Interstitial washdown and vascular albumin refill during fluid infusion: novel kinetic analysis from three clinical trials

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Short title: Interstitial washdown
Abstract

Background and Aims. Increased capillary filtration may paradoxically accelerate vascular refill of both fluid and albumin from the interstitial space, which are claimed to be edema-preventing. We characterized “interstitial washdown” by kinetic analyses of the hemodilution induced by intravenous infusion of crystalloid fluid during 3 distinct physiological states.

Methods. The dilution of blood hemoglobin and plasma albumin was compared by population volume kinetic analysis during and after intravenous infusion Ringer’s solution over 30 min in 24 conscious volunteers and 30 anesthetized patients. Data were also retrieved from 31 patients with ketoacidosis from hyperglycemia who received 1 L of 0.9% saline. Greater plasma dilution of hemoglobin as compared to albumin indicated recruitment of albumin.

Results. “Interstitial washdown” increased plasma albumin concentration by 0.6 g/L in volunteers, by 1.0 g/L during anesthesia, and by 0.3 g/L in ketoacidosis patients. The albumin concentration in extravascular fluid returning to the plasma was approximately 29, 29, and 22 g/L during the respective infusions, but decreased to an average of 50% to 75% lower during the subsequent 2-3 h. Pronounced washdown was associated with increased capillary filtration (high \( k_{12} \)) and, in conscious subjects, with fluid retention due to restricted urine flow. During anesthesia, the main effect was an increase the non-exchangeable fluid volume (“third-spacing”).

Conclusions. Fluid infusion induces interstitial washdown by accelerated lymphatic flow and an increase in plasma albumin. The mechanism becomes exhausted after 2-3 hours. Albumin refill helps retain infused volume within the vascular compartment.

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body water, physiology; crystalloid solutions, pharmacokinetics; extracellular space, physiology; pharmacokinetics; saline solution, isotonic
Introduction

Capillary refill is the movement of fluid from the interstitial space back into the vascular compartment to maintain plasma volume. The best-known example of this process is the translocation of fluid following hemorrhage, which represents a powerful compensatory mechanism to restore plasma volume. Slower refill processes have been observed that compensate for vasodilatation, such as when general anesthesia is induced without volume loading [1] and in response to the change in body position from standing to supine [2].

Capillary refill of fluid and protein also occurs in response to volume loading. Arthur Guyton's physiology textbook suggests that such refill, which he called “interstitial washdown”, counteracts peripheral edema [3]. The concept is poorly studied but implies that interstitial albumin is transferred to the plasma either by acceleration of the lymphatic flow or by some other mechanism that recruits albumin. Lymphatic flow increases promptly in response intravenous volume loading in the dog [4] but whether the induced flow is sufficient to prevent edema in humans is unknown. However, understanding the process by which fluid and proteins, especially albumin, move within and between compartments in response to hemodynamic stresses may aid in improving resuscitation strategies.

In this analysis, data from three series of human trials (volunteers, anesthesia, and ketoacidosis patients) were used to quantify the plasma protein enrichment during crystalloid fluid therapy in humans. The method of study was volume kinetics, which resembles drug pharmacokinetics but uses the hemodilution induced by an infusion fluid instead of a drug concentration as the dependent variable [5]. Hemodilution can be calculated based on either hemoglobin (Hb) or albumin, and the difference between the two dilutions is used as a basis for further calculations. Besides quantifying the albumin recruitment, our objective was to: 1) determine whether redistributed fluid is likely to represent lymphatic flow, 2) how effectively the "washdown" expands the plasma volume and, 3) how the process dehydrates the interstitial space.
Materials and Methods

 Evaluated trials
This retrospective study of interstitial washdown was based on the difference in plasma dilution when calculated from the blood hemoglobin (Hb) and plasma albumin concentrations during and after infusion of Ringer’s acetate in three populations (volunteers, anesthesia, and intensive care). Data from three settings were included:
1. Infusion of 25 mL/kg of Ringer’s acetate in 24 healthy euvolemic male volunteers [6,7].
2. Infusion of 25 mL/kg of Ringer’s acetate to 30 patients undergoing thyroid surgery under general anesthesia [8]. No fluid was infused during induction of the anesthesia.
3. Infusion of 1 L of 0.9% saline on 31 occasions to 17 patients (mean body weight 73 kg) with diabetes who were treated for ketoacidosis in an intensive care unit [9].

All infusions were given over 30 min.

 Procedures
The studies of volunteers and surgical patients were performed in a similar way. Both the subjects and the patients had a light breakfast consisting of one glass of water or milk and one sandwich at least 2 h before the infusion, which began at 9.00 am. They voided and were weighed just before the infusion started. The subjects rested comfortably on a bed, covered with blankets, and cannulas were inserted into the antecubital veins of both arms; one was used for infusion and the other for blood sampling. A recumbent equilibration period of 30 min was allowed before the experiments were initiated.

When an infusion had started, venous blood (3 mL) was drawn repeatedly during the infusion and for 2-3 h thereafter. The hematocrit and the blood hemoglobin (Hb) and plasma albumin concentrations were analyzed at the hospital’s clinical chemistry laboratory. Details are given the respective studies [6-9].

The diabetic patients underwent their infusion experiment soon after their arrival at the ICU. Most patients also had a repeat experiment on the next day. The choice of 0.9% saline as infusion fluid is common practice in Sweden when treating severe hyperglycemia
(mean plasma glucose on arrival was 36 mmol/L) and is intended to alleviate hyponatremia and prevent cerebral edema. Here, arterial blood was sampled.

**Index of interstitial washdown**

Interstitial washdown of lymph was assumed to have taken place when the recruitment of albumin to the plasma exceeded the capillary leakage of albumin. For this purpose, a comparison was made of the plasma dilution based on blood Hb vs. plasma albumin. This difference was obtained as:

\[
\left(\frac{(Hb / hb) - 1)}{(1 - Hematocrit)}\right) - \left(\frac{(Albumin / albumin) - 1)}{\right) \quad \text{(Eqn. 1)}
\]

Symbols in capital letters denote baseline values. For both molecules, a minor correction was made for the effects of blood sampling on the plasma dilution [8].

The difference is 0 if the recruitment of albumin to the plasma equals the capillary leakage of albumin. Positive values imply that the plasma dilution of albumin is smaller than dilution of Hb which, as Hb remains constant in the bloodstream, shows that more albumin has been added to the plasma than is lost.

The balance between albumin recruitment and capillary leakage is reported by multiplying the Hb-albumin difference in plasma dilution with the plasma albumin concentration to make the “central albumin balance” (unit: g/L), which then indicates the plasma albumin concentration that could be attributed to the washdown.

**Volume kinetic analysis**

The central albumin balance was compared to the distribution of fluid as obtained by population volume kinetic analysis, which is based on dilution of the Hb concentration [5]. Infusion fluids contain almost exclusively water, and the Hb dilution is therefore an index of the infused water volume that rapidly equilibrates with the circulating plasma (\(V_c\)).

Fluid is distributed to a peripheral fluid space (\(V_t\)) from which re-distribution later occurs back to \(V_c\). Elimination takes place by urinary excretion. Three rate constants govern the distribution of fluid between \(V_c\), \(V_t\) and the urine are \(k_{12}\), \(k_{21}\), and \(k_{10}\) (the same as in conventional pharmacokinetics). A schematic drawing of the model is shown in Fig. 1.
This kinetic model with volume exchange between two expandable body fluid compartments is intended to reflect normal physiology. However, fluid may also accumulate in a "third space" which implies elimination from the kinetic system that is not recovered as urine. This flow represented by the rate constant \( k_b \) was called "non-exchangeable volume expansion" [10].

Differential equations for the kinetic model, in which \( R_o \) is the infusion rate, are:

\[
\frac{dv_c}{dt} = R_o - k_{12} (v_c - V_c) + k_{21} (v_l - V_l) - k_{10} (v_c - V_c) - k_b (v_c - V_c) \quad \text{(Eqn. 2)}
\]

\[
\frac{dv_l}{dt} = k_{12} (v_c - V_c) - k_{21} (v_l - V_l) \quad \text{(Eqn. 3)}
\]

Dependent (input) variables were the plasma dilution, which equals \((v_c - V_c) / V_c\) in the model, and the urinary excretion, which is usually measured 2-3 times during an experiment. The urine volume is used to stabilize the model by setting \( k_{10} \) equal to urinary excretion divided by the area under the central volume-time curve [11].

The kinetic model was fitted to these two dependent variables in all experiments in each cohort on a single occasion, using the Phoenix software for nonlinear mixed effects, version 1.3 (NLME, Pharsight, St. Louis, MO) and the First-Order Conditional Estimation Extended Least Squares (FOCE ELS) as search routine.

Special attention was given to the modeled flows of fluid in and out of the plasma space. As indicated by Eqn. 2, the flow of fluid from \( V_c \) to \( V_l \) (in mL/min) is given by \( k_{12} (v_c - V_c) \) and the returning flow by \( k_{21} (v_l - V_l) \).

The influence of interstitial washdown on the distribution and elimination of the infused Ringer’s was analyzed by using the difference in plasma dilution when based on blood Hb and plasma albumin (as written in Eqn. 1) at each point in time as a potential covariate to each of the model parameters when Hb was used as dependent variable. The covariance was included if it reduced the residual error, expressed here as \(-2(\text{LL})\) (log likelihood), by \( >3.8 \) points \((P< 0.05)\). The rate constant \( k_b \), which represents or “non-exchangeable volume expansion”, was included in the model if its inclusion reduced \(-2\text{LL}\) by \( >3.8 \) points. The linear covariate model was applied as the difference in plasma dilution could be negative [12]. No other covariance was sought. Details about how covariance is modeled and used for simulation are given elsewhere [11].
Simulations were performed to illustrate the effect of the intensity of the albumin recruitment on the distribution of infused fluid between the body fluid compartments. This was done by contrasting the bottom 5% and the top 5% differences in the Hb-albumin dilution against each other in each of the kinetic parameters for which covariance with the dilution difference was statistically significant. Graphic output was created by using MATLAB R2019b (Math Works, Inc., Natick, MA).

Demographic data were reported as the mean (standard deviation) and the kinetic data were reported as the best estimate and standard error.

Results

Wash-down curves
Infusion of 25 mL/kg of Ringer’s acetate solution yielded transient albumin recruitment in conscious volunteers with a maximum at the end of the 30-min infusion (Fig. 2A). Recruitment was prolonged when infused during anesthesia (Fig. 2B) but less pronounced and transient in patients with ketoacidosis (Fig. 2C). However, the ketoacidosis patients received only half as much fluid as the others.

Volume kinetics versus wash-down
Volume kinetic analyses were used to characterize the prerequisites for the albumin recruitment in association with fluid therapy. Figs. 3A, B show the volume expansion of the central fluid compartment (plasma) and the peripheral compartment in the Volunteer Group. Fig. 3C gives the average excess volume in the central compartment due to interstitial washdown, as given by the difference in modeled plasma volume expansion when volume kinetic analyses was based on the Hb and on the albumin dilution. The same illustrations for the other two series of infusions are shown on the subsequent rows in Fig. 3.
Covariance with the Hb-albumin dilution difference

The volume kinetics was re-calculated using Hb as the dependent variable and with sequential examination of the Hb-albumin difference in plasma dilution at each data point (sign of albumin recruitment) as a potential covariate to the four parameters in the model. Covariance was then statistically significant in 10 of the 12 possible combinations, which confirmed that albumin recruitment affected the fluid kinetics (Table 1).

This covariance analysis was used to create plots that contrast minimal albumin recruitment (lowest 5%) from pronounced albumin recruitment (highest 5%) from each other. Fig. 3D shows how washdown affected the flow of fluid from the peripheral to the central fluid space. Fig. 4 illustrates how the washdown affected the distribution of infused Ringer’s between modeled body fluid spaces.

Calculations were performed to examine to what degree the modeled inflow of fluid to the plasma consisted of lymph. Capillary leakage of albumin in healthy volunteers is considered to occur at a rate of 5% of the intravascular pool per hour in volunteers [13], which corresponds to a clearance (CL) of 3.5 mL/min if the plasma volume is 3 L.

The build-up of excess plasma volume due to interstitial washdown required approximately 30 min in all three experiments (Fig. 3C, G, and K). A turnover equation was used to estimate the albumin concentration of the inflow during this time period. This equation holds that the recruited amount of albumin per minute equals the input minus the elimination during the same period of time.

For the Volunteer Group, the increase in central albumin difference was 0.5 g/L (Fig. 2A), the average inflow of fluid 6 mL/min between 0 and 30 min, plasma albumin 36 g/L, and the plasma volume approximately 3 L. Hence, for 30 min:

\[0.5 \times 3 \times 10^3 = 6 \times 30 \times X - 3.5 \times 36 \times 30; \quad X = 29 \text{ g/L}\]  \(\text{(Eqn. 4)}\)

In the Anesthesia Group, inflow averaged 11 mL/min and washdown increased plasma albumin by 1.0 g/L (Fig. 2B). On the assumption that CL was doubled during surgery [14], the albumin concentration of the inflow was estimated to be 29 g/L, i.e., the same as in the volunteers. The same calculation for the Ketoacidosis Group yielded 22 g/L.

During the period of steady state, the inflow of albumin (inflow rate * X) equals the outflow (CL * plasma albumin) [15]. The inflow rates during these periods averaged 9, 28, and 31 mL/min and the average plasma albumin 36, 31, and 31 g/L for the three study
groups, respectively. The albumin concentrations so obtained were 14, 8, and 7 g/L. Hence, the albumin concentration in the accelerated inflow decreased over time.

The baseline inflow before the Ringer infusion was calculated by assuming that the albumin concentration in lymph is half that of the plasma [16]. Plasma albumin at steady state (C_{ss}) then equals the albumin inflow divided by the CL. This means that the baseline lymph flow will be twice the CL, i.e. 7 mL/min, regardless of plasma albumin.

Discussion

We undertook a novel analytical approach to plasma albumin refill that occurs during fluid administration by assessing kinetics in multiple compartments in order to characterize the temporal relationship of fluid and albumin changes. This approach has never been applied to albumin refill and the results present novel findings that provides evidence as to the mechanism(s) of albumin refill that have previously evaded the physiologist and clinicians. The results show that by infusing 1-2 L of crystalloid fluid in humans, interstitial washdown increased plasma albumin by 0.3-1.0 g/L. The increase in plasma albumin occurred over approximately 30 min, which was also the infusion time. The albumin concentration in the inflowing fluid during the build-up phase was the same as the 29 g/L in interstitial fluid of the forearm of adult males measured by the wick method [17]. However, the concentration clearly decreased over time, suggesting that washdown of albumin becomes exhausted after a couple of hours. Similarly, the protein concentration of collected lymph of instrumented dogs had dropped by 50% after 2 h in response to three 5-min bolus infusions of saline [4].

Capillary refill has two distinct components: the first one is the translocation of fluid and the second the return of protein, specifically albumin, into the plasma. This indicates that albumin refill occurs as part of fluid refill and, in fact, might be crucial for maintaining the process [20]. The source and mechanism(s) of albumin refill have been a matter of controversy for over 40 years [21-23] but may have important physiological and therapeutic consequences. Francis D. Moore and colleagues were the first to comment that
while transcapillary refill results in marked hemoglobin dilution while plasma albumin remains constant, suggesting that albumin is returned to the vascular compartment at a rate proportionately greater than fluid [22-26]. However, albumin enrichment in the plasma can occur despite slow recruitment of albumin because fluid leaks out 75 times faster from the plasma than albumin does.

Certain known differences in the kinetics of crystalloid fluid between the three clinical settings should be acknowledged before reviewing the effect of interstitial washdown on the fluid distribution. The most important difference is that diuretic response to volume loading is strong in volunteers but much weaker (~90%) during general anesthesia [11]. “Non-exchangeable” volume expansion is pronounced during general anesthesia [10], intermediate in diabetic ketoacidosis [9], and very small or even absent in healthy volunteers [5].

The simulated effect of the washdown on the distribution and elimination of Ringer’s shown in Fig. 4 depicts fluid volume changes that are statistically associated with the albumin recruitment at each point in time. These simulations showed slightly different effects depending on clinical setting. Pronounced washdown in conscious subjects was associated with greater central and peripheral volume expansion as well as with reduced urinary excretion. Surprisingly, no protection from peripheral edema was apparent. However, the covariance analysis showed that pronounced interstitial washout is associated with a very high $k_{12}$, which means that the peripheral accumulation of fluid could have been even greater without the washdown. By contrast, during general anesthesia the main effect of the washdown was an increase of the non-exchangeable (“third space”) volume expansion, which is known to occur when urinary excretion is restricted despite adequate body hydration [10].

Translocation of fluid to the plasma likely occurs due to the oncotic properties of recruited albumin. However, as each gram of albumin binds approximately 10-11 mL of fluid [18,19] which, with a plasma volume of 3 L, accounts for 17 mL. Volunteer Group and twice as much in the Anesthesia Group. Four factors may contribute to make fluid recruitment greater than the amount predicted by oncotic pressure of the translocated albumin. First, lymphatic immunoglobulins with oncotic properties accompany the translocated albumin. Second, the concentrations of albumin and immunoglobulins in the interstitium, with which the plasma is at balance, decrease. Third, the inhibitory effect of the interstitial washdown on the urinary excretion increases both the plasma and the
interstitial fluid volumes. Fourth, some of the redistribution shown in Fig. 4 might still be due to hydrostatic and viscosity consequences of the high $k_{12}$ values associated with albumin recruitment.

The albumin concentration in the early inflow averaged 70-80% of the baseline plasma albumin, which supports that lymph was recruited. Similar ratios have been obtained in volunteers [17] and dogs [4] while being only 50% in rabbits [16]. We hypothesize that the albumin concentration of the inflow is not regulated but as a summation of the hydration status and the capillary filtration of fluid and albumin. Increased capillary leakage of albumin would probably increase of albumin concentration of the inflowing fluid while persistently increased fluid filtration would dilute the albumin concentration. The process will eventually subside as the amount of available albumin in the interstitial space decreases.

The thoracic duct has often been considered as the main route of albumin recruitment. Thoracic duct lymph albumin concentration shows no change or actually decreases in response to blood loss, which has been explained as a selective retention of albumin within the circulation. However, thoracic duct albumin increases when hemorrhage is treated by rapid infusion of lactated Ringer’s, which might be explained by increased filtration and subsequent acceleration of the lymphatic flow. These results only account for changes in visceral lymph and do not represent what happens in the total body [21]. Our approach provides an analysis of whole body albumin refill which provides a more complete characterization.

Crystalloid fluid leaves the vascular system with a distribution half-life of only 8 min [5] leading some to question their utility in fluid resuscitation [27]. In the present subjects, fluid loading resulted in a 5-6-fold increase in capillary filtration. Our view is that such rapid leakage of crystalloid into the interstitial space drives an increase in lymph flow resulting in a decrease in interstitial protein concentration. This occurs because the transendothelial leakage of protein occurs more slowly than the return of proteins from the lymphatic system to the plasma, hence, interstitial protein "washdown" should considered to be a safety factor against tissue edema [3]. More importantly, however, the protein concentration of the plasma would increase under such circumstances, and this could act to improve the plasma volume expansion induced by the infused fluid.

Little enhancement of the plasma volume could be discerned during the acute build-up phase of albumin enrichment, but the plasma volume expansion was twice as
large 3 h post-infusion in conscious subjects who had pronounced washdown than in the others (Fig. 4). This late effect is not apparent in the Anesthesia Group and is mostly due to the inhibitory effect of interstitial washout on urinary excretion.

Limitations of our study include that data used for the analyses stem from previously published works that were performed for other purposes. The mass balance calculations report only mean data because the differences in dilution between Hb and albumin were so small that interindividual variability would be strongly affected by measurement precision. Albumin clearance values were taken from the literature.

The volume kinetic analysis is likely to closely capture real physiological events [28] but uncertainties exist about the nature of the non-exchangeable volume expansion [10]. This fluid remains in the body but without equilibrating with the plasma within the 3-4 h of the experiment. During anesthesia and surgery one third of the infused crystalloid fluid is at least temporarily unavailable for redistribution and excretion, which probably contributes to postoperative weight increase and edema.

Benefits with our approach include minimal invasiveness and that our model for studying albumin refill is devoid of the many sympathetically mediated compensatory responses induced by hemorrhage [1]. In terms of clinical importance, rapid fluid infusion is a first line strategy to treat hemorrhage, hypovolemia and changes in vascular capacitance such as sepsis and following the induction of general anesthesia. Therefore, studying fluid infusion on albumin refill has widespread clinical importance.

**Conclusion**

Our novel analytical approach demonstrates that crystalloid volume loading induces capillary refill of both fluid and albumin. The increase of plasma albumin is modest while the plasma volume expansion becomes prolonged in conscious subjects but not in anesthetized patients. The albumin concentration of the recruited fluid is similar to the interstitial fluid early on while a reduction by 50-75% has occurred after 1-2 h. These data contribute to an enhanced understanding of the physiological effects of fluid administration on plasma volume expansion and dispel long held thinking about fluid and peripheral edema.
**Declarations**

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**Author’s contributions**
RGH and RD came up with the study idea. RD made the background research. RGH performed the kinetic analyses and the mass balance calculations and created the illustrations. RGH and RD co-wrote the manuscript and approved the final version.

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**Availability of data and material**
The original data are available upon request from the RGH.

**Ethics approval and consent to participate**
The protocols for the first two cohorts were approved by the Ethics Committee of Huddinge University Hospital on June 2, 1998 (reg. nr. 228/98), September 2, 2002 (269/02) and March 6, 1995 (reg. nr. 54/95) while the protocol for the third cohort was approved by the regional Ethics Committee of Linköping on June 24, 2014 (reg. nr. 2014/123-31).

**Consent for publication**
Not applicable.

**Competing interests**
RGH holds a grant from Grifols for the study of 20% albumin as infusion fluid.
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Table 1.
Volume kinetic analysis of the three series of crystalloid fluid infusions. The fluid distribution is given by the four top rate constants. These are modified by covariance with the difference between the Hb and albumin dilution, representing the washdown of interstitial albumin, at each point in time in each subject (time-varying covariate). Linear covariance models were used.

| Parameter base model | Volunteers | Anesthesia | Ketoacidosis |
|----------------------|------------|------------|--------------|
| $k_{12}$ ($10^{-3}$ min$^{-1}$) | 34.0 ± 3.0 | 66.2 ± 7.7 | 83.3 ± 2.2 |
| $k_{21}$ ($10^{-3}$ min$^{-1}$) | 12.4 ± 2.1 | 33.3 ± 4.5 | 79.4 ± 2.2 |
| $k_{10}$ ($10^{-3}$ min$^{-1}$) | 11.8 ± 0.2 | 2.4 ± 0.5 | 13.2 ± 2.6 |
| $k_b$ ($10^{-3}$ min$^{-1}$) | 1.1 ± 0.1 | 5.4 ± 1.6 | 5.8 ± 2.6 |

| Covariance | Volunteers | Anesthesia | Ketoacidosis |
|------------|------------|------------|--------------|
| $k_{12}$   | 6.7 ± 1.9  | 2.3 ± 0.7  | None         |
| $k_{21}$   | 7.3 ± 4.9  | 2.7 ± 1.2  | -0.9 ± 0.1   |
| $k_{10}$   | -4.2 ± 0.9 | 2.9 ± 1.4  | -1.7 ± 0.8   |
| $k_b$      | None       | 5.2 ± 2.8  | -2.3 ± 0.3   |

Data are the mean ± standard error.
Fig. 1

**Kinetic model.** Schematic drawing of the kinetic model used to analyze the distribution and elimination of Ringer’s solution.

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**Fig. 2**

**Albumin recruitment during crystalloid fluid therapy.** The y axis shows plasma albumin concentration that is due to interstitial washdown. Technically, each data point is the product of the Hb-albumin difference in plasma dilution and the plasma albumin concentration in (A) 20 volunteers receiving 1.7 L of Ringer’s acetate, (B) 30 patients given 1.7 L of Ringer’s acetate thyroid surgery, and (C) 31 infusions of 1 L of 0.9% saline in patients treated for diabetic ketoacidosis. Each infusion was given over 30 min.
Fig. 3

**Volume kinetic analyses.** These analyses were based on the dilution of blood Hb and shows the distribution of infused fluid between the (A) central and the (B) peripheral fluid compartment, (C) the excess fluid in the central compartment when analyzing the volume kinetics based on Hb minus the volume expansion as obtained when albumin was used as the marker of plasma dilution. (D) return flow of fluid from the peripheral to the central space (the plasma) when contrasting the influence of high-degree versus low-degree interstitial washdown (approximately 5% - 95% span).
Fig. 4. Influence of interstitial washdown on the distribution of crystalloid fluid.

Volume kinetic analysis of the fluid distribution when 1.7 L of Ringer’s was infused in volunteers (top row), 1.7 L to patients undergoing surgery (middle row) and 1.0 L of 0.9% saline was given to patients with ketoacidosis (bottom row). All infusions were given over 30 min. All volumes are shown depending on whether the interstitial washdown was in the low or high range (approximately 5% - 95% span). For the volunteers, the range was between -0.10 and +0.10 (mean -0.019), for the anesthesia patients -0.01 to +0.15 (mean, +0.05), and for the patients with ketoacidosis the Hb-albumin difference in plasma dilution varied from -0.10 to +0.40 (mean, +0.046).