

Arteriovenous Differences in Plasma Dilution and the Distribution Kinetics of Lactated Ringer's Solution

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BACKGROUND: Conventional concept suggests that infused crystalloid fluid is first distributed in the plasma volume and then, since the capillary permeability for fluid is very high, almost instantly equilibrates with the extracellular fluid space. We challenge whether this view is consistent with findings based on volume kinetic analysis.

METHODS: Fifteen volunteers received an IV infusion of 15 mL/kg of lactated Ringer's solution during 10 min. Simultaneous arterial and venous blood hemoglobin (Hgb) samples were obtained and Hgb concentrations measured. The arteriovenous (AV) difference in Hgb dilution in the forearm was determined and a volume kinetic model was fitted to the series of Hgb concentrations in arterial and venous blood.

RESULTS: The AV difference in plasma dilution was only positive during the infusion and for 2.5 min thereafter, which represents the period of net flow of fluid from plasma to tissue. Kinetic analysis showed that volume expansion of the peripheral fluid space began to decrease 14 min (arterial blood) and 20 min (venous blood) after the infusion ended. Distribution of lactated Ringer's solution apparently occurs much faster in the forearm than in the body as a whole. Therefore, the AV difference in the arm does not accurately reflect the distribution of Ringer's solutions or whole-body changes in plasma volume.

CONCLUSIONS: The relatively slow whole-body distribution of lactated Ringer's solution, which boosts the plasma volume expansion during and for up to 30 min after an infusion, is probably governed by a joint effect of capillary permeability and differences in tissue perfusion between body regions.

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Cystalloid fluids, such as lactated Ringer's solution, are commonly used during anesthesia and surgery. When infused into the circulation hemodilution occurs which correlates with the increase in plasma volume (PV). Therefore, hemoglobin (Hgb) changes have been used to indicate the PV or blood volume (BV) over time,¹⁻⁴ although the large-vessel: whole-body hematocrit (Hct) ratio of 0.9 should be applied to correct for anticipated unequal distribution of the Hgb molecules.⁴⁻⁷ Since fluid can be assumed to distribute faster than molecules of any size, infused fluid is believed to simultaneously and almost instantly spread throughout the PV and extracellular fluid space.

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This conventional "physiological view" is rational^{8,9} but has been challenged by volume kinetics in which crystalloid fluid becomes distributed between two functional body fluid spaces over a period of time, as long as 20-30 min.¹⁰⁻¹³ The relatively slow distribution process is of clinical relevance since it implies that the PV expansion during and shortly after administration is much greater than the 20%-25% of the infused volume suggested by the physiological view model. Moreover, the reason for slow distribution is unclear. The time might be too long to be explained solely by local equilibration of fluid across the capillary membrane, and we have questioned whether Hgb changes also reflect differences in tissue perfusion.¹⁴

This issue can be explored by comparing the Hgb level in arterial and venous samples (arteriovenous [AV] difference) simultaneously by a kinetic analysis. The AV difference shows the direction of the fluid flux between plasma and the interstitial fluid space in the vicinity of the venous sampling site (Fig. 1), whereas volume kinetics can be used to indicate the direction of the fluid flux for the whole body (Fig. 2). Hence, the purpose of this study in volunteers was to compare the direction of fluid flow based on AV differences and the direction of fluid flow as obtained by volume kinetic analysis. Moreover, we wanted to examine the similarity of the kinetic parameters when based on

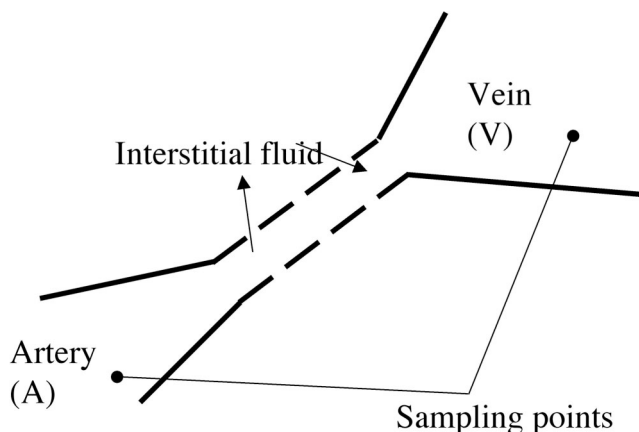


Figure 1. Interpretation of the arteriovenous (AV) gradient in hemoglobin (Hgb) dilution along one single blood vessel. During the time that the fluid is translocated from the plasma to the tissue, the dilution of $A_{Hgb} > V_{Hgb}$, and when fluid is translocated from tissue to plasma, the dilution of $A_{Hgb} < V_{Hgb}$.

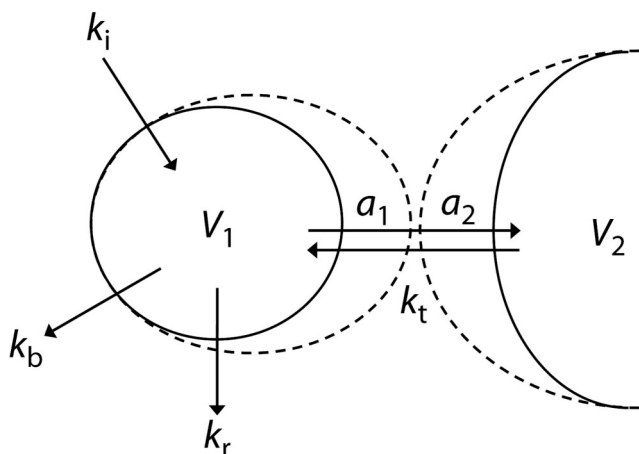


Figure 2. Schematic drawing of the kinetic model used to analyze the arterial and venous plasma dilution-time profiles, respectively.

arterial versus peripheral venous blood. All kinetic analyses of infusion fluids in humans have been based on venous samples, although it is known from drug kinetics that arterial samples better represent whole-body events.

METHODS

Fifteen healthy volunteers, 8 females and 7 males, aged between 20 and 32 (mean 27) years with a body weight of 51–103 kg (mean 75 kg) were studied. The protocol was approved by the IRB of the University of Texas Medical Branch at Galveston and each patient gave his/her written consent to participate.

The volunteers were admitted to the research center the evening before the experiment began. The following morning at approximately 8 AM, the volunteers voided, were weighed, and placed comfortably on a bed with their trunk and legs (not the arms) covered with blankets. Cannulae were inserted into one radial artery and the antecubital veins in both arms. The arm

with both arterial and venous access was used for blood sampling and the other side for the infusion of fluid. Monitoring consisted of electrocardiography, pulse oximetry and noninvasive arterial blood pressure measurements. The cuff was placed on the arm of the infusion, and no external pressure was applied to facilitate the withdrawal of blood.

After a 30-min equilibration period to obtain a hemodynamic steady-state, an IV infusion of 15 mL/kg of body-warm lactated Ringer's solution was given for 10 min (Baxter Healthcare, Deerfield, IL) by an infusion device (Flo-Gard 6201, Baxter). The fluid contained the following ions: Na 130, K 4, Ca 2, Cl 110, lactate 30 (mEq/L).

Arterial and venous blood were simultaneously sampled at precisely timed intervals for analysis of the blood Hgb concentration, using a Technicon H2 (Bayer, Tarrytown, NY) which determines Hgb by colorimetry at 546 nm. Sampling was made at 0, 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 13.5, 15, 16.5, 18, 19.5, 21, 22.5, 24, 25.5, 27, 28.5, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 min. Each sample was drawn in duplicate from both the arterial and the venous line, except the baseline Hgb and Hct, which were based on the mean of quadruplicate samples. Hence, 4 Hgb samples were drawn at each time point requiring a total of 6 mL of blood, except the first which required 12 mL. Randomly selected duplicate samples (800 pairs) yielded a coefficient of variation for this Hgb analysis of 0.8%. The volunteers voided *ad libitum* during the experiments and always after they ended. The urine volume was measured.

Both the arterial and the venous Hgb series were analyzed by volume kinetics, which is pharmacokinetics adapted for infusion fluids, according to a two-volume model developed by Drobin.¹⁵ The benefit of Drobin's approach is that all parameters can be estimated by the same model, even in cases where the urinary excretion is so large that it should normally be accounted for by applying a one-volume kinetic model.

The model consists of one central compartment, V_1 , which expands to the volume v_1 at time t by an infusion given at the rate k_i (mL/min) (Fig. 2). The expanded volume, v_1 , strives to assume the baseline volume V_1 , and communicates with a distant compartment, the expansion of which is termed a_2 , at a rate proportional to the volume expansion by the rate parameter k_t (min^{-1}). Elimination is proportional to expansion of V_1 (a_1) by a rate parameter k_r (min^{-1}) and basal elimination is considered by k_b , which is set to 0.5 mL/min.^{10,11}

The volume changes in the central compartment, a_1 , and in the peripheral compartment, a_2 , are then given by:

$$\frac{da_1}{dt} = k_i - k_b - k_r \cdot a_1 - k_t \cdot (a_1 - a_2) \quad (1)$$

Table 1. Baseline Hemoglobin (Hgb) Concentration and Kinetic Parameters Calculated Depending on Whether Sampling was from Either Arterial or Venous Blood

Parameter	Arterial samples		Venous samples	
	Median	25th–75th percentile	Median	25th–75th percentile
Baseline Hgb (g/dL)	13.69	13.14–14.66	13.72	12.87–14.78
V_1 (L)	2.73	2.34–3.16	2.92	2.65–3.60
k_r (10^{-3} , min^{-1})	37	20–50	36	11–47
k_t (10^{-3} , min^{-1})	79	38–144	51	25–150
a_{ref} (mL)	–43	–85 to 2	–41	–80 to 0
Time to $a_{2,\text{max}}$ (min)	24	17–37	30	15–47

V_1 = baseline volume of the central body fluid space expanded by infused fluid; k_r = rate constant for elimination; k_t = exchange rate parameter between V_1 and periphery; a_{ref} = the amount, in mL, of baseline shift between pre- and postinfusion fluid balance.

$$\frac{da_2}{dt} = k_t \cdot (a_1 - a_2) \quad (2)$$

where $a_1 = v_1(t) - V_1$ represents the expansion of V_1 .

The Hgb-derived plasma dilution was used as input data as it equals the dilution of V_1 , which can be written $(v_1 - V_1)/V_1$ or, in the present model, as a_1/V_1 . The reference equation for this relationship is:

$$\frac{v_1(t) - V_1}{V_1} = \frac{\text{Hgb}/\text{Hgb}(t) - 1}{1 - \text{Hct}} \quad (3)$$

where Hct is the Hct at baseline. Symbols without an index denote baseline values and (t) those obtained at a later point in time. The Hgb-derived plasma dilution had to be multiplied by V_1 before it could be applied as a_1 on the right side of the sign of equality in Eq. 1 and 2. On the left side, a_1 was not transformed.

The Hgb-derived plasma dilution as given in Eq. 3 was corrected for the sampled volume of blood as described mathematically in previous work.¹⁶ This correction is based on the following predictions of the relationship between BV and the length and weight of subjects published by Nadler et al.⁸:

$$\text{BV (L)} = 0.03219 \text{ weight (kg)} + 0.3669 \text{ length}^3 \text{ (m)} + 0.6041 \text{ (Males; Eq. 4)}$$

$$\text{BV (L)} = 0.03308 \text{ weight (kg)} + 0.35612 \text{ length}^3 \text{ (m)} + 0.1833 \text{ (Females; Eq. 5)}$$

The kinetics of the IV infused fluid was modeled separately for each subject, using Matlab version 7.0.1 (Math Works, Natick, MA), whereby a nonlinear least-squares regression routine based on a modified Gauss-Newton method was repeated until none of the three unknown parameters (V_1 , k_v , and k_r) changed by more than 0.001 (0.1%) in each iteration. No correction was applied for the transit time for blood between the radial artery and the cubital vein since we believed this would be <10 s.

The results were presented as median and 25th and 75th percentiles. The Wilcoxon matched pair test was applied to disclose differences in parameter estimates

between sampling sites. Linear regression analysis, in which k is the slope and r the correlation coefficient, was used to study the relationship between the size of V_1 and the predicted PV; the latter was obtained as the product of BV and $(1 - \text{Hct})$. $P < 0.05$ was considered significant.

RESULTS

All dilution-time curves were possible to analyze by volume kinetics. Arterial samples yielded a slightly smaller size for V_1 ($P = 0.064$) and a higher distribution rate constant, k_v , than venous samples ($P = 0.83$; Table 1).

During infusion, and immediately afterwards, curves based on arterial samples showed less interindividual variability than venous curves, which is also illustrated by the greater variation of all parameter estimates when based on venous samples (Table 1). The kinetic analysis also demonstrated a lowering of the baseline for the fluid balance after the infusion, a change that corresponded to a volume deficit in a_1 of 20–30 mL.

The mean AV difference in plasma dilution was positive during the infusion and for 2.5 min thereafter (Fig. 3). The AV crossover point corresponds to the point in time when a_2 begins to decrease in a volume kinetic analysis (Fig. 4). This point was determined by satisfactory iteration by the computer program Matlab. On the average, it occurred at 14 min and 20 min after the infusion ended for the arterial and venous samples, respectively (Table 1).

Volume-time plots indicated that 65%–70% of the infused fluid volume remained in V_1 at the end of the 10-min brisk infusion, whereas this fraction reached 20%–25% after the whole-body distribution had been completed 30 min later (Fig. 4).

At the end of the experiment (2 h), the urinary excretion amounted to 570 mL, (380–800) which is 47% (31–72) of the infused fluid volume.

The regression plot between the predicted PV and V_1 in arterial blood had a slope was 1.00 (the equation being $V_1 = 1.00 \times \text{PV} - 0.12$ with $r = 0.70$; $P < 0.001$). Their median difference was 0.21 L (–0.21 to 0.43). The slope was steeper, however, when the PV was

Figure 3. Arteriovenous (AV) difference in plasma dilution in the forearm of 15 volunteers receiving 15 mL/kg of lactated Ringer's solution over 10 min. Negative values indicate that fluid is translocated from the interstitial space to plasma. The smoothed curve represents the mean of all calculated curves.

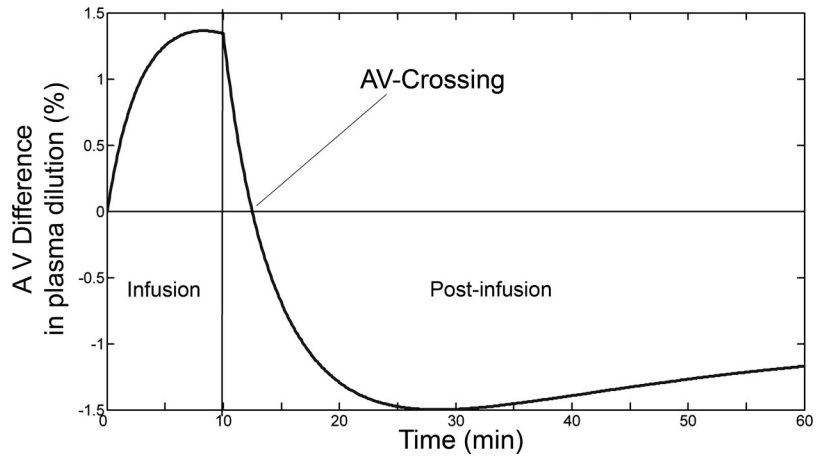
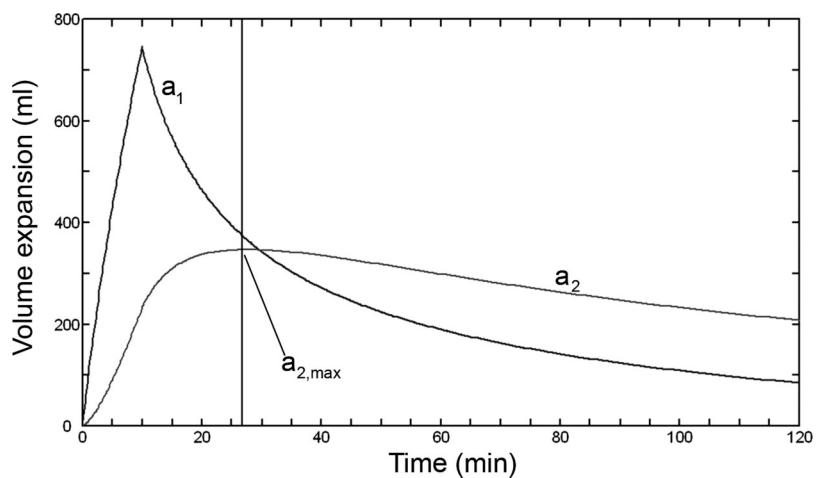


Figure 4. Illustration of when a_2 reaches its highest point, that is, when peripheral accumulation of fluid is at its maximum. The curves are a computer simulation using the kinetic parameters derived from venous blood samples in 1 volunteer. Although being visibly similar in this figure, the maximum a_2 is not equivalent to the crossing point of the curves. Here, it occurs 17 min after the end of the infusion.



plotted versus V_1 based on venous blood (the equation was $V_1 = 1.37 \times PV - 0.81$; $r = 0.69$; $P < 0.01$). Their median difference was -0.18 L (-0.86 to 0.19).

DISCUSSION

Most previous studies of volume kinetics in human subjects have been based on venous blood samples. In the present study, we wanted to compare venous to arterial samples during a series of fluid infusion experiments, since it is accepted in drug kinetics that arterial samples better reflect whole-body events and, in particular, early distribution. The results show that the sampling sites provided quite similar Hgb curves. Both yielded robust data for kinetic analysis, although arterial blood indicated a slightly lower size of V_1 and a higher distribution rate constant, k_i . These parameters are primarily determined during and immediately after the infusion, as evidenced by partial derivatives yielded during curve-fitting,¹⁷ and the differences may, therefore, be due to the fact that the last portion of any infused fluid is sampled before it reaches the capillaries.

Arterial samples also showed lesser interindividual variability, which is probably due to lack of influence of AV shunts. The combined effects of these differences were still relatively minor, however, and none of the parameter estimates differed significantly between

the arterial and venous sampling site data. Therefore, our conclusion is that both arterial and venous blood can be used for kinetic analysis and that earlier works based on venous samples do not need to be reevaluated.

The study was also conducted to better understand the profile of plasma dilution-time curves. The steep downward slope in Hgb dilution just after an infusion ends is usually thought to represent distribution of fluid from the plasma to the interstitial space, which continues until they are equally diluted. However, this view seems to be too simplistic since the AV difference in plasma dilution and the kinetic analyses show that the rate of equilibration is much higher in the arm than for the body as a whole.

In the forearm, the AV difference in plasma dilution is positive for as long as fluid accumulates in the interstitial fluid space, whereas a change in the direction of the net flow of fluid has occurred when the AV difference becomes negative. For the body as a whole, the corresponding change in the direction of the net mass flow of fluid takes place when a_2 begins to decrease. One should note that the crossover point for the sizes of a_1 and a_2 , as plotted in Figure 4, does not indicate this change in net flow. A dilution-time plot would always crossover when a_2 obtains its highest value, but the volume kinetic model used here focuses on volume expansion rather than on dilution.

The AV difference in the forearm became negative 2.5 min after the infusion ended whereas, for the whole body, our kinetic calculations imply that the mass flow of fluid does not change direction from tissue to plasma until between 14 min and 20 min later. This finding is consistent with the relatively long period of time required for the whole-body equilibration of fluid to be fully completed. The entire distribution phase has been demonstrated to last for 20–30 min based on venous Hgb samples in volunteers^{10,11,13} and in surgical patients.¹⁶

The time required for distribution of lactated Ringer's solution is similar to that obtained for ethanol, which is extremely soluble and easily crosses all membranes.¹⁸ As for Ringer's solution, the AV difference changes from positive to negative in the forearm within 5 min after IV infusion, whereas the distribution process in the whole body takes 20–30 min to be completed.¹⁹ The permeability of the capillary membrane can hardly account fully for the distribution process. Differences in perfusion between vascular beds in different regions of the body must be considered as a factor of importance to the slow distribution of ethanol as well as for lactated Ringer's solution.

The slow distribution process of lactated Ringer's solution is clinically important since it boosts the PV expansion during and for 20–30 min after an infusion. In the present study, the venous hemodilution indicated that as much as 69% of the infused fluid was retained in V_1 at the end of the quite brisk 10-min infusions. The corresponding value was 60% for a continuous infusion during surgery³ and 40% at the end of a 30-min infusion in volunteers.¹¹ Medical textbooks do not even indicate that the volume equilibration between plasma and tissue is time-consuming. The conventional "physiological view" rather holds that Ringer's solution distributes very quickly throughout the plasma and interstitial fluid spaces. Therefore, the PV expansion is said, without exception, to be 20%–25% of the infused volume.

The complexity of the distribution process explains indirectly why we cannot be sure that V_1 equals the baseline PV. Similarly, we cannot be sure that the sum of V_1 and a_1 equals the dynamic PV during and after the infusion. Although being of quite similar size, the PV is a physiological space while V_1 is a functional fluid space. The semantic problem can be illustrated by the fact that, even if we infuse a bolus of lactated Ringer's solution into the plasma, some of the fluid will have left this physiological space even before the rest of it has become distributed throughout the entire PV. Interstitial fluid spaces in the lungs (blood flow 14 L/min per L tissue water) probably become expanded quickly and easily, whereas some of the lactated Ringer's solution might not even reach the interstitium of poorly perfused areas with resting muscle (blood flow 0.04 L/min per L tissue water). The Hgb changes represent the sum of all such occurrences.

As venous sampling is usually made from the forearm where the AV equilibration occurs relatively fast, the changes in Hgb obtained during the distribution phase of a crystalloid fluid load cannot very accurately reflect the PV in the whole body. The reason that Hgb changes are more safely related to the functional fluid space V_1 is that distribution of Ringer's solution represents a continuous process that occurs at various rates in different body regions, rather than being a fixed-rate single process. This view has been validated for drugs but not previously for fluids.

One issue during the kinetic analysis was that the Hgb concentration in arterial blood was 0.4% lower (median 0.2%) than in venous blood before the experiments started (Table). The reason for this minor baseline AV difference in Hgb is unclear. It might be explained by lymphatic flow since it indicates the presence of a slow internal transport of fluid from the periphery to the central part of the body. This transport is completely overrun by the impact of the quite massive and rapid fluid load.

In conclusion, equilibration of infused lactated Ringer's solution between plasma and interstitial fluid occurs much faster in the forearm than the body as a whole. The relatively slow whole-body distribution therefore seems to represent a complex and continuous process governed by capillary permeability and also by differences in perfusion between different vascular beds. The net result is that PV expansion is greater than commonly believed during and for 20–30 min after an infusion.

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