
venous catheters (Intracath; Becton Dickinson, Sandy,
UT). After surgery, the sheep were given a continuous
infusion of lactated Ringer’s solution at 5 ml·kg\(^{-1}\)·h\(^{-1}\)
and connected to hemodynamic monitors via continu-
ously flushed transducers. Analgesia consisted of bu-
prenorphine administered intramuscularly. The sheep
were maintained in metabolic cages with free access to
food and water. Twenty-four hours before each experi-
ment, the animals were instrumented with a urinary
bladder catheter (Sherwood Medical, St. Louis, MO) and
food and water were discontinued. All sheep were sub-
jected to three protocols in random order. On different
days, separated by at least 24 h, they received an intra-
venous infusion over 20 min of 0.9% saline in volumes of
25 ml/kg, 50 ml/kg, or 100 ml/kg body weight.

Hemodynamic Measurements

During each experimental protocol we measured heart
rate, direct mean arterial blood pressure, cardiac output,
pulmonary arterial pressure, pulmonary diastolic arterial
pressure, and central venous pressure every 5 min.

Kinetic Calculations

We analyzed the distribution and elimination of in-
fluenced fluid according to a two-volume kinetic model
as described in Equation 1.\(^2\) The infused fluid expands
a central body fluid space \( V_2 \) from which elimination oc-
curs according to a mechanism proportional by a param-
eter \( k_r \) to the dilution of \( V_1 \), and also by a baseline fluid
loss \( k_{mb} \), which was set to 0.2 ml/min.\(^12\) Fluid also equi-
librates with a peripheral body fluid space \( V_1 \) at a rate
proportional by a parameter \( k_1 \) to the difference in dilu-
tion between \( V_1 \) and \( V_2 \). The input for the calculations
was the dilution of arterial plasma, which was taken to
indicate the dilution of \( V_1 \). For this purpose, at 5-min
intervals we measured the relative change in blood he-
moglobin concentration (HemaVet; CDC Technologies,
Oxford, CT), divided by \((1 - \text{hematocrit})\) to obtain the
corresponding plasma dilution. We corrected the calcu-
lated dilution for the loss of 2 ml of blood for each sample
withdrawn throughout the experiments based on an esti-
mated baseline blood volume of 6% of body weight.

Each dilution-time curve from each experiment was
modeled using MATLAB version 4.2 (Math Works Inc.,
Notich, MA), wherein a nonlinear least-squares regres-
sion routine based on a modified Gauss-Newton method
was repeated until none of the parameters in the kinetic
model \((V_1, V_2, k_r, \text{ or } k_1)\) changed by more than 0.001
(0.1%) in subsequent iterations.\(^13\) The mathematical de-
tails have been published previously.\(^2\)–\(^4\) The computer
program was modified to estimate a bidirectional \( k_r, k_1 \)
for the translocation of fluid out of \( V_1 \) and \( k_1, k_r \) for the
flow into \( V_1 \) (Appendix). The magnitude of \( V_2 \) for each
sheep was then set to the mean volume of \( V_2 \) obtained
for the 25 ml/kg and 50 ml/kg infusions. Because non-
linear least-squares regression yields an estimate rather
than a precise result, the output consists of the best
estimate of each parameter and the uncertainty of that
estimate, the uncertainty given as a SE. Because the SE is
calculated for an estimate in a single experiment, SE,
calculated as SD/\(\sqrt{n}\), is equivalent to the SD (i.e.,
SD/\(\sqrt{1}\)).

The residual errors for the best curve fit were obtained
directly from the MATLAB program as the difference
between predicted and measured data points. The area
under the curve (AUC) for the measured data points was
obtained by the linear trapezoidal method. AUCs for
predicted curves were taken as the sum of the simulated
plasma dilution every minute for as long as plasma dilu-
tion exceeded zero. Further, the ratio of AUC to dose
was calculated according to the following equation:

\[
\text{AUC/Infused volume} = \text{dilution (dimensionless)} \\
\times \text{ time (min)/infused volume} \quad (\text{Eq. 2})
\]

where \(\text{AUC/Infused volume}\) is expressed as kg \times
min/ml, dilution is dimensionless, and infused volume is
expressed as ml/kg.

Statistical Analysis

Volume kinetic parameters are presented as the medi-
ans (25th–75th percentiles). Hemodynamic data are pre-
sented as plots of medians. Kinetic parameters were
analyzed using analysis of variance for the randomized

Anesthesiology. V 101, No 3, Sep 2004
complete-block design. Hemodynamic measurements at the peak (20 min) were also analyzed using analysis of variance for the randomized complete-block design (block = sheep). The effects of the three infusion volumes were assessed at the 0.05 level of significance. Fisher’s least significant difference procedure was used for multiple comparisons with Bonferroni adjustment for the number of comparisons. P < 0.05 was considered statistically significant.

Results

Hemodynamic Measurements

At 20 min after the infusion of the three different volumes, mean arterial blood pressures were not significantly different (fig. 1). At 20 min after the infusion of 50 ml/kg, cardiac output, pulmonary arterial pressure, and central venous pressure were significantly greater than 20 min after infusion of 25 ml/kg. Similarly, 20 min after infusion of 100 ml/kg, cardiac output, pulmonary arterial pressure, and central venous pressure were significantly greater than 20 min after infusion of 50 ml/kg. At 20 min after infusion of 50 and 100 ml/kg, pulmonary diastolic arterial pressure was significantly higher than 20 min after infusion of 25 ml/kg. Beginning 40 min after infusion and continuing throughout the remainder of the experiment there were no significant differences among the three infusion rates.

Volume Kinetic Analysis

One animal was excluded because nonlinear least-squares regression could not calculate parameters successfully in two of three experiments in that animal. All three experiments were successfully analyzed in the other six sheep. The values for the kinetic parameters are shown in table 1, curve fits for two representative

Table 1. Volume Kinetic Parameters for the Experiments With Intravenous Infusions of Three Volumes of 0.9% Saline over 20 min in Six Sheep

<table>
<thead>
<tr>
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<th>25 ml/kg</th>
<th>50 ml/kg</th>
<th>100 ml/kg</th>
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</thead>
<tbody>
<tr>
<td>V₁ (mL)</td>
<td>1086 (516–1273)</td>
<td>1386 (1295–1546)</td>
<td>1606 (1286–2071)</td>
</tr>
<tr>
<td>SE</td>
<td>455 (274–645)</td>
<td>150 (132–189)</td>
<td>200 (155–218)</td>
</tr>
<tr>
<td>V₂ (mL)</td>
<td>5187 (2740–6768)</td>
<td>5713 (4351–8429)</td>
<td>11459 (8087–13170)*</td>
</tr>
<tr>
<td>SE</td>
<td>651 (464–1345)</td>
<td>566 (522–635)</td>
<td>1110 (328–2196)</td>
</tr>
<tr>
<td>kᵣ (mL/min)</td>
<td>38.3 (15.0–75.1)</td>
<td>32.2 (14.9–60.4)</td>
<td>36.7 (18.0–55.1)</td>
</tr>
<tr>
<td>SE</td>
<td>4.5 (3.7–5.0)</td>
<td>4.2 (3.8–5.2)</td>
<td>7.0 (2.5–11.0)</td>
</tr>
<tr>
<td>kᵣ (mL/min)</td>
<td>230 (185–280)</td>
<td>167 (154–202)</td>
<td>307 (287–356)*</td>
</tr>
<tr>
<td>SE</td>
<td>57 (39–86)</td>
<td>21 (13–39)</td>
<td>23 (21–26)</td>
</tr>
</tbody>
</table>

Data are expressed as median (25th–75th percentiles) for analyses of all experiments. The first line gives the medians of the best estimates and the second line gives the uncertainty of the prediction expressed as the medians (25th–75th percentiles) of the standard errors (SE) from the experiments.

* P < 0.05.
sheep are displayed in figure 2, and the residual errors for all experiments in figure 3. The theoretical dilution-time curve based on the average parameter estimates of $V_1$, $V_2$, $k_r$, and $k_t$ (table 1) corresponded well to the individually measured dilution-time curves (fig. 4).

As hypothesized, $k_r$ was similar for the three infusion volumes and was independent of the magnitude of expansion of the central body fluid space $V_1$. As table 2 illustrates, over 180 min, urinary output was effective in eliminating much of the 25 and 50 ml/kg infusions (93% and 89%, respectively) but was less effective ($P < 0.01$) in eliminating the 100 ml/kg infusion (59% of infused fluid).

As infusion volume increased, $V_1$ increased (fig. 5). $V_2$ calculated for the 100 ml/kg infusion volume was significantly higher than $V_2$ for the 25 ml/kg and 50 ml/kg infusion volumes, although there was no significant difference between 25 ml/kg and 50 ml/kg for $V_2$ (table 1 and fig. 6). The $k_t$ for the 25 ml/kg infusion volume was not significantly different from the 50 ml/kg or 100 ml/kg infusion volumes. However, the $k_t$ for the 100 ml/kg infusion volume was significantly greater than the $k_t$ for the 25 ml/kg infusion volume (table 1). Calculation of the bidirectional $k_t$ (table 3 and Appendix) demonstrated that $k_{t1}$ (translocation of fluid out of $V_1$) was twice as high ($P < 0.0034$) for the 100 ml/kg infusion as was $k_{t2}$ (translocation of fluid into $V_1$). For the two lower infusion rates, the $k_{t1}$ and $k_{t2}$ were similar. Calculation of the bidirectional $k_t$ did not alter the increase in $V_1$ associated with increasing infusion volumes.

**Accumulation of Fluid in $V_2$**

When the kinetic parameters derived from the 100-ml/kg experiments (table 1) were used to simulate an infusion of 25 ml/kg, a 25% smaller dilution of $V_1$ was calculated than in the original experiment using 25 ml/kg. The simulation also indicated that more fluid accumulated in $V_2$ (47% more fluid at 180 min) than in the actual experiment using 25 ml/kg. In contrast, simulated substitution of the kinetic parameters between the 25 ml/kg and the 50 ml/kg infusions did not significantly alter the model.

The smaller-than-proportionate depression of plasma dilution associated with the 100 ml/kg infusion in comparison to the 25 ml/kg and 50 ml/kg infusions was further studied by comparing the AUC divided by the infused volume (Equation 2) for the individual experiments. The AUC for the 100 ml/kg infusion (0.43 [0.35–0.56] kg·min$^{-1}$·ml$^{-1}$) was significantly smaller ($P < 0.03$) than for the 25 ml/kg infusion (0.56 [0.45–0.82] kg·min$^{-1}$·ml$^{-1}$) and the 50-ml/kg infusion (0.53 [0.48–0.62] kg·min$^{-1}$·ml$^{-1}$). However, when each of the three sets of kinetic parameters (for the 25 ml/kg, 50 ml/kg, and 100 ml/kg infusions) were used to simulate plasma dilution until plasma dilution had decreased completely to baseline after infusion of 100 ml/kg, the resulting AUC/dose ratios were 0.90, 1.05, and 0.90, respectively, for the parameters for the 25 ml/kg, 50 ml/kg, and 100 ml/kg infusions. In these simulations, when the parameters for the 25 ml/kg, 50 ml/kg, and 100 ml/kg infusions were used, plasma dilution returned to baseline or zero at 600, 1200, and 1200 min, respectively.

**Discussion**

These data are the first to compare, in a randomized study, the kinetics of clearly supraphysiological boluses of crystalloid fluids in conscious, normovolemic sheep. These data support our hypothesis that the elimination rate constant $k_r$, which corresponds to plasma clearance in conventional pharmacokinetics, is dose-independent when calculated from experiments done under otherwise similar circumstances. This demonstrates that the rate of elimination of fluid from $V_1$ correlates directly with the magnitude of plasma dilution because $k_t$ is multiplied by the difference between the expanded volume ($V_1$) and target volume ($V_2$). However, $V_2$, the expanded functional body fluid space, increased significantly at the highest dose.

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**Fig. 2.** Measured data points (open circles) and the optimal curve fit generated by volume kinetic analysis (lines) in two representative sheep undergoing three experiments in which three volumes of 0.9% saline were infused intravenously over 20 min on separate days. Note the different scales on the y-axis.
Previous studies of fluid infusions using clinically relevant volumes have reported kinetic parameters that were little influenced by modest differences in the dose of infused fluid.\textsuperscript{2,4} However, in normovolemic female volunteers, Hahn et al.\textsuperscript{7} reported that kinetic parameters did change when the volunteers were challenged with a more rapid infusion of a crystalloid solution (25 ml/kg in 15 min in comparison to 25 ml/kg in 30, 45, and 80 min). The target volume of the peripheral fluid space $V_2$ calculated after the most rapid infusion in that study was 9 l in comparison to 4.5 l in the slower infusions. Because the normovolemic female volunteers were smaller than the normovolemic male volunteers studied in most of the other volume kinetic studies in humans, the change in the calculated $V_2$ suggests that a threshold exists above which progressively more supraphysiologic infusions will distort some of the calculated parameters. Hence we performed the current study in which the two higher doses were larger than we considered safe to infuse in normovolemic humans (the highest dose is equivalent to infusion of 7 l over 20 min in a 70-kg adult). Nevertheless, examining physiologic handling of very large infusions of fluid is important because excessive volume loading remains an important source of morbidity and mortality in surgical patients.\textsuperscript{14} In addition, it is important to determine the range over which simulations of responses can be confidently constructed based on data from previous experiments.

In pharmacokinetic/pharmacodynamic research, there are examples of common drugs in which parameters change when either very high doses or very high infusion rates are compared with more clinically relevant doses or infusion rates.\textsuperscript{8–11} For instance, when healthy volunteers received 30-min infusions of gentamicin in doses of 2.0 mg/kg, 4.5 mg/kg, or 7.0 mg/kg, and the data were fit to a two-compartment model, the distribution half-lives of the two lower doses were similar but the distribution half-life of the largest dose was approximately 50\% greater.\textsuperscript{9} When (+)-propranolol was infused into the pyloric veins of rats for 8 h at two rates (40 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\) or 20 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\)) in random order, the steady-state concentrations of the second infusion, whether high or low dose, were nearly twice as high.\textsuperscript{10} When a racemic mixture of propranolol was administered orally in doses of 40, 80, or 120 mg/kg or intravenously at rates of 0.5 or 10 mg/kg, the highest oral dose showed impaired clearance of (S)-(-)propranolol whereas after the intravenous injection (S)-(-)proprano-
lol was eliminated more rapidly, suggesting saturation of hepatic (S)-(-)propranolol clearance. These examples illustrate that estimated parameters from high doses or infusion rates of drugs may be substantially different than calculated parameters from smaller doses or lower infusion rates and that altered metabolism or altered pharmacodynamics may explain the differences.

Although estimated volume kinetic parameters are similar when clinically relevant volumes are infused, we speculate that markedly supraphysiologic infusion volumes distort those parameters, in part because of the increasing effects of larger volumes on systemic hemodynamics. Large, rapid infusions of fluid should distend the venous capacitance bed and increase capillary hydrostatic pressure. In the current study, dramatically increased central venous pressure measurements during the largest infusions (fig. 1) support this argument. The kinetic analysis demonstrates that plasma dilution does not, however, increase proportionately when the infusion volume is doubled from 50 ml/kg to 100 ml/kg and that relatively more fluid accumulates in $V_2$. The peripheral accumulation of fluid with extremely high doses can most likely be attributed to high capillary hydrostatic pressures that drive fluid from the intravascular to the interstitial space and thus more greatly expand the peripheral space.

This effect is suggested by the residual plots for the 50 ml/kg and 100 ml/kg infusions (fig. 3), in which plasma dilution increased rapidly in the early phase of the infusion, leading to negative residuals. At the end of the 20-min infusions the residuals were usually positive, suggesting that the limited elasticity of the vascular system restrained further expansion. The fluid equilibration between the central and peripheral body fluid space $V_2$ was also clarified by splitting the parameter $k_t$ into two separate constants. The results in table 3 show that $k_{t1}$ (flow out of $V_1$) was twice as high as $k_{t2}$ (flow into $V_1$).

![Fig. 5. The size of $V_1$ increases in proportion to the infused volume in sheep.](image)

![Fig. 6. The volumes of $V_2$ expressed as medians of the individual sheep for the three different infusions. The error bars are the 25th–75th percentiles. The volume of $V_2$ is not equivalent to a physiologic space but reflects an apparent volume of distribution of the infused fluid. $V_2$ for the 100 ml/kg infusion is significantly higher than for the 25 ml/kg and 50 ml/kg infusions ($P < 0.05$).](image)

### Table 2. Urinary Excretion During and after Intravenous Infusions of Three Volumes of 0.9% Saline over 20 min In Six Sheep

<table>
<thead>
<tr>
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<th>25 ml/kg</th>
<th>50 ml/kg</th>
<th>100 ml/kg</th>
</tr>
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<tbody>
<tr>
<td>Urinary Output 20 min</td>
<td>78 (60–160)</td>
<td>218 (146–225)</td>
<td>294 (193–320)</td>
</tr>
<tr>
<td>Urinary Output 60 min</td>
<td>445 (338–445)</td>
<td>806 (716–898)</td>
<td>842 (760–1083)</td>
</tr>
<tr>
<td>Urinary Output 90 min</td>
<td>616 (450–766)</td>
<td>1084 (973–1232)</td>
<td>1282 (986–1513)</td>
</tr>
<tr>
<td>Urinary Output 120 min</td>
<td>679 (528–902)</td>
<td>1220 (1161–1427)</td>
<td>1778 (1331–1918)</td>
</tr>
<tr>
<td>Urinary Output 180 min</td>
<td>853 (752–1092)</td>
<td>1524 (1423–1751)</td>
<td>2244 (1858–2569)</td>
</tr>
<tr>
<td>Ratio of Urinary Output to Infused Volume (%) 20 min</td>
<td>9 (6–17)</td>
<td>11 (8–23)</td>
<td>8 (6–9)</td>
</tr>
<tr>
<td>Ratio of Urinary Output to Infused Volume (%) 60 min</td>
<td>49 (40–60)</td>
<td>42 (37–52)</td>
<td>25 (22–28)</td>
</tr>
<tr>
<td>Ratio of Urinary Output to Infused Volume (%) 90 min</td>
<td>68 (53–79)</td>
<td>57 (50–66)</td>
<td>34 (29–42)</td>
</tr>
<tr>
<td>Ratio of Urinary Output to Infused Volume (%) 120 min</td>
<td>74 (62–95)</td>
<td>72 (59–75)</td>
<td>46 (38–53)</td>
</tr>
<tr>
<td>Ratio of Urinary Output to Infused Volume (%) 180 min</td>
<td>93 (89–115)</td>
<td>89 (72–92)</td>
<td>59 (53–73)*</td>
</tr>
</tbody>
</table>

Data are expressed as medians (25th–75th percentiles).

* $P < 0.01$. 

Anesthesiology, V 101, No 3, Sep 2004
for the largest infusion than for the two smaller infusions, perhaps because high intravascular hydrostatic pressure limited free flow of fluid into $V_1$. In effect, fluid could have been “locked out” of the vascular system because the compliance of peripheral tissues in response to excessive volume expansion exceeds that of the vascular system. These effects on kinetic parameters have not been observed for infusions of crystalloid fluid in more moderate dose ranges.4

Two measurements that are independent from the kinetic calculations corroborate these conclusions regarding the 100 mL/kg infusion. First, the AUC of the measured dilution-time curves during the 180-min study was smaller in relationship to the infused fluid volume in the 100 mL/kg infusion than in either of the two smaller infusions. Second, the proportion of infused fluid that was eliminated during the course of the 180-min study by urinary excretion was smaller when the animals received 100 mL/kg in comparison with 25 mL/kg and 50 mL/kg. Total urinary excretion was approximately 90% of the infused fluid by 180 min after infusion of 25 mL/kg or 50 mL/kg, whereas only 59% was excreted by 180 min after infusion of 100 mL/kg. In other words, the highest dose exceeded short-term renal excretory capacity, a phenomenon that occurs even with smaller doses during in isoflurane-anesthetized sheep.3,5 If plasma dilution was not proportional to infused volume at the highest volume and if urinary output was also not proportionately increased, fluid must have accumulated peripherally.

Although it is tempting to equate physiologic volumes with the functional fluid spaces defined by volume kinetic analysis, the functional target volume $V_1$ should not be considered equivalent to baseline plasma volume nor should $V_2$ be considered equivalent to baseline interstitial volume. We speculate that the estimate of $V_1$ is influenced both by plasma volume and differential perfusion of various tissues (i.e., more rapid equilibration with blood in more highly perfused tissues) and that the peripheral space $V_2$ is influenced by but is not equivalent to interstitial fluid volume. This effect is consistent with microcirculatory research suggesting that the interstitial fluid space has progressively increasing compliance as volume expansion continues.15,16 Excessive crystalloid fluid administration during anesthesia might be inevitably associated with peripheral edema.3,5 Moreover, peripheral accumulation of fluid is likely to be even more pronounced during surgical stress and blood loss, which are associated with a reduction of the contribution of urinary excretion to $k_t$, thereby increasing retention of infused fluid.15,17

Perhaps the most important issue raised by the current data is whether they suggest that the volume kinetic model lacks linearity. Linearity implies that the rate of elimination should be proportional to hemodilution per se and that the kinetic parameters calculated from the entire range of doses and infusion rates can be used to simulate the outcome of other experiments. The issue of dose dependency is clinically important because when the kinetic system changes with dose, the clinical behavior in response to infused fluid will also change as a function of dose. An example of this would be reduced renal function during the transurethral resection syndrome.18 Previous work suggests that the volume kinetic model is linear within the range of fluid volumes usually given clinically.4,6,7 However, in this study, the largest dose exceeds the linearity of the system. A simulation of the dilution and volume changes of the functional body fluid spaces $V_1$ and $V_2$ during and after infusions of 0.9% saline using the average parameter estimates given in table 1 and the actual infused volumes (25 mL/kg, 50 mL/kg, and 100 mL/kg) is shown in figure 7. If the average kinetic parameters for the three infusion volumes (table 1) are used to predict the outcome of a hypothetical 25 mL/kg infusion, the curves generated using 25 mL/kg and 50 mL/kg infusions are nearly superimposable, but the curve generated by the parameters from the 100 mL/kg infusion is different. Therefore, based on this assessment, rapid infusion in a normovolemic sheep of a volume exceeding estimated blood volume by approximately 50% exceeds the limits of linearity of the model.

An alternative way to examine model linearity is to plot dose versus AUC/dose and test for significant slope. The largest dose yielded 20% lower values for AUC/dose than the two smaller volumes. However, the elimination of all infused fluid was not completed at the end of data.

### Table 3. Volume Kinetic Analysis Separating $k_{t1}$ (Translocation of Fluid Out of $V_1$) from $k_{t2}$ (Translocation of Fluid Into $V_1$)

<table>
<thead>
<tr>
<th></th>
<th>25 ml/kg</th>
<th>50 ml/kg</th>
<th>100 ml/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$</td>
<td>1175 (738–1226)</td>
<td>1373 (1305–1546)</td>
<td>1610 (1289–2087)</td>
</tr>
<tr>
<td>SE</td>
<td>473 (266–496)</td>
<td>148 (122–186)</td>
<td>198 (154–218)</td>
</tr>
<tr>
<td>$k_{t1}$</td>
<td>231 (184–279)</td>
<td>168 (157–203)</td>
<td>310 (287–356)</td>
</tr>
<tr>
<td>SE</td>
<td>56 (37–63)</td>
<td>16 (10–21)</td>
<td>23 (21–25)</td>
</tr>
<tr>
<td>$k_{t2}$</td>
<td>257 (205–302)</td>
<td>160 (105–211)</td>
<td>164 (117–207)</td>
</tr>
<tr>
<td>SE</td>
<td>65 (51–71)</td>
<td>27 (18–30)</td>
<td>21 (19–28)</td>
</tr>
<tr>
<td>$k_r$</td>
<td>34.1 (13.4–75.0)</td>
<td>37.6 (17.6–65.6)</td>
<td>33.2 (13.9–53.9)</td>
</tr>
<tr>
<td>SE</td>
<td>4.8 (3.8–5.0)</td>
<td>5.0 (3.7–7.6)</td>
<td>7.2 (2.5–11.4)</td>
</tr>
</tbody>
</table>

Data show that $k_{t1}$ for the 100 mL/kg infusion (310) is twice as high as $k_{t2}$ (164). $P < 0.0034$.
collection at 180 min (figs. 2 and 4), in large part because the rate of renal excretory capacity was exceeded. Extrapolation of the curves to complete elimination of the infused fluid, i.e., to zero plasma dilution, yields similar AUC/dose ratios for the three infusion volumes. Nevertheless, because large portions of those curves were simulated, further studies in which data are collected for a longer interval would be necessary to accumulate empirical evidence to support the extrapolated curves. Regardless, the current data, in conjunction with previously published data, suggest that the volume kinetic model is linear within clinically applicable dose ranges.

The main hypothesis in this study was that the elimination rate constant, \( k_r \), would be independent of infused volume. Despite extreme doses that were associated with nonlinearity, \( k_r \) did not change. Hence, elimination from the central fluid space is proportional to plasma dilution per se, regardless of whether massive fluid volumes are infused. It is important to point out that the kinetic parameters were estimated with good confidence in this study, i.e., the fit of the model equations to the data were good, as shown by the two sheep chosen in figure 2 and the small errors in the residual plots shown in figure 3. Factors promoting peripheral fluid accumulation comprise any reduction of \( k_t \) from fasting, surgery, or bleeding. Here, the overnight fast probably promoted sufficient fluid retention to make all curves fit the two-volume model better than the one-volume model, in contrast to previous studies in which some individual experiments were more consistent with a one-volume model (more likely in well-hydrated subjects or experimental animals) and some with a two-volume model.\(^2,4,7\)

We have previously shown that \( k_t \) is little altered by isoflurane anesthesia despite reduction of urinary output in isoflurane-anesthetized conscious sheep.\(^3,5\) We attributed this to an effect of isoflurane anesthesia per se by demonstrating that it was not attributable to mechanical ventilation. Those results, in combination with the current results, suggest another possibility: that removal of excess fluid from the central fluid space functions through a highly efficient set of mechanisms; if renal function is adequate to remove excess fluid, \( k_t \) reflects urinary output. If renal function cannot remove excess fluid sufficiently rapidly, then fluid accumulates in a peripheral fluid space.

In summary, the elimination of rapidly infused intravenous saline solution from the central volume is independent of infused volume; larger volumes are cleared from the central volume by expansion of a peripheral volume.

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Appendix

A new form of the two-volume fluid-space model, in which fluid diffusion from \( V_1 \) to \( V_2 \) is governed by a constant \( k_1 \) while diffusion in the opposite direction is governed by \( k_2 \), is used for the first time in the present study. The solution to this two-fluid-space model is based on the matrix exponential \( e^{At} \). During infusion, we have

\[
\begin{align*}
\dot{w}_1(t) &= \left( \frac{w_{1a}(t)}{w_{2a}(t)} \right) = \left( \frac{k_2 - k_1}{k_1} \right) \left( 1 - e^{-kt} \right) \left( \frac{1}{k_2/k_2} \right), \quad 0 \leq t \leq t_1 \\
\dot{w}_2(t) &= \left( \frac{w_{1d}(t)}{w_{2d}(t)} \right) = \left( \frac{k_2 - k_1}{k_1} \right) \left( 1 - e^{-kt} \right) \left( \frac{1}{k_2/k_1} \right) + e^{kt} \left( \frac{w_{1d}(t_1)}{w_{2d}(t_1)} \right), \quad t_1 \leq t \leq t_2
\end{align*}
\]

and after infusion

\[
\begin{align*}
\ddot{w}_1(t) &= \left( \frac{w_{1a}(t)}{w_{2a}(t)} \right) = \left( \frac{k_2 - k_1}{k_1} \right) \left( 1 - e^{-kt} \right) \left( \frac{1}{k_2/k_2} \right), \quad 0 \leq t \leq t_1 \\
\ddot{w}_2(t) &= \left( \frac{w_{1d}(t)}{w_{2d}(t)} \right) = \left( \frac{k_2 - k_1}{k_1} \right) \left( 1 - e^{-kt} \right) \left( \frac{1}{k_2/k_1} \right) + e^{kt} \left( \frac{w_{1d}(t_1)}{w_{2d}(t_1)} \right), \quad t_1 \leq t \leq t_2
\end{align*}
\]

where the matrix \( A \) is

\[
A = \begin{pmatrix}
-k_1 + k_i & k_i \\
\frac{k_i V_2}{V_1} & -\frac{k_i V_2}{V_1}
\end{pmatrix}
\]

This form is well suited for numerical computation of the solution with the mathematical program Matlab, which has the matrix exponential \( e^{At} \) implemented as a standard function.

In another form of the two-fluid-space solution, the biexponential form is clearly seen:

\[
\begin{align*}
\dot{w}_1(t) &= Q_1 e^{Xt} + Q_2 e^{Yt} + Q_3 \\
\dot{w}_2(t) &= Q_4 e^{Xt} + Q_5 e^{Yt} + Q_6
\end{align*}
\]

where \( X \) and \( Y \) are eigenvalues of \( A \), that is,

\[
0.5 \left( \frac{k_i V_2}{V_1} + \frac{k_i V_2}{V_2} \right) = \sqrt{\left( \frac{k_i V_2}{V_1} + \frac{k_i V_2}{V_2} \right)^2 - 4 k_i k_i V_1 V_2}
\]

and the coefficients \( Q_1, Q_2, Q_3 \ldots \) are nonlinear functions in the parameters \( k_1, k_2, k_i, k_b, V_1, \) and \( V_2 \).