A volume loading test for the detection of hypovolemia and dehydration

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Key words: dehydration; fluid therapy; hemodilution; pharmacokinetics.

Summary. *Background and objectives. There is a need for simple method allowing detection of dehydration and hypovolemia. Based on a new theory of homeostatic blood states, we hypothesized that hemodilution following standardized crystalloid fluid bolus can be used to discriminate between baseline normohydration and dehydration, also normovolemia and hypovolemia.*

Methods. Computer simulations based on previously published kinetic data were used to define the best time points for discrimination between baseline normohydration and dehydration, also normovolemia and hypovolemia. Hemodilution was compared at the proposed timing in 20 volunteers who received 40 infusions of Ringer's solution of 25 mL/kg during 30 minutes.

Results. Simulations indicated that preexisting hypovolemia could be best detected at the end of infusion, while dehydration 20–30 min later. In baseline hypovolemia, the peak reduction of hemoglobin concentration was 16.0% at the end of infusion, while it was only 11.8%, when participants were normovolemic (P<0.004). In baseline dehydration, the residual hemodilution was 8.6%, when measured 30 min after the end of infusion. It was only 3.1% in baseline normohydration (P<0.006).

Conclusions. In response to fluid load, the baseline dehydration exaggerates the lowering of residual hemoglobin in respect to baseline. Meanwhile, baseline hypovolemia exaggerates the lowering of peak hemoglobin concentration. The volume loading test that deploys interpretation of hemoglobin dynamics in response to the test volume load could possibly serve as an easily available guide to indicate an individual patient's baseline hydration state and volemia. The introduction of continuous noninvasive monitoring of hemoglobin concentration would expand the applicability of the new method.

Introduction

Modest dehydration, not readily detected, is probably common in patients awaiting surgery due to fasting, bowel preparation, medication, and preoperative stress. The "goal-directed fluid therapy" before surgery aims at an optimal hydration state, and this is associated with shorter postoperative hospital stay (1–3). Once a patient's optimal plasma hydration has been established, the amount of fluid infused during surgery only needs to replace an ongoing loss. However, for this routine, the need for monitoring the dynamics of cardiac output in response to the consecutive small amounts of colloids increases the cost and limits goal-directed fluid therapy for a selected group of patients.

Colonic lavage implicates dehydration and increases the hemodilution resulting from a standard load of Ringer's solution (4). Similar observations have led Lithuanian anesthetist Audrius Andrijauskas to hypothesize in his thesis that patient's preexisting hydration state in respect to his/her optimal hydration can be determined by a volume loading (VL) test (5). Such a test could presumably be used as minimally invasive or even noninvasive and conventionally available method providing target parameters for goal-directed fluid therapy, when the red cell content is constant.

In the present report, we test whether his hypothesis is true by re-assessing data obtained from the two series of volunteer experiments. In a first series, dehydration in combination with hypovolemia was caused by an overnight fast followed by withdrawal of blood. Additionally, in a second series, patients were just dehydrated by an overnight fast. The time points, at which the difference in hemodilution could be expected to occur, were simulated by the computer.

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Material and methods
Mathematical study

A computer simulation session was undertaken to establish the time points during and after the test volume load, when plasma dilution in respect to baseline would differ in patients with preexisting normohydration and dehydration, also normovolemia and hypovolemia in combination with dehydration. For this purpose, simulated two-volume kinetic analysis of the distribution and elimination of the 25 mL/kg of acetated Ringer's solution was based on calculations performed by Svensén and Hahn (6). The following parameter values were used: central fluid space (V_1), 3327 mL; peripheral body fluid space (V_2), 6926 mL; distribution rate constant (k_t), 295 mL/min; and elimination rate constant (k_r), 91 mL/min. To simulate hypovolemia, the size of V_1 was reduced by 1000 mL and elimination rate k_r by 20%. Dehydration was simulated by decreasing V_2 by 1000 mL and k_r by 20%.

The mathematical basis of the volume kinetic model has been described previously (6, 7). In short, fluid infused at the rate k_i is distributed between V_1 and V_2, the sizes of which then increase to v_1 and v_2 at a later time (t). The net rate of fluid exchange between v_1 and v_2 is proportional to the relative difference in deviation from V_1 and V_2 by a constant (k_t) (Fig. 1). Elimination occurs by virtue of a zero-order parameter, k_b, and a first-order elimination rate constant, k_r. The volume changes in v_1 and v_2 are described by the following differential equations:

Volunteer studies

An intravenous infusion of 25 mL/kg of acetated Ringer's solution (Pharmacia, Uppsala, Sweden; electrolyte content in mmol/L; Na 130, K 4, Ca 2, Mg 1, acetate 30, and Cl 110) was given via an infusion pump at a constant rate during 30 min on 40 occasions in two groups of healthy male volunteers. Each of the 20 volunteers received two infusions of the same fluid. Both studies had been approved by the Ethics Committee in Stockholm, and each volunteer gave his informed consent.

The 10 volunteers in the first group were aged between 23 and 33 years (mean age, 28 years) and had a body weight of 65–85 kg (mean weight, 76 kg). In random order, they underwent two infusion experiments – one for the detection of dehydration and another for dehydration combined with hypovolemia originating from blood withdrawal. The effect of dehydration on the volemic status was considered being negligible. Experiments were separated by at least 7 days. On the first occasion, the volunteers received 25 mL/kg of acetated Ringer's solution at 8 AM while being in a normovolemic state, but they can be assumed as slightly dehydrated due to a complete overnight fast. On the other occasion, after the overnight fast, the volunteers received the same infusion immediately after being made hypovolemic by withdrawing 900 mL of blood during 10–15 min.

The second group of volunteers was 28 to 40 years of age (mean age, 31 years) and had a body weight of

$$\frac{dv_1}{dt} = k_i - k_b - k_r \frac{(v_1(t) - V_1)}{V_1} - k_t \left[\frac{(v_1(t) - V_1)}{V_1} - \frac{(v_2(t) - V_2)}{V_2} \right],$$

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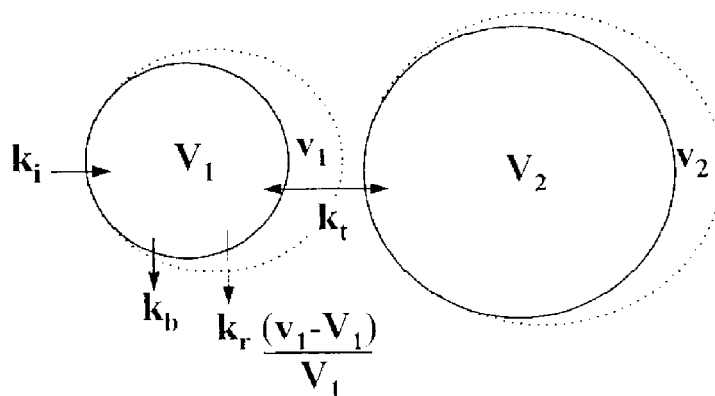

Fig. 1. The kinetic model used for the simulation experiments

70–97 kg (mean weight, 82 kg). They also underwent two infusion experiments. In contrast to the first group of volunteers, they were allowed to drink a glass of water, tea, or coffee early in the morning. On the first occasion, they received 25 mL/kg of acetated Ringer's solution at 8 AM. On another occasion, they received the same infusion starting at noon. By that time, normal hydration has been ensured by the previous early morning infusion, of which any excess fluid would have been excreted at noon.

Samples (5 mL) were drawn repeatedly from the venous cannula not used for infusion before any fluid was given, every 5 min during the infusion and every 5–10 min after it was completed. The blood hemoglobin concentration (Hb) was measured by a Technicon H.2 (Bayer, Tarrytown, N.Y., USA), using colorimetry at 546 nm, with a coefficient of variation of 1.0%. The volunteers voided just before the infusions were started. The urinary excretion was measured during all experiments. More details about how the data were collected have been presented elsewhere (8, 9).

The hemodilution was calculated from Hb values at 30, 50, 60, and 90 min from the beginning of experiment divided by the baseline Hb value, the later being drawn in duplicate just before the fluid was given.

The results are expressed as the mean and the standard deviation (SD). The statistical evaluation was made by using the paired *t* test and two-way analysis of variance (ANOVA). $P<0.05$ was considered significant.

Results

The computer simulation of plasma dilution in response to the 25 mL/kg infusion of acetated Ringer's solution was based on the two-volume kinetic analysis model (Fig. 1). It indicated that hypovolemia and dehydration would be best detected at the end of infusion and 20–30 min later, respectively (Fig. 2).

When compared to infusions in volunteers with preexisting normal hydration or normovolemia, the Hb deviation in respect to baseline was greater at all points in time, when volunteers have been "slightly dehydrated" after overnight fast or "hypovolemic and slightly dehydrated" after overnight fast combined with blood withdrawal (Table).

Plots of individual volunteers confirmed that the best separation of the groups was achieved at the end of infusion for the hypovolemic patients (Fig. 3) and at 60 min (30 min after the end of infusion) for the dehydrated patients (Fig. 4).

Two-way ANOVA was used to assess the importance of the glass of water or drink taken before the experiments in the second study group (factor 1) as
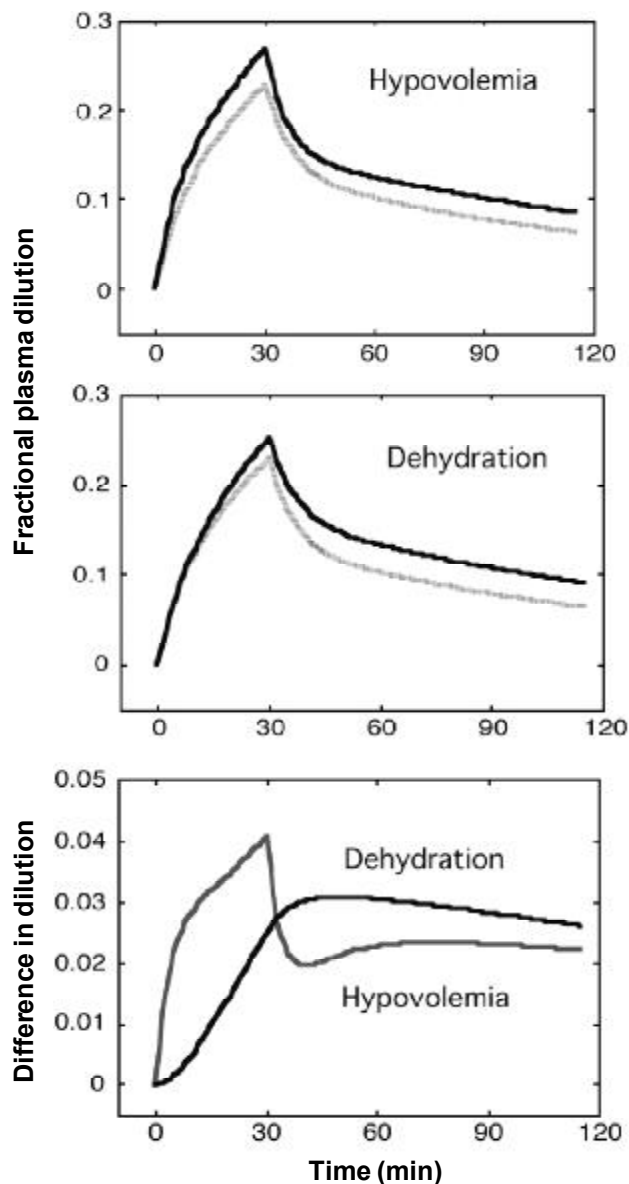
Fig. 2. Computer simulations of the difference in plasma volume dilution in the normal state (grey line) and when the fluid balance is disturbed (black line) by hypovolemia (top figure) and dehydration (middle figure) when a crystalloid fluid is infused within 30 min
The difference between the curves (bottom figure) highlights when a fluid balance disturbance is best detected.

opposed to hypovolemia or absence of having a pre-experiment infusion (factor 2). The first factor was statistically significant by $P<0.05$ only at 30 and 50 min, while the other interference with the fluid balance exerted by factor 2 was statistically significant by at least $P<0.01$ at all points in time.

The total urinary excretion tended to be smaller in hypovolemia (mean 35%) as compared to normovolemia (44%). The volunteers more clearly voided less

***Table.* The hemodilution, expressed in percent of baseline, at the end of a 30-min infusion of 25 mL/kg of acetated Ringer's solution, as well as 20 min and 30 min later, in hypovolemic (left columns) and slightly dehydrated (right columns) volunteers**

Time	Normo-volemia	Hypo-volemia	P	Normo-hydration	Dehyd-ration	P
30 min	88.2 (2.1)	84.0 (2.2)	<0.004	90.8 (5.0)	86.7 (3.3)	<0.045
50 min	94.0 (2.6)	89.9 (2.4)	<0.002	96.3 (3.0)	91.3 (2.8)	<0.002
60 min	95.2 (2.5)	91.5 (2.4)	<0.004	96.9 (2.9)	91.4 (3.1)	<0.006
90 min	96.5 (2.0)	92.6 (2.9)	<0.004	97.5 (2.4)	93.9 (3.3)	<0.013

Data are the mean (SD), and the paired *t* test was used for statistics.
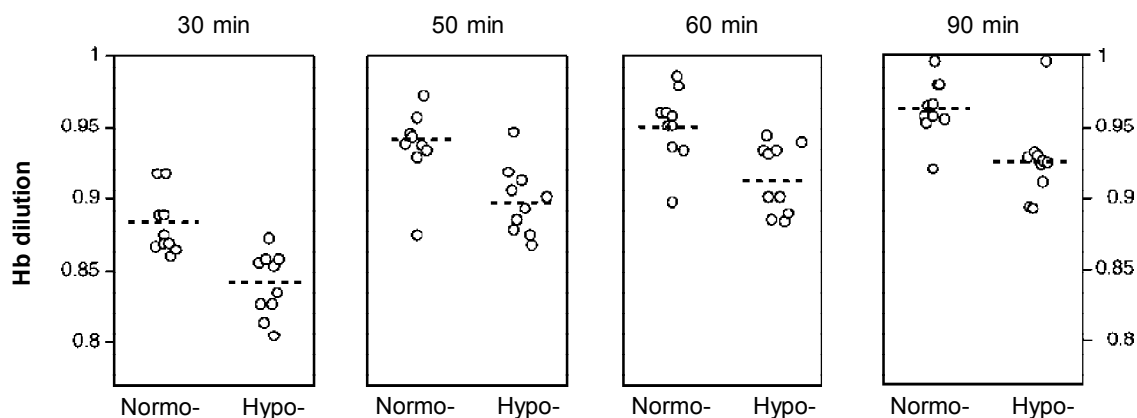

Fig. 3. The Hb dilution after an infusion of 25 mL/kg of acetated Ringer's solution depending on whether a volunteer is normovolemic or has lost 900 mL of blood
Each point represents one infusion experiment. The broken line is the mean value.
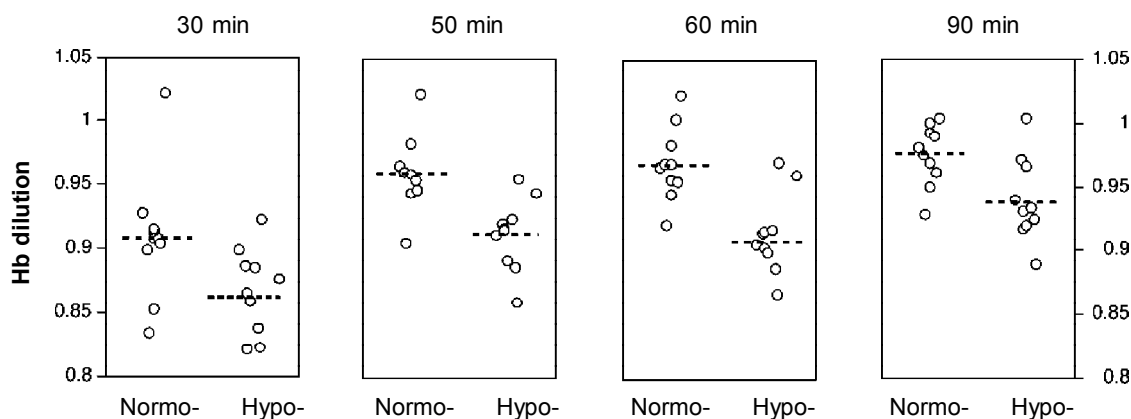

Fig. 4. The Hb dilution after an infusion of 25 mL/kg of acetated Ringer's solution depending on whether a volunteer is normohydrated or slightly dehydrated
Each point represents one infusion experiment. The broken line is the mean value.

when being dehydrated than normohydrated (30% versus 46%, $P<0.02$). When comparing the percentages between the two series, one must consider that urine was collected during 3 hours in the first normo/hypovolemic study but only half as long in the normo/dehydration study.

Discussion

The results show that hemodilution in response to the infusion of crystalloid fluid is dependent on the preexisting state of fluid balance. Both – hypovolemia and slight dehydration or slight dehydration alone – were followed by a significantly greater decrease in

Hb concentration as compared to the control situation. The early Hb response even seemed to be alleviated by one single glass of water, tea, or coffee taken before the infusion experiment, although this effect should be interpreted with some caution since it is based on comparing two different groups of volunteers.

The data on hemodilution in response to the crystalloid infusion show that the best timing for the detection of hypovolemia is the end of infusion. Meanwhile, dehydration is better identified 20–30 min after the end of infusion. The equilibration of infused fluid with an extracellular fluid space should be complete by that time. Although some overlapping may exist, our findings suggest a way of using test boluses of isosmotic crystalloid fluid and subsequent Hb measurements as a means to evaluate the preexisting hydration and circulating volume status of a patient.

This view was recently suggested, based on theoretical grounds, in Audrius Andrijauskas' thesis from 2006 (5). The volume loading test is a part of the theory of homeostatic blood states, which has recently been described in detail (10–13). This new theory investigates the physiological and clinical characteristics of the normal plasma hydration state, which is referred to as optimal or target plasma hydration. In this state, an individual is considered to be optimally hydrated. If this state is reached before anesthesia and operation, only basal and apparent losses need to be replaced during subsequent surgery. In the new theory, the state of optimal hydration is described in relationship with the circulating blood volume, the later being dependent on the red cell volume (10). Assumably, patients having a fluid deficit originating from dehydration show the more pronounced residual hemodilution 20–30 min after the end of infusion when compared to those with normal hydration, because the former strive to change their baseline Hb and hematocrit (Hct) for the optimal plasma hydration consistent values. From the practical point of view, it is important that the investigated cases of normal preexisting hydration and dehydration have demonstrated that residual Hb deviation from baseline exceeded 7.5 g/L (mean 14.06 g/L) in the setting of baseline dehydration, while it did not (mean 3.44 g/L) in case of normal baseline hydration.

The search for a fluid balance baseline is important in many medical specialties, but might be particularly valuable in anesthesia since a patient's preoperative fluid status sets the need to know how much fluid one should be given during surgery. By using the VL test, conventionally available tracers of plasma dilution – Hb and Hct – could possibly be used as target parameters for "goal-directed fluid therapy," which aims at placing the patient in a state of optimal hydration.

This approach is known to reduce the postoperative hospital stay (1–3), but is cumbersome to apply since it requires repeated measurements of cardiac output. The practical and economical advantages of the test volume loading approach, provided it is accurate, should be of important benefit. In contrast to cardiac output monitoring, the VL test followed by interpretation of Hb dynamics is simple, potentially noninvasive, and reasonably inexpensive to allow the wide applicability of the new method.

A drawback with this preliminary investigation of the volume loading test is that it is apparently not precise enough to effectively discriminate between the normal and disturbed fluid balance in every single subject, because the average change in Hb for a group of 10 volunteers differed by as much as 45% (Fig. 3). The new theory argues that depending on the circulating red cell volume, there are different homeostatically acceptable limits of normal fluctuations in plasma hydration (5, 10). Thus, residual Hb deviations originating from dehydration from baseline might be case specific as red cell volume differs from individual to individual, and pooled data analysis may be misleading. Specially designed nomograms could probably be helpful as proposed by the theory (5). In addition, the above reported variability in Hb deviation from baseline in dehydration might be explained by the argument that fluid balance status of these volunteers had to be better standardized before the infusions started. Like in all humans, the volunteers had variability in their hydration state before any action was taken by the investigators. A new study should therefore be designed for the further challenge of the VL test ability to discriminate between normohydrated and dehydrated patients on the individual level. This could be done by first optimizing the hydration status of all subjects by infusing a small volume load and then allowing time to correct the fluid status by voiding. Variability in their hydration state could then be induced in a controlled way by injecting furosemide, and again a rapid fluid test infusion could be applied in the similar way as in the current presentation.

It might be an improvement by incorporating the excreted urine volume in the assessment of hydration status. In the present experiments, the urine volume was clearly smaller in the presence of slight dehydration as compared to the normovolemic state. The urine excretion was also smaller in hypovolemia as compared to normovolemia. These differences could help to identify patients with a fluid balance disturbance on a later occasion, when the peak hemodilution at the end of infusion has subsided.

An obvious limitation of the new method is the need for frequent blood sampling in order to trace the Hb dynamics in response to volume load. However, it may not be an issue anymore in the nearest future, because during the 14th World Congress of Anesthesiology (WCA) in Cape Town, South Africa, the Masimo Corporation has introduced their revolutionary device for noninvasive measurements of total hemoglobin. The large volume load and relatively long time required to conduct the volume loading test, even without awaiting a 90-min sample, could still be issues. The original suggestion by Audrius Andrijauskas was to infuse 10 mL/kg of Ringer's solution within 20 min and to measure Hb 20 min later. This volume and corresponding time frame are probably more appropriate than the fluid bolus of 25 ml/kg during 30 min that was used in the current report. However, we cannot rule out that even smaller amounts of Ringer's solution should allow for discrimination between dehydrated and normohydrated patients. Therefore, in a subsequent study, testing will be conducted to find the smallest fluid bolus that would allow the assessment of a patient's fluid status. However, the volume loading test is uncertain in diseases that alter a patient's handling of water. For example, the hemodilution at the end of the infusion resulting from a fluid infusion in healthy pregnant women did not differ from those who were preeclamptic. At 60 min, however, the Hb level was 95% of baseline in the healthy women, just as it could be expected from the present study, while it was 99% in the mothers with preeclampsia (14).

Conclusion

The hemodilution resulting from an intravenous infusion of crystalloid fluid is more pronounced when the patient is hypovolemic or dehydrated. The first fluid balance disturbance is best detected at the end of the infusion while the second is likely to be most apparent 20–30 min later. Further refinement of this volume loading test will show whether it can be made precise enough to become a clinical method to assess the fluid balance in clinical patients.

Acknowledgement

Infuzinis plazmos atskiedimo mėginys hipovolemijos ir dehidratacijos nustatymui

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Raktažodžiai: dehidratacija, skysčių terapija, hemodiliucija, farmakokinetika.

Santrauka. *Tikslai.* Iki šiol nėra kliniškai nesudėtingo metodo dehidratacijai ir hipovolemijai nustatyti. Remiantis nauja homeostazine kraujo būklių teorija, iškelta hipotezė, kad kraujo atskiedimas, sukeliamas standartizuotos kristaloido infuzijos, gali būti panaudotas diferencijavimui tarp normalios hidratacijos ir dehidratacijos bei normovolemijos ir hipovolemijos, buvusių iki infuzijos pradžios.

Metodai. Kompiuterinis simuliavimas, pagrįstas anksčiau skelbtu tūrio kinetinės analizės metodu, panaudotas norint nustatyti, kuriuo atskiediminio atsako į infuziją metu geriausiai būtų galima nustatyti skirtumus tarp normalios hidratacijos ir dehidratacijos bei normovolemijos ir hipovolemijos. Simuliavimo vertinimo laikas buvo panaudotas vertinant hemoglobino atskiedimo dinamiką 20 savanorių. Kiekvienam savanoriui skirtos dvi Ringerio tirpalo infuzijos. 25 ml/kg šio tirpalo buvo sulašinta per 30 minučių. Iki infuzijos pradžios dehidratacija buvo sukelta badavimu, o hipovolemija – paėmus 900 ml kraujo.

Rezultatai. Kompiuterinis simuliavimas parodė, kad hipovolemija geriausiai galėtų būti nustatoma Ringerio infuzijos pabaigoje, o dehidratacija – 20–30 min. vėliau. Tyrimais su savanoriais nustatyta, kad pagal simuliacijos laiką hipovolemijos atveju hemoglobino koncentracijos sumažėjimas buvo 16,0 proc., o normovolemijos – 11,8 proc. (p<0,004), dehidratacijos – 8,6 proc., o normalios hidratacijos – 3,1 proc. (p<0,006).

Išvados. Prieš infuziją buvusi dehidratacija reikšmingai didina hemoglobino atskiedimo atsaką į Ringerio infuziją, vertinant jį 20–30 min. po infuzijos, o hipovolemija – infuzijos pabaigoje. Tai rodo, kad infuzinis plazmos atskiedimo mėginys (pasiūlytas naujos teorijos) galbūt gali tapti šiuo metu trūkstamu paprastu būdu hidratacijai ir volemijai vertinti. Be to, metodo galimybes gerokai išplėstų hemoglobino koncentracijos neinvazinio stebėjimo prietaisų įdiegimą į klinikinę praktiką.

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