MINI VOLUME LOADING TEST (MVLT) FOR THE EVALUATION OF HYDRATION STATUS: INITIAL VALIDATION IN PATIENTS

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ABSTRACT

Introduction — The hydration status of patients is mostly unknown. The aim of this prospective clinical trial was to determine the ability of a mini Volume Loading Test (mVLT) to detect the difference in hydration status between pre-operative and post-operative patients by administration of three relatively small boluses of crystalloids.

Patients and methods — Twelve patients (9 females, 3 males) undergoing elective primary total knee arthroplasty completed the study. The mVLT was performed on two different occasions for each subject — before anaesthesia induction (preoperative session), and after a 24 hour postoperative stay in the PACU (postoperative session). Three boluses (5 ml kg — 1 each) of Ringer´s were given, separated by 5 min periods without infusion (3 mini fluid challenges). Arterial and venous haemoglobin was sampled for dilution calculation purposes. Conventional haemodilution and new derivatives of haemoglobin concentration calculated by the novel mathematical model of Bolus Induced Response of Deviations (BIRD-math) were used for the comparison between the preoperative and postoperative mVLT sessions.

Results — There was no difference in haemodilution, but the new variables — residual dilution efficacy and its inter-step tendency — showed that residual plasma volume expanding efficacy was similar in the first two mini fluid challenges of both sessions, but significantly higher in the third postoperative mini fluid challenge ($P < 0.01$).

Conclusion — The mVLT suggested that patients were better hydrated postoperatively since they required fewer steps to fulfil the criteria for the optimization of hydration status.

KEYWORDS

plasma dilution, mini volume loading test, fluid therapy, hydration status, crystalloids, goal directed fluid therapy

INTRODUCTION

The clinician often struggles with decisions concerning the choice of type, amount and time of fluid infusion during the peri-operative period. Recently, the focus has been on using fixed volume protocols restricting fluids, or individualized goal-directed regimes which more consistently address efficacy of fluid administration [1, 2]. Fixed volume strategies do not, however, observe individual differences such as gender, age and baseline hydration status [3]. Maximization of stroke volume, as in goal-directed fluid therapy, is thought to better reflect individual needs. Although goal-directed protocols have improved outcome for particular groups of patients [4], there is still a risk of imprecise fluid administration.

To assess baseline hydration status for individual subjects, a volume loading test (VLT) was introduced [5]. The VLT is a method to evaluate the body hydration status and its changes from the plasma dilution response to a single fluid load [6]. The interstitial space can be regarded as a two-phase structure while having a dense fibre framework which prevents albumin from entering the matrix. This makes it more resistant to the development of oedema, but the framework can be disturbed by tissue injury, increased lymph flow and increased capillary pressure. The physiologic background of the VLT method is that interstitial space will move from a low-compliance state with small pressure increases with increasing hydration status to a high-compliance state with further infusion. Thus, a plasma dilution efficacy of fluid bolus will decrease because of progressively increasing interstitial fluid accumulation in higher levels of interstitial hydration. The increase of renal elimination with better hydration status will have additive impact. Identifying this point would theoretically imply an optimized hydration status. A series of small boluses would probably more easily detect the change in interstitial fluid compliance than a single bolus. Thus, a mini Volume Loading Test (mVLT) was suggested. It implies evaluation of plasma

dilution response during stepwise infusion.

The aim of this study is to describe whether a mVLT could detect a difference between preoperative and postoperative baseline hydration status of patients by administration of three relatively small (5 ml kg^{-1} each) boluses of crystalloids. The hypothesis is that the patients with a better initial baseline hydration status will require fewer boluses to reach optimized hydration status during stepwise infusion of a crystalloid.

PATIENTS AND METHODS

Ethical approval (Approval N° 158200-9-071-22) was obtained. Fifteen patients (12 females, 3 males) scheduled to undergo elective primary total knee arthroplasty (TKA) surgery were enrolled. They had ASA physical status I-II, Body Mass Index 30.0±3.1, and were 68.2±7.1 years old. All TKA operations were performed by the same senior surgeon.

On arrival at the operating theatre at 07:00, the standard peri-operative monitoring (ECG, pulse oximetry and non-invasive blood pressure measurement) was applied. An intravenous line for fluid infusion was placed in the independent arm. Additionally, cannulation of an antecubital vein solely for venous blood sampling was performed in the other arm. Cannulation of a radial artery in the same arm was performed for arterial blood sampling and for continuous monitoring of arterial blood pressure (DASH 3000®, GE Medical Systems Information Technologies, Inc, Milwaukee, Wisconsin, USA) and stroke volume by the arterial pulse contour analysis technique (LiDCO™Plus, London, UK). This monitoring continued for the duration of the trial.

Induction of spinal anaesthesia with 2.5–3.0 ml of 0.5% bupivacaine solution was performed immediately after the preoperative mVLT. Each patient underwent two consecutive mVLTs during the peri-operative period. A preoperative mVLT session was performed after an overnight fasting period. A postoperative mVLT was administered after a 24 hour stay in the post-anaesthesia care unit. Each mVLT session consisted of three mVLT steps (Fig. 1). Each step consisted of an infusion of 5 ml/kg of acetated Ringer's. The boluses were infused over 5 min followed by a 5 min steady-state period when no fluid was given. The boluses were given to incrementally increase plasma dilution from individual *baseline* at timepoints 0, 10 and 20 min to *peak* values measured at the end of infusions at timepoints 5, 15 and 25 min (Fig. 2). Seven pairs of arterial (aHb) and venous (vHb) blood haemoglobin samples were simultaneously taken during each mVLT: before each bolus (baseline Hb), at the end of bolus (peak Hb) and 5 min later (residual Hb). Prior to taking the blood samples for analyses, three millilitres of blood were drawn and immediately returned via the other arm's cannula. All blood samples were analysed for aHb and vHb using a bedside device (HemoCue®, Ängelholm, Sweden). Additionally, the first and seventh samples in each series were analysed in the laboratory for both Hb and haematocrit (Hct).

All data were collected by the study coordinators and entered into a database sheet. The aHb and vHb records were processed in a mathematical model, Bolus Induced Response of Deviations (BIRD-math), aiming to derive variables that would represent plasma volume expansion (PVE) and plasma volume expanding efficacy (PVEE) of a single mVLT step or the whole session (See ***Appendix*** which describes the BIRD-math model). The specific abbreviations (Table 1), mathematical description and physiological meaning (Table 2) and diagnostic criteria are applied (See Table 3, which describes the diagnostic criteria for the evaluation of hydration status). Intermediate Hb derived variables were therefore calculated as follows (Fig. 3). The *Residual Continuous Dilution* (resC_D) was defined as the dilution at timepoint 10, 20 or 30 min compared to the initial invasive arterial baseline value at timepoint 0 min. *Continuous Residual to Baseline Deviation of Dilution* (C_RBD) is the difference between resC_D of consecutive steps. The resC_D corresponds to the sum of all C_RBDs which is equivalent to a *total* PVE of all previous steps.

The *Residual Shifting Dilution* (resS_D) is a fractional change of continuous dilution (C_D) between timepoints 10 and 0, 20 and 10, 30 and 20 min, respectively. Thus, in contrast to resC_D, which represents the total PVE during mVLT, the resS_D corresponds to the individual residual PVEE of a single mVLT step. *Shifting Residual to Baseline Deviation of Dilution* (S_RBD) is the difference between resS_D of consecutive steps, thus representing the difference in individual residual PVEE of consecutive steps.

The BIRD model will, by using Hb samples for plasma dilution calculations, identify an interstitial "*hydration plateau*". This is a transitory state and will appear when two resC_Ds are equal, and the corresponding resS_D is zero (Fig. 3). When this occurs, interstitial compliance is said to have moved from a low-compliance state to a high-compliance state.

When hydration status is at its optimum, interstitial compliance will be at its maximum [16]. *Continuous and shifting Residual to Baseline Deviations of Dilution* (C_RBD and S_RBD, respectively) were used to investigate the differences in dilution in two separate mVLT sessions.

To achieve normalized fluid balance between mVLTs, normal saline infusion targeted to compensate for urine output plus basal physiological fluid needs

(1.0 ml/kg/hr) was administered. A decrease in arterial blood pressure of more than 30% and/or in stroke volume of more than 10% from the individual baseline was an indication of additional fluid load of 5 ml/kg of normal saline infused over 5 min. Blood or colloids were not administered during the study period. If these interventions did not restore SV and/or blood pressure, a titrated intravenous infusion of epinephrine was administered.

All patients were transferred to the post anaesthesia care unit for a 24-hour postoperative stay. Continuous epidural analgesia with an individually titrated dosage of fentanyl and 0.25% bupivacaine was administered. The treatment was stopped 30 min before the start of the postoperative mVLT. The postoperative mVLT protocol was similar to the preoperative. Statistical analysis was performed using PASW (PASW Statistics 17, SPSS, IBM Corporation, NY). Data are presented as mean ± SEM where appropriate. Mean values were compared by using the Student's *t*-test and Levene's test was used for comparison of variances. $P<0.05$ was considered significant.

RESULTS

Fifteen participants were enrolled in the study. Three female patients were excluded from analysis because of blood transfusion administered between mVLTs. Thus, a total of 24 mVLT procedures were performed in 12 TKA patients in two sessions.

There was a significant difference between the preoperative and postoperative mean Hb after the mVLTs in the two separate sessions. Mean preoperative aHb as well as vHb were significantly higher than the corresponding values in the postoperative session (120 ± 1.3 vs. 95 ± 1.2, $P<0.00$ for aHb and 119 ± 1.29 vs. 93 ± 1.2, $P < 0.00$ for vHb), with no statistical difference in variances (Fig. 2).

The residual continuous dilution (resC_D at time point 30 min) which corresponds to the total PVE for all steps was similar in both preoperative and postoperative mVLT sessions as follows: mean arterial resC_D was similar (0.144 ± 0.015 vs. 0.129 ± 0.017, $P<0.5$) with no statistical difference in variances ($P<0.79$), and mean venous resC_D was also similar (0.141 ± 0,015 vs. 0.127 ± 0.016, $P<0.52$) with no statistical difference in variances (Fig. 3).

In Figure 3, the hydration plateau in the preoperative session appears between step 2 and 3, where resC_D in step 3 is equal to resC_D in step 2. In step 3, resS_D is zero. In the postoperative mVLT session resC_Ds were not equal, nor did resS_D reach zero. However, there was no difference between mean preoperative and postoperative total residual PVE (resC_D in the 3rd step) or individual residual PVEE (resS_D) variables in any step. The significant differences between the preoperative and postoperative mVLT sessions were found by comparing the RBDs (Table 3). The hemodiluting impact of the 3rd step on the total residual PVE (C_RBD) was significantly more pronounced in step 3 of the postoperative mVLT session: the arterial difference of C_RBD means was statistically significant ($P<0.01$), while the difference of variances was not; similarly, the venous difference of C_RBD means was also significant ($P<0.04$), while the difference in variances was not.

Similarly, the difference in individual residual PVEE between the 2nd and 3rd steps (S_RBD) was significantly more pronounced in the postoperative mVLT session: the arterial difference in S_RBD means was statistically significant ($P <0.03$), while the difference in variances was not ($P<0.250$); similarly, the venous difference in C_RBD means was also statistically significant ($P<0.04$), while the difference in variances was not ($P<0.11$) (Table 4). The significance of RBD changes (Fig. 4) during a single mVLT session was evaluated (Table 5).

In the preoperative mVLT session, the decrease in continuous arterial (Fig. 4-A) and venous (Fig. 4-C) RBD was not significant between step 1 and 2, but the decreases in the corresponding shifting arterial (Fig. 4-B) and venous (Fig. 4-D) RBDs were significant.

Meanwhile, the only significant shift in RBD between steps 2 to 3 was the decrease in continuous arterial RBD (Fig. 4-A). The decrease in continuous and shifting, arterial and venous RBDs (Fig. 4 A-D) was significant between steps 1 and 2 in postoperative mVLT.

Meanwhile, only the increase in shifting arterial (Fig. 4-B) and venous (Fig. 4-D) RBDs was significant between steps 2 and 3.

The hydration plateau could only be identified in step 3 of the pre-operative mVLT session where the mean resC_D were equal in steps 2 and 3 and the resS_D and C_RBD were both close to zero and S_RBD was negative. In contrast, using the same criteria, the hydration plateau was not identified in the postoperative session. Nevertheless, the shift in S_RBD from negative to positive in the 3rd postoperative mVLT step suggests that the plateau was reached in step 2 during the postoperative mVLT session.

DISCUSSION

This study focused on the ability of the mVLT to detect differences between preoperative and postoperative hydration levels by administration of relatively small (5 ml kg-1) boluses of crystalloid separated by 5 min steady states with no fluids. Changing levels of haemodilution is a sign of volume loading. Inference

is made to changed interstitial compliance and when pertinent parameters are fulfilled a "hydration plateau" is reached interstitially [7]. This should be an indication that the tissue is well hydrated.

Since our concept of defining the hydration status is based on the acknowledgement that intravascular fluid retention is highly dependent on the hydration of perfused tissues, the mVLT mathematically investigates the dynamics of haemodilution related variables. Aiming for the most appropriate clinical applicability, the method deploys the above described fast relatively small volume infusions and short steady states between them. The induced changes of haemodilution are relatively minor. Thus, more sensitive markers were proposed by the novel mathematical model of Bolus Induced Response of Deviations (BIRD-math; see Appendix for details). It provides calculation of haemoglobin concentration derived variablesthat enable sufficiently sensitive monitoring of changes in haemodilution efficacy of consecutive mVLT steps. Only these new variables — residual dilution efficacy and its inter-step tendency — showed the significant difference between two mVLT sessions, while conventional trends of dilution have failed.

This study aimed to see whether this method could be used to detect such a transitory state and difference between hydration levels in a surgical setting. The impact of a fluid bolus on plasma dilution is not always easy to predict since the response differs depending on the clinical situation [8]. Conventionally, a crystalloid is allocated in the plasma space and should eventually distribute to the interstitium [9]. This flux is prolonged during surgery and bleeding [10]. Kinetically, fluid distribution is a mixture of perfusion and distribution to adjacent tissues [11, 12]. Volume kinetics is a tool to describe this mixture of perfusion to distant parts of the body and the actual translocation of fluids between fluid spaces [13, 14]. Volume kinetic analysis does not require knowledge of the hydration baseline but is hampered by repetitive sampling of haemoglobin samples [12]. However, to use the kinetic models better it would be beneficial to know the actual baseline of hydration in order to plan intravenous fluid therapy. In this study, a key concept is the "hydration plateau", which can be said to be a point where interstitial compliance changes from a low to a high-compliance state. This study aimed to determine the baseline by trying to identify a transitory state, hydration plateau, based on repetitive observations of plasma dilution. The criteria for the detection of that state are defined in Figure 1 and Figure 3 (Table 3). The criteria are fulfilled when two consecutive steps reach the same resC_Ds and the resS_D is zero at the same time.

This occurred in step 3 in the preoperative session, but was not obvious in the postoperative. The BIRD-math was used for the evaluation of differences between the fluid handling in preoperative and postoperative mVLT sessions (Fig. 4). The evaluation provided support for the mVLT method by detecting significant difference in the last of a series of three boluses. The PVEE were similar in the first two mVLT steps, but the 3rd postoperative step showed a significant increase in PVEE, while it was negligible in the 3rd preoperative step. Plausibly, the explanation could be that it is a result of different interstitial fluid compliance. We speculate that, according to the model, the negligible preoperative PVEE is a result of maximal interstitial fluid compliance together with a transcapillary flux of fluid into the interstitium. The activation of urine output and other routes of fluid elimination in states of higher hydration status may have additive effect. We suggest that the postoperative increase of PVEE in step 3 is explained by a steep rise in interstitial hydraulic pressure when interstitial fluid compliance falls after exiting the state of interstitial hydration plateau. It can further be explained by an increase in lymphatic flow. The evacuation of interstitial lymphatics significantly increases the lymphatic flow, which in turn promotes central venous plasma dilution in addition to the prior venular plasma dilution induced by the drop of transcapillary hydraulic pressure as a result of the falling interstitial compliance. That causes a steep increase in central plasma dilution. The physiologic background to this concept lies in the previously established relationships of interstitial volume-pressure and lymphatic flow-interstitial pressure [15, 16]. When the former relationship turns from linear to a plateau of hydraulic pressure (hydration plateau) it significantly reduces intravascular fluid retention in the capillary beds. When the lymphatic flow-interstitial pressure relationship turns into a stable lymphatic influx into circulation, the impact on the changes in venous plasma dilution is negligible. This pattern, which is considered as a marker of hydration plateau, was seen in the 2nd and 3rd steps of the preoperative mVLT (Fig. 2 and 3). It was expected that these criteria would be met in both the preoperative and postoperative mVLTs, with its earlier manifestation in better hydrated subjects. However, this was not the case since the markers of the hydration plateau were missing in the postoperative mVLT. However, in contrast to the preoperative plasma dilution in the last two fluid loading steps, there was a steep rise of plasma dilution in the corresponding postoperative steps 2 and 3. Acknowledging that the hydration plateau is a short-lasting transitory state during a fluid loading interstitially, it can obviously be missed. Thus, aiming to

verify the interstitial hydration states in the range before and after the hydration plateau, and to predict the plasma dilution response and related shift of interstitial hydration in the upcoming mVLT step, also addressing the inherently low sensitivity of changes in Hb and its first-line derivative continuous plasma dilution (C_D), the second and third line derivative variables were calculated by the equations from BIRD-math (Table 1) (See Text, Supplemental Digital Content 1, which describes the Mathematical Model of Bolus Induced response of Deviations or BIRD-math). Despite this complexity, all these derivative variables are required and equally important since none of them is fully sufficient.

This study has several weaknesses. First, it is a small sample size. We assume that patients in the postoperative state are better hydrated although this was not validated. Furthermore, the model is based on a theoretical concept that has not been validated in a controlled model. Several concepts have been defined for model development that may be difficult to grasp and may seem unfamiliar to the non-specialist reader. Furthermore, this is a model that deals with fluid translocation across a semi-permeable membrane that may change significantly due to stress and surgery [17].

The concept of different levels of body hydration that can be identified by simple plasma dilution estimations is, however, very attractive. If such a test can be performed with accuracy before surgery and particularly if it can be based on non-invasive samples, it would be possible to determine the hydration status of patients. This would facilitate planning of intravenous fluid peroperatively and ensure that patients receive more precise amounts of fluid. Our research team's investigations [18–26] are therefore focused on investigating the applicability on noninvasive haemoglobin measures for the mVLT purposes.

CONCLUSION

The findings of the mVLT suggest that TKA patients were better hydrated postoperatively than preoperatively, since preoperatively they required three and postoperatively only two mini fluid challenges during mVLT to reach the same transitory state of interstitial hydration referred to as the dilution plateau.

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APPENDIX

Mathematical model of Bolus Induced Response of Deviations (BIRD-math)

Dilution

1. Residual continuous dilution (resC_D) – Fractional change of the hemoglobin concentration in respect to arterial obtained just before the start of mVLT:

$$resC\_xD_n = (aHb_0/xHb_n - 1) / (1 - aHct_0) \quad [1]$$

where resC_xDn — Residual continuous dilution at the variable's measuring time n; xHbn — Hemoglobin concentration at the variable's measuring time n; n — Time point 10, 20 or 30 min during mVLT.

2. Residual shifting dilution (resS_D) — Fractional change of continuous dilution (C_D) in a single mVLT step derived by comparing dilution after the 5 min steady state and dilution before the bolus:

$$resS\_xDn = (aHb_0 (xHb_{n-10} \cdot xHb_{n-1} - 1)) \times \times (aHb_0 + aHct_0 xHb_{n-10}) - 1 \quad [2]$$

where resS_xDn — Residual shifting dilution at the variable's measuring time n (min) during mVLT; n — time point 10, 20 or 30 min during mVLT.

Bolus Induced Response of Deviations (BIRD)

BIRD is the dilution difference — continuous or shifting — between the two time-points of a single mVLT step:

1. Continuous residual-to-baseline deviation (C_RBD) — Continuous dilution difference between the residual and baseline time points of a single mVLT step:

$$C\_xRBDn = aHb_0 (xHb_{n-1} - xHb_{n-10} - 1) \times \times (1 - aHct_0) - 1 \quad [3]$$

where C_xRBDn — Continuous residual-to-baseline deviation at the variable's measuring time n; n — Time point 10, 20 or 30 min during mVLT.

2. Shifting residual-to-baseline deviation (S_RBD) — Shifting dilution difference between theresidual and baseline time points of a single mVLT step:

$$S\_xRBD_n = (aHb_0 (xHb_{n-10} \cdot xHb_n^{-1} - 1)) \times \times (aHb_0 + aHct_0 xHb_{n-10})^{-1} - - (aHb_0 (xHb_{n-20} \cdot xHb_{n-10}^{-1} - 1)) \times \times (aHb_0 + aHct_0 xHb_{n-20})^{-1} \quad [4]$$

where S_xRBDn — the shifting residual-to-baseline deviation at the variable's measuring time n; n — Time point 10, 20 or 30 min during mVLT.

In all equations — aHb_0 and $aHct_0$ — the initial baseline value of *arterial* blood samples (time-point 0 min just before the start of mVLT; lab scan results); x — the blood sampling site — arterial or venous.

Table 1. *Definitions, abbreviations and physiological meaning of variables from the mathematical model of Bolus Induced Response of Deviations (BIRD-math)*

Plasma (Hb) dilution 1. Residual continuous dilution (resC_D) — Fractional change of the residual hemoglobin concentration (timepoints 10, 20 or 30 min) in respect to arterial concentration obtained just before the start of mVLT. *Physiological meaning*: **Total residual PVE** represents the total (summarized) residual plasma volume expansion after 5 min following each bolus.
2. Residual shifting dilution (resS_D) — Fractional change of continuous dilution (C_D) in a single mVLT step derived by comparing dilution after the 5 min steady state and dilution before the bolus. *Physiological meaning*: **Individual residual PVEE** represents individual residual plasma volume expansion efficacy of a single mVLT step.
Bolus Induced Response of Deviations (BIRD) is the dilution difference — continuous or shifting — between the two time-points of a single mVLT step: 1. Continuous residual-to-baseline deviation (C_RBD) — Continuous dilution difference between the residual and baseline time points of a single mVLT step (available at timepoints 10, 20 or 30 min). *Physiological meaning*: **Difference of total residual PVE** between two consecutive mVLT steps evaluates the impact of the latest step on the total PVE (was it hemodilution or hemo-concentration).
2. Shifting residual-to-baseline deviation (S_RBD) — Shifting dilution difference between the residual and baseline time points of a single mVLT step (available at timepoints 10, 20 or 30 min). *Physiological meaning*: **Difference of individual residual PVEE** between two consecutive mVLT steps (thus, not applies to the 1st mVLT step) evaluates its tendency — increase or decrease.

Table 2. *Variables calculated by the BIRD-math model*

Generic variable		Derivative variable		Initial	mVLTstep			Equation # in BIRD-math	Mathematical description of derivative variable	Physiological definition / meaning of the derivative
Definitions	Abbreviations	Definition	Abbreviation	baseline	1	2	3			
				Timepoint (min)						
				0	10	20	30			
Arterial and venous hemoglobin concentration	aHb and vHb	Residual continuous dilution	res.C_D	A	A	A	A	1	Fractional change of Hb at timepoints 10, 20 and 30 min in respect to intial baseline (0 min)	**Total residual PVE** represents the total (summarized) residual plasma volume expansion after 5 min following each bolus
Residual continuous dilution		Residual shifting dilution	res.S_D	NA	A	A	A	2	Fractional change of C_D during a single mVLT step considering res.C_D and C_D before the bolus	**Individual residual PVEE** represents individual residual plasma volume expansion efficacy of a single mVLT step
	res.C_D	Continuous residual-to-baseline continuous deviation of dilution	C_RBD	NA	A	A	A	3	Residual continuous dilution difference between two consecutive mVLT steps	**Difference of total residual PVE** between two consecutive mVLT steps evaluates the impact of the latest step on the total PVE (hemodilution vs hemoconcentration)
		Shifting residual-to-baseline deviation of dilution	S_RBD	NA	A	A	A	4	Residual shifting dilution difference between two mVLT steps	**Difference of individual residual PVEE** between two consecutive mVLT steps (thus, not applies to the 1st mVLT step) evaluates its tendency — increase vs decrease.

Generic — Measured parameter or previously calculated derivative used to calculate new derivatives. Derivative — Non-measurable variable that was derived by equations of the BIRD-math model.
mVLT step — Minimal volume loading test step.
Hb — Hemoglobin concentration (aHb-arterial and vHb-venous).
PVEE — Plasma volume expansion efficacy.
PVE — Plasma volume expansion. A — Available variable or criteria met. NA — Not applicable.

Table 3. *Diagnostic criteria for the evaluation of hydration status*

Criteria	Diagnosis	Diagnostic criteria in perioperative mVLT sessions						
		Preop. step #				Postop. step #		
Variables in dynamics	Transitory hydration status	1	2	3		1	2	3
		10	20	30	(min)	10	20	30
≈ equal res.C_D in *two consecutive* mVLT steps	NORMOHYDRATION*: maximal interstitial fluid compliance and *minimal* PVEE of the *last of two* mVLT steps			A				
res.S_D ≈ 0	NORMOHYDRATION*: maximal interstitial fluid compliance and *minimal* PVEE of a *single* mVLT step			A				
C_RBD ≈ 0	NORMOHYDRATION*: maximal interstitial fluid compliance and minimal impact of a single mVLT step on the total residual PVE			A				
S RBD ≤ 0 (not applies to the 1st mVLT step)	DEHYDRATION**: *increasing* interstitial fluid compliance and *decreasing individual residual* PVEE	NA	A	A		NA	A	
S RBD >0 (not applies to the 1st mVLT step)	OVERHYDRATION***: *decreasing* interstitial fluid compliance and *increasing individual residual* PVEE	NA				NA		A

* **Normohydration** is haemodilution associated with optimized interstitial hydration.
Note: These criteria are the specific markers of hydration plateau.

** **Dehydration** is optimized interstitial hydration with maximized interstitial fluid compliance or hydration plateau.
Note: dehydration turns into normohydration when res.S RBD < 0 is associated with at least one of the NORMOHYDRATION (hydration plateau) specific criteria.

*** **Overhydration** is maximized interstitial hydration with minimized interstitial fluid compliance.

Table 4. *The residual to baseline deviation of dilution*

Parameter		Residual to baseline deviation of plasmadilution (RBD)											
		Pre-operative mVLT						Post-operative mVLT					
		Step 1		Step 2		Step 3		Step 1		Step 2		Step 3	
		Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
C_RBD	Arterial	0.084	0.014	0.055	0.024	-0.007	0.015	0.098	0.012	0.017	0.011	0.058	0.019
	Venous	0.083	0.010	0.082	0.030	-0.041	0.029	0.110	0.018	0.021	0.018	0.034	0.020
S_RBD	Arterial	0.083	0.014	-0.031	0.029	-0.056	0.034	0.096	0.012	-0.080	0.019	0.036	0.021
	Venous	0.083	0.010	-0.008	0.029	-0.104	0.046	0.109	0.018	-0.088	0.030	0.010	0.025

SEM — Standard error of the mean.
RBD — Residual to baseline deviation of plasmadilution as marker of plasma volume expansion efficacy.
C_RBD — Continuous residual to baseline deviation of plasmadilution.
S_RBD — Shifting residual to baseline deviation of plasmadilution.

Table 5. *The significance of changes in residual to baseline deviation of dilution*

Diagnostic (matrix- BIRD)	RBD type		Difference of RBD between consecutive mVLT steps											
			Pre-operative mVLT						Post-operative mVLT					
			Between step land 2			Between step 2 and 3			Between step land 2			Between step 2 and 3		
			Significance between		Significant	Significance between		Significant	Significance between		Significant	Significance between		Significant
			means	variances		means	variances		means	variances		means	variances	
			P	*P*		*P*	*P*		*P*	*P*		*P*	*P*	
$RBD_n > RBD_{n+1}$	C_RBD	Arterial	0.314	1.154	–	0.043	0.172	+	0.000	0.565	+			
		Venous	0.967	0.014	–	0.617	0.991	–	0.002	0.836	+			
	S_RBD	Arterial	0.003	0.017	+	0.059	0.889	–	0.000	0.034	+			
		Venous	0.009	0.013	+	0.816	0.718	–	0.000	0.104	+			
$RBD_n < RBD_{n+1}$	C_RBD	Arterial										0.074	0.316	–
		Venous										0.064	0.477	–
	S_RBD	Arterial										0.001	0.938	+
		Venous										0.018	0.359	+

n — Sequence number of the mVLT step. + Statistically significant difference.
RBD — Residual to baseline deviation of plasmadilution.
C_RBD — Continuous residual to baseline deviation of plasmadilution.
S_RBD — Shifting residual to baseline deviation of plasmadilution.

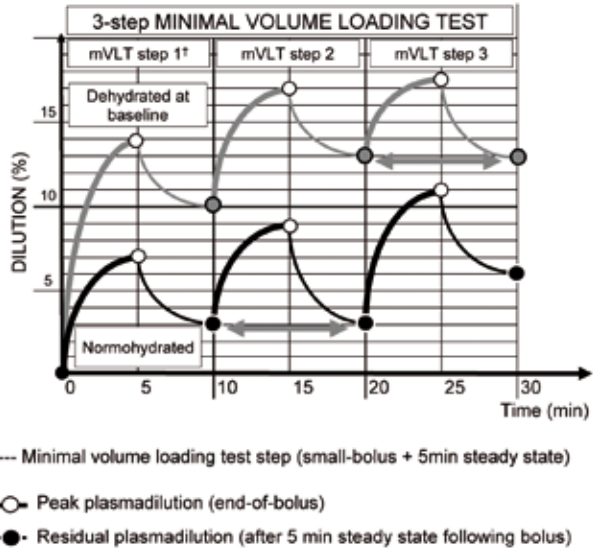

Figure 1. *Dilution trends during a theoretical 3-step minimal volume loading test*

Plasma dilution values (dimensionless, in per cent) during a theoretical three-step minimal volume loading test (mVLT). Three small boluses (5 ml/kg) of acetated Ringer's solution are given. Each step is followed by a 5 min steady state period when no fluid was given. Peak points are at 5, 15 and 25 min. Residual plasmadilution is defined as dilution value at time point 10, 20 and 30 minutes in respect to initial baseline at time point 0 minutes. The figure shows two hypothetical initial baseline states of body hydration — hydrated and dehydrated. A *hydration plateau* is reached when two residual dilution values are equal (values connected by the bidirectional horizontal arrows). Presumably, the better hydrated patients will reach this plateau earlier than less hydrated subjects.

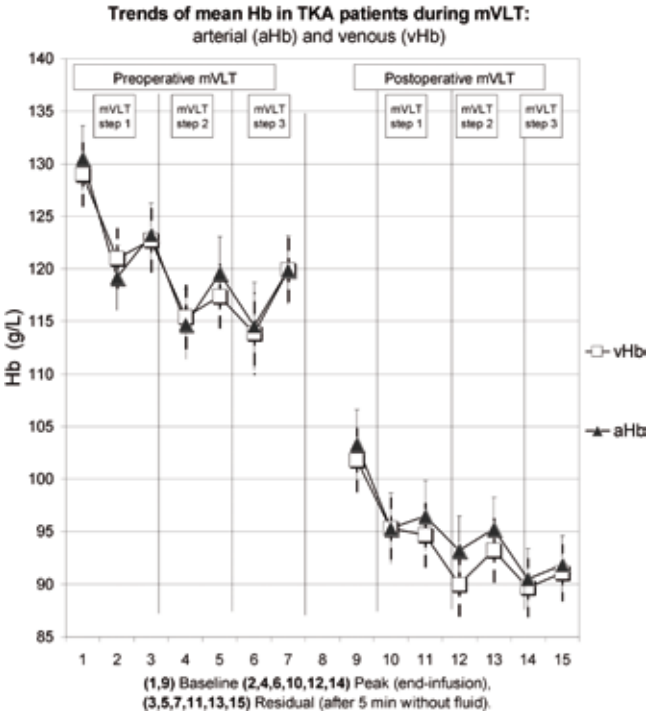

Figure 2. *Trends of arterial and venous henoglobin concentration*

Arterial (aHb) and venous (vHb) haemoglobin concentration at baseline before each infusion, at the end of the bolus (peak) and after 5 min steady state (residual). There was no significant difference between mean aHb and vHb and their variances, but preoperative Hb was significantly higher than postoperative due to perioperative blood loss. Data are expressed as means ± SEM.

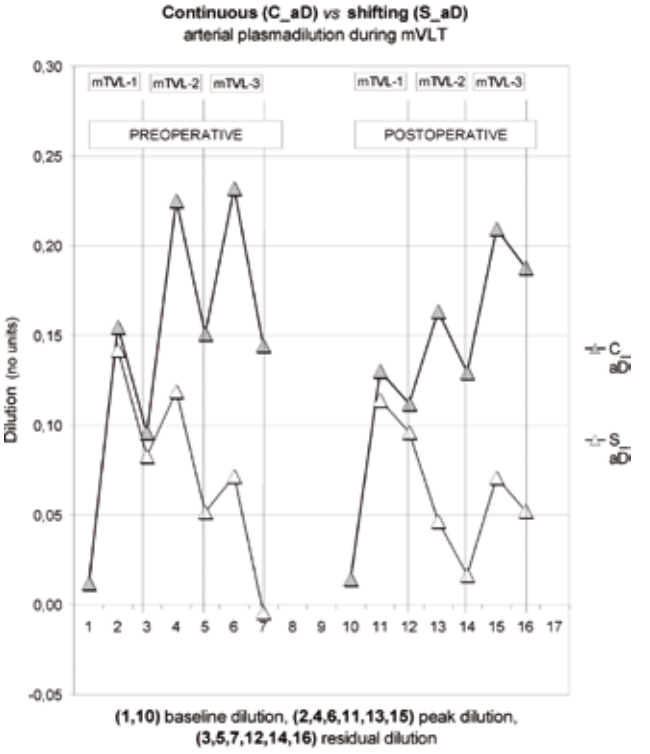

Fig. 3. *Continuous and shifting arterial dilution trends*

The minimal residual individual PVEE of the fluid challenge is seen in the 3rd preoperative and 2nd postoperative mVLT steps. The mean residual shifting arterial dilution (resS_aD) is close to zero at checkpoint 7 preoperatively and 14 postoperatively. The mean residual continuous arterial dilution (resC_aD) at these checkpoints is close to residual dilution of the preceding step. Both patterns are markers of maximized interstitial fluid compliance (hydration plateau).

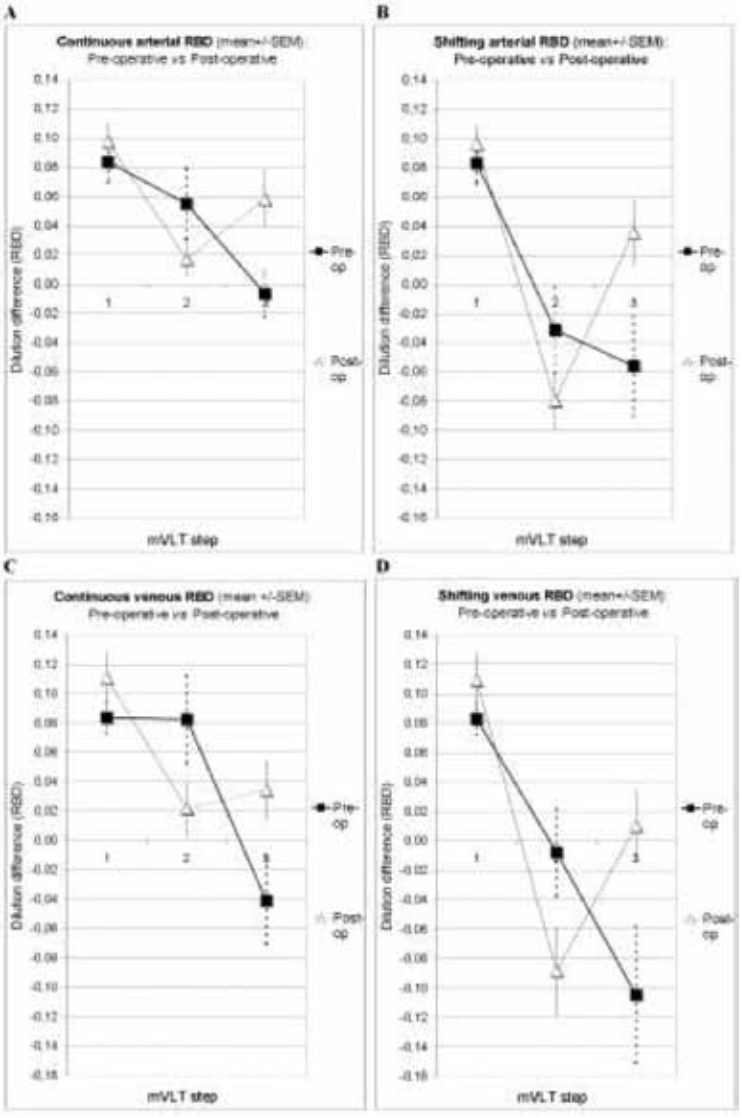

Figure 4. *Continuous and shifting residual to baseline deviation of dilution*

The significant differences between preoperative and postoperative mVLT sessions were found by comparing the residual to baseline deviation of dilution (RBD) of preoperative and postoperative mVLT sessions. The x-axis is a sequence number of the mVLT step, the y-axis is the continuous or shifting residual to baseline deviation of dilution (C_RBD and S_RBD respectively). (A) preoperative and postoperative continuous arterial RBD (C_aRBD), (B) preoperative and postoperative shifting arterial RBD (S_aRBD), (C) preoperative and postoperative continuous venous RBD (C_vRBD), (D) preoperative and postoperative shifting venous RBD (S_vRBD). Data are expressed as means ± SEM.

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