Original Research Article

A mini volume loading test for indication of preoperative dehydration in surgical patients

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ABSTRACT

Background and objective: Previously, a mini volume loading test (mVLT) detected signs of dehydration in healthy volunteers after an overnight fast. Our objective was to investigate whether mVLT could indicate preoperative dehydration in patients after an overnight fast.
Materials and methods: The mVLT was performed in 36 elective primary total knee arthroplasty patients. Each subject received three fluid challenges before anesthesia induction. These consisted of 5 mL/kg boluses of Ringer's acetate infused over 3–5 min and followed by a 5-min period without fluids. Invasive (arterial, venous) and noninvasive (capillary) measurements of hemoglobin concentration were performed before and after each fluid challenge, as well as after a 20-min period without fluids which followed the last bolus. Arterial, venous and capillary plasma dilutions were calculated in every data point. Dilution values were used to calculate the plasma dilution efficacy of each fluid challenge.
Results: Venous dilution was higher than capillary after the first fluid challenge ($P = 0.030$), but lower than capillary after 20 min period following the last bolus ($P = 0.009$). Arterial dilution was lower than capillary ($P = 0.005$) after 20 min following the last bolus. Veno-capillary and arterio-capillary plasma dilution efficacy differences decreased ($P = 0.004$ and $P = 0.033$, respectively) from positive to negative during mVLT. These are signs of re-hydration from pre-existing dehydration according to a transcapillary reflux model.

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Conclusions: Signs of dehydration were observed during mVLT in patients after pre-operative overnight fast. A revised transcapillary reflux model was proposed to explain the results.

1. Introduction

An estimated 234 million surgeries are performed every year worldwide. Of these, approximately 12.5% are considered high-risk surgeries [1]. Fluid administration is part of the perioperative treatment. Thus, it is an important field of research in surgery and anesthesia [2]. One of the main tasks when planning perioperative fluid therapy is to determine the baseline hydration status of the patient. If the patient cannot maintain a normal hydration state due to lack of fluid the patients enter a state of dehydration. Parameters such as blood pressure, heart rate, urinary output, and central venous or pulmonary artery pressures are nonspecific for determination of hydration status and insufficient for guiding fluid therapy [3]. Despite progressive understanding of fluid distribution, and mechanisms of edema formation based on physiology [4–7], a robust method for estimating normal hydration state is lacking.

As suggested by a recently proposed mini volume loading test (mVLT), a parameter that could be used as an indication of hydration status is plasma dilution [8]. In volunteers, this model has successfully identified dehydration in healthy volunteers after an overnight fast [9].

Our objective is to investigate whether mVLT could indicate dehydration in surgical patients after an overnight fast.

2. Materials and methods

This was an open interventional clinical study conducted at the Vilnius University Hospital in Vilnius, Lithuania. The protocol is part of a larger interdisciplinary RCT (Fig. 1)
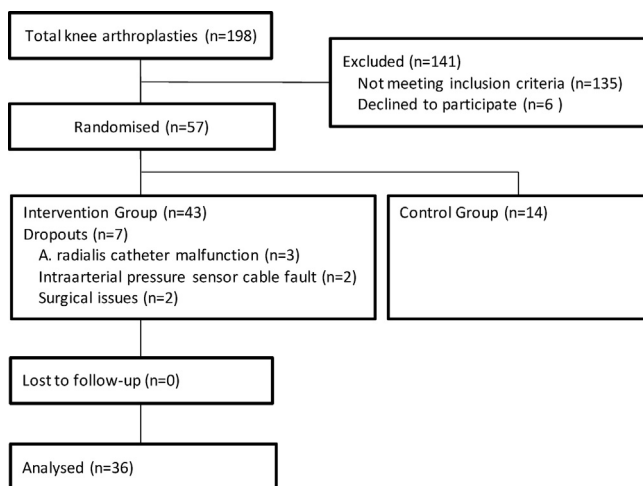

Fig. 1 – CONSORT diagram of the open prospective randomized clinical trial.

with the primary objective to evaluate the impact of three pneumatic tourniquet inflation strategies on outcomes following unilateral total knee arthroplasty [10]. Ethical approval for this project was provided by the Vilnius Regional Bioethics Committee, Vilnius, Lithuania (Ethical Committee No. 158200-9-071-22, chairperson G. Andrulionis) on September 16, 2009. The study is registered at clinicaltrials.gov with identifier NCT01355900.
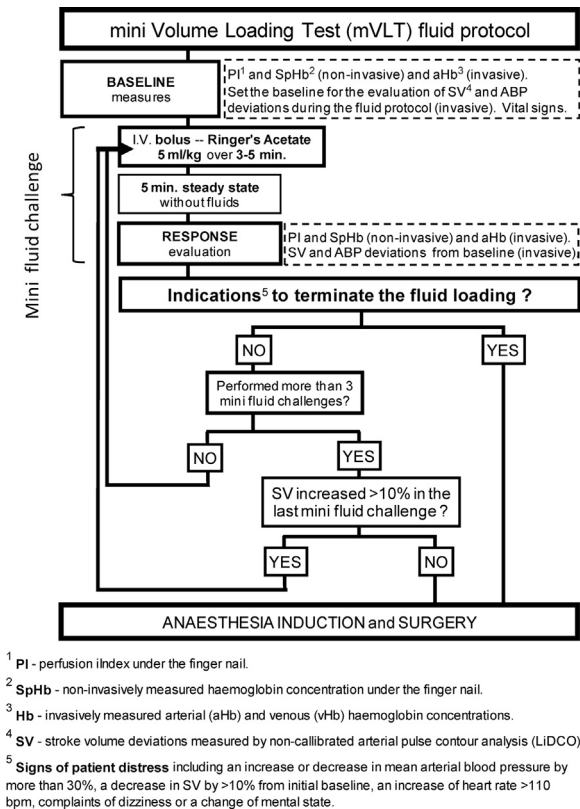
Forty-three ASA II physical state adult patients scheduled for unilateral elective primary TKA surgery were enrolled from January 2010 to July 2011.

2.1. Procedures

Patients arrived in the operating room at 7:00 AM after an overnight fast. On arrival, standard monitors (ECG, pulse-oximetry, and noninvasive blood pressure measurement) were applied. Oxygen was provided by a facemask. An antecubital cannula was placed in one hand. This line was used for fluid infusion and for sampling venous blood. A radial artery cannula was placed in the same arm. This line was used for sampling arterial blood and for continuous monitoring of blood pressure (DASH 3000®, GE Medical Systems Information Technologies Inc., Milwaukee, WI) and stroke volume (SV) deviations (LiDCO™ Plus, London, UK). A spectrophotometric adhesive sensor (Masimo Inc., Irvine, CA) was attached to the nail of the middle finger of the same hand to measure SpHb™. The sensor was connected to a Radical-7 Pulse CO-Oximeter (Masimo Inc., Irvine, CA). The device was set to "arterial" mode and a "short" averaging time for SpHb.

The mVLT was applied before the induction of anesthesia (Fig. 2). A gravity driven stepwise infusion of acetated Ringer's solution at room temperature was given. Each patient received a series of fluid challenges. These consisted of 5 mL/kg fluid boluses infused for 3–5 min and followed by a 5-min periods without fluid after each bolus. Each patient received at least three fluid challenges, with an additional bolus indicated if the SV increased >10% after the third mini fluid challenge. Termination of the protocol was indicated at any stage if there were signs of patient distress including, but not limited to, an increase or decrease in mean arterial blood pressure by more than 30%, a decrease in SV by >10% from the initial baseline, an increase of heart rate >110 bpm, complaints of dizziness or a change of mental state. Additional 15 min period without fluids was applied after the last fluid challenge (the net period following the last bolus is therefore 20 min). The fluid protocol was terminated thereafter.

Arterial and venous blood samples were obtained to determine the hemoglobin concentration (Hb) – arterial (aHb) and venous (vHb) – immediately before the first and after each fluid challenge during mVLT, as well as after a 20-min period without fluids after the last bolus. Blood (2 mL) was

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│   mini Volume Loading Test (mVLT) fluid protocol │
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Fig. 2 – Preoperative mini volume loading test.

[1] **PI** - perfusion iIndex under the finger nail.

[2] **SpHb** - non-invasively measured haemoglobin concentration under the finger nail.

[3] **Hb** - invasively measured arterial (aHb) and venous (vHb) haemoglobin concentrations.

[4] **SV** - stroke volume deviations measured by non-calibrated arterial pulse contour analysis (LiDCO).

[5] **Signs of patient distress** including an increase or decrease in mean arterial blood pressure by more than 30%, a decrease in SV by >10% from initial baseline, an increase of heart rate >110 bpm, complaints of dizziness or a change of mental state.

drawn before each sampling to preclude any admixture of rinsing or infusion solutions. The aHb and vHb were analyzed by a laboratory CO-Oximeter (COULTER® LH750, Beckman Coulter Inc., Chicago, IL) with a coefficient of variation ≤0.8%. The readings of SpHb and SV deviation were manually recorded at the same time when blood samples were taken.

Invasive and noninvasive Hb measurements were used for calculation of PD. A comparison of the PD after repetitive boluses cannot fully reflect differences in intravascular fluid retention due to short time interval between infusions. It allows overlapping of dilution from consecutive boluses. Thus, PD is further used to calculate the plasma dilution efficacy (PDE) of a single fluid challenge. The PDE is used to evaluate the ability of a fluid challenge to increase the PD from a preceding fluid challenge. Finally, the plasma dilution efficacy difference (PED) between the Hb measuring sites is calculated. The following variables were calculated: (a) the PD, arterial (aPD), venous (vPD) and capillary (cPD); we labeled the SpHb™ as capillary (cHb) referring to the anatomy of the site of measures, as well as aiming to ease the reference to the derivative variables such as PD; (b) the PDE, arterial (aPDE), venous (vPDE) and capillary (cPDE); (c) plasma dilution efficacies, arterial (aPDE), venous (vPDE) and capillary (cPDE); and (d) the PED, arterio-capillary (acPED) and veno-capillary (vcPED). The equations used for these calculations were described elsewhere [9]. The 144 estimates of PD (Fig. 3B) – aPD, vPD and cPD were calculated from 180 simultaneous measurements of aHb, vHb and SpHb™ – at 5 data points (Fig. 3A). The first Hb measurement serves as baseline for the calculation of the PD

induced by the first fluid challenge. The 108 estimates of aPDE, vPDE and cPDE – of the three fluid challenges (Fig. 3C) were calculated from 108 estimates of aPD, vPD and cPD (see data points No. 1–3 in Fig. 3B). The 108 estimates of the acPED and vcPED (Fig. 3D) in three fluid challenges were calculated from 108 estimates of the aPDE and cPDE (Fig. 3C). We used an arbitrary unit – the procedure defined unit (p.d.u.) [11] – for the estimates of PD and its derivatives because there are no specific units for these variables [12].

2.2. Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the pooled data for normality. Data are presented as median, 25th and 75th percentiles, and the Wilcoxon signed rank test was applied for nonnormally distributed data. A statistical analysis was performed using PASW (PASW Statistics 17, SPSS, IBM Corporation, NY). The significance level was set to alpha = 0.05 (two-sided).

A priori power analysis was based on the previously reported finding of 5% difference in plasma dilution between the dehydrated and normally hydrated volunteers after a single bolus of crystalloid [13]. A sample size of 36 subjects is required to achieve a 95% power with a significance level (alpha) of 0.05 using a two-sided one-sample t test for the comparison of plasma dilution in consecutive fluid challenges.

3.   Results

A total of 43 patients were enrolled, and of these 36 (31 women and 5 men) completed the study, which comprised 36 fluid experiments altogether (Fig. 1). Patients were 68.5 ± 6.8 years of age, weighed 84.5 ± 13.7 kg and BMI was 31.0 ± 4.6 (kg/m^2). Seven patients who dropped out of the study had a malfunctioning radial artery catheter ($n = 3$), a faulty cable to the arterial pressure sensor ($n = 2$), or there were unpredicted deviations from the surgical protocol ($n = 2$). All subjects received three fluid challenges during mVLT (Fig. 2). Three patients responded to the first fluid challenge with a SV increase by >10% (19%, 20% and 24%, respectively). These subjects were considered responders while patients in the second and third fluid challenges who responded with a SV increase with less than 10% were considered non-responders. Thus, according to the mVLT fluid protocol (Fig. 2), there was never any indication to administer a fourth bolus. The net increase of SV at the end of the fluid protocol was >10% in 12 (33%) patients.

The three observations of dilution induced by the three fluid challenges revealed that vPD was higher than cPD after the first fluid challenge (0.101 [0.070–0.135] vs. 0.061 [0.000–0.121]), $P = 0.030$ (T1 in Fig. 4A), but lower than cPD after the 20 min without fluids following the last bolus (0.067 [0.047–0.108] vs. 0.142 [0.079–0.216]), $P = 0.009$ (T4 in Fig. 4A). The only difference between aPD and cPD occurred after 20 min following the last fluid bolus where the aPD was lower than cPD (0.066 [0.041–0.098] vs. 0.142 [0.079–0.216]), $P = 0.005$ (T4 in Fig. 4A).

The vPDE was higher than cPDE ($P = 0.030$) in the first fluid challenge (T in Fig. 4B). The aPDE of the three fluid challenges
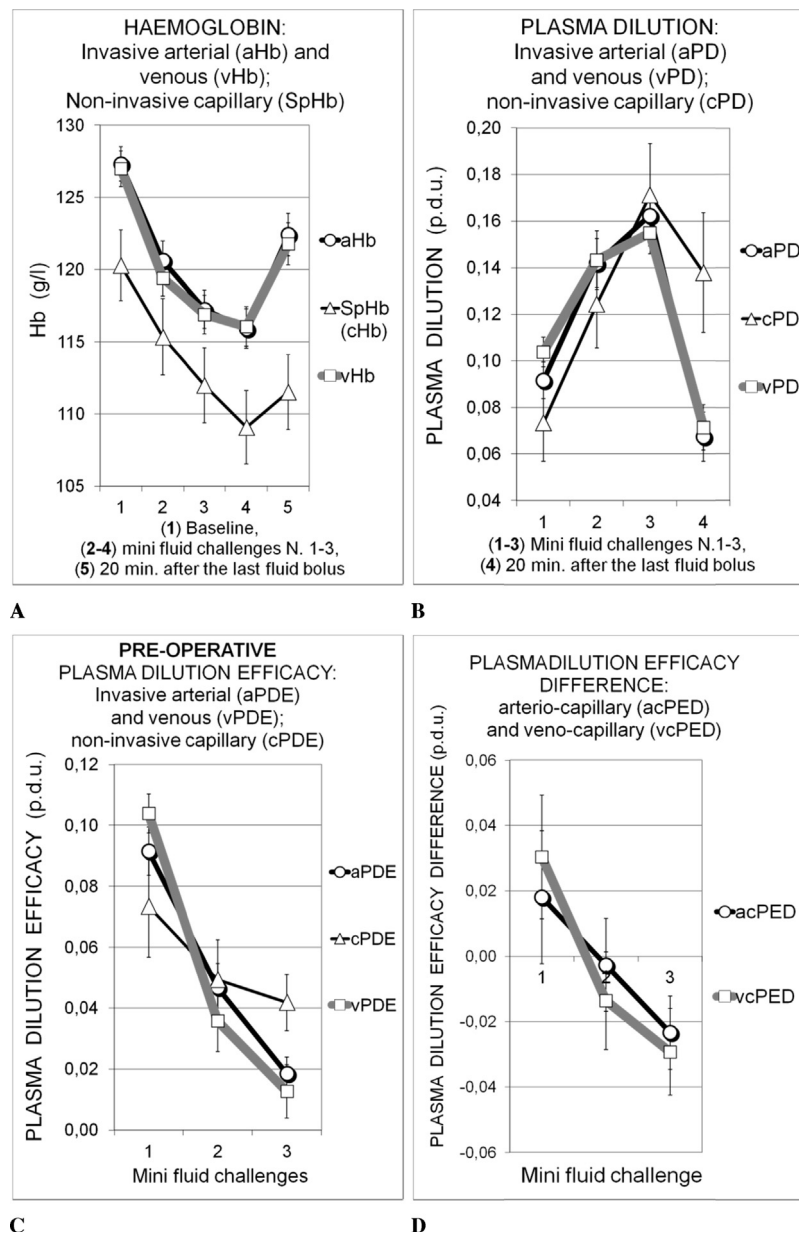
Fig. 3 – Invasively (arterial, venous) and noninvasively (capillary) determined variables during the mini volume loading test (mVLT). (A) Hemoglobin concentration, (B) plasma dilution, (C) plasma dilution efficacy and (D) plasma dilution efficacy differences between arterial and capillary, as well as venous and capillary measures. Data point referred to as baseline is the measure before the first crystalloid bolus. Data points referred to as mini fluid challenges No. 1–3 are the measures determined after the 5-min period without fluids which followed each of the three crystalloid boluses. Data are presented as means ± SEM.

decreased during the mVLT (0.0825 [0.0525; 0.1261] vs. 0.0404 [0.0259; 0.664] vs. 0.0141 [0.0129; 0.0387]), $P = 0.001$ and $P = 0.029$, respectively (T1–T3 in Figs. 3C and 4B). The vPDE decreased only in the second fluid challenge (0.101 [0.070; 0.134] vs. 0.026 [0.012; 0.053]), $P = 0.001$ (T1–T2 in Figs. 3C and 4B).

Plasma dilution efficacy differences decreased significantly during the mVLT: acPED decreased from 0.042 [−0.025 to 0.094] in the first fluid challenge to −0.022 [−0.059 to 0.023] in the third one ($P = 0.033$), as well as vcPED decreased from 0.054 [−0.014 to 0.102] to 0.012 [−0.066 to 0.023], $P = 0.004$.

4.   Discussion

The aim of the present study was to investigate if signs of pre-existing dehydration could be observed in preoperative surgical patients after a fasting period using an mVLT method. As shown in Fig. 2, the mVLT fluid protocol in the present study consisted of three 5 mL/kg boluses of crystalloid followed by 5-min periods without fluid.

The most important finding was that after the first mini fluid challenge the vPD and vPDE were higher than cPD and
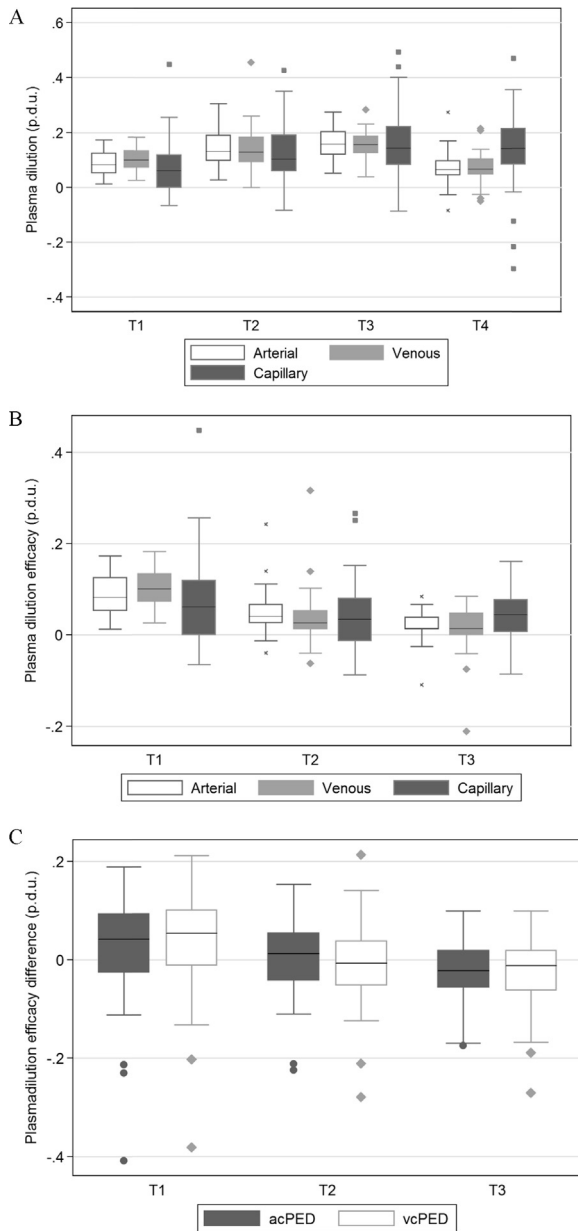
Fig. 4 – Box plots of nonnormally distributed variables. (A) The plasma dilution (PD) after each of the three mini fluid challenges and after the 20-min period without fluids following last bolus; (B) the plasma dilution efficacy (PDE) in each of the three mini fluid challenges; (C) the difference between arterial and capillary plasma dilution efficacies (arterio-capillary plasma dilution efficacy difference; acPED), as well as between venous and capillary plasma dilution efficacies (veno-capillary plasma dilution efficacy difference; vcPED). Data are presented as box plots.

capillaries soon after the bolus. Due to that influx of interstitial fluid, the vPD may become slightly higher than aPD, and that may be enough for the vPD to become higher than cPD while there is no difference between aPD and cPD. The flush of interstitial waste products into capillaries decreases during further rehydration. Assuming the intact endothelial glycocalyx, the transcapillary fluid movement becomes dependent on interstitial fluid compliance. Interstitial fluid expansion during rehydration in derma and skeletal muscles increases the fluid compliance of these tissues [14]. Thus, transcapillary filtration–absorption ratio (FAR) increases. These factors may explain why there was no difference between vPD, aPD and cPD after the second and third fluid challenges. Activation of fluid elimination from the circulation may be responsible for the aPDE decrease during all the three fluid challenges. The vPDE, however, decreased only during second fluid challenge. Presumably it was because the interstitial fluid compliance has overcome its maximum value during the third bolus, and therefore, a transcapillary reflux of excessive fluid has commenced soon after infusion. It could have advanced the venous dilution. Further release of excessive interstitial fluid into capillaries can explain the significantly higher cPD than vPD and aPD during 20 min following the last bolus. The net effect of the above-described processes may explain why vcPED and acPED decreased during the stepwise infusion. The physiologic reasoning supports these speculations despite the evidence what actually happened in the pertinent fluid compartments.

In a study with healthy volunteers [9], the vPD was higher than cPD in all the three fluid challenges. In the present study we used a bolus volume that was twice higher. The resulting faster time course of rehydration in patients may therefore explain why the vPD was higher than cPD after the first fluid challenge, but there was no difference between these variables after the second and third fluid challenges (Fig. 3B–D). The flux of excessive interstitial fluid into capillaries may explain why vPD became lower than cPD during the 20-min period without fluids following the last bolus.

The volume of a bolus during mVLT was intended to be similar by its volume expansion efficacy to the 100 mL of colloid that was previously used for mini-fluid challenges to evaluate the fluid responsiveness in hemodynamic target guided goal directed therapy [15]. Thus, we may refer to the mVLT fluid protocol as a series of "mini fluid challenges." However, even the minimum volume of a bolus required for conventional goal directed therapy is continuously debated [16] and remains unclear [17]. The "fluid challenge" has to be as minimal as possible while still being sufficient for the evaluation of fluid responsiveness [17]. Thus, lower volume boluses should be investigated in future trials to establish the "true" minimum volume of a bolus required for evaluation of hemodynamic and plasma dilution responses. This is an interim report from our larger study [10] because after finishing the part of the study addressed in this article the bolus was reduced from 5 mL/kg to 2.5 mL/kg and the target number of mini fluid challenges was increased from 3 to 6. This change in our study protocol was an attempt to investigate lower volume boluses for mVLT.

Since vcPED decreased during the mVLT only in dehydrated healthy volunteers [9], the same finding in the present study suggests that patients were dehydrated before the start of the

cPDE, respectively (Figs. 3B, C and 4A, B). According to the transcapillary reflux model [9], these may be apparent signs of pre-existing dehydration before the first bolus. However, at that point there was no difference between arterial and capillary variables. Interstitial accumulation of infused crystalloid during rehydration may be followed by an increase of metabolism-guided flux of waste products into the venular part of true

mVLT session. Presumably they became overhydrated by the end of the fluid protocol. This is consistent with our estimates that a total amount of 15 mL/kg volume of crystalloid used in the present study should replace an estimated 10 mL/kg basal physiological fluid deficit related to an overnight fast [18], as well as provide an additional 5 mL/kg volume. Thus, our subjects should have been rehydrated by the first two fluid challenges and overhydrated by the third one. Meanwhile, our finding of nonresponsive SV during mVLT is consistent with the previous report of hemodynamic nonresponsiveness [19] and normal blood volume after preoperative overnight fasting [20]. That can be explained by weak correlation between intravascular volume and interstitial hydration status because only the water fraction of plasma equilibrates with extravascular space. Our study has addressed the interstitial fluid deficit that normally occurs after an overnight fast. Thus, during the rehydration related increase in interstitial fluid compliance plasma dilution efficacy of consecutive crystalloid boluses decreased. This suggests that intravascular volume expansion was also decreasing.

Two methods are proposed for the evaluation of hydration status using the PD response, which is characterized as the PD trend obtained during consecutive crystalloid boluses followed by periods without fluid infusion. The mVLT is the development of a previously published method, the volume loading test (VLT) [13]. Both the mVLT and VLT are based on the concept that changes in PD induced by a fluid challenge are more pronounced when the impact of net fluid elimination and net interstitial fluid accumulation on intravascular fluid retention is low, such as when the patient is dehydrated (Fig. 5). The main differences between the mVLT and the VLT are: (a) the VLT uses crystalloid boluses larger than those used in the mVLT, (b) the period without fluid following a bolus in VLT is at least four times longer than in mVLT, and (c) the mVLT allows for both diagnosis and management of hydration status while the VLT is used for diagnosis only. Fig. 5 compares the VLT and mVLT methods. Despite different baseline hydration status, the VLT yields similar PD at the peak but shows a difference 20 min after the end of infusion. This is because the peak PD is presumably dependent on the volume status, while residual PD after 20 min after the end of infusion is hydration status dependent [13]. Dehydrated subjects showed higher PD 20 min after the end of infusion. In the mVLT, similar PD differences will be detected at the end of the experiment but significant differences can be detected earlier due to the repetitive boluses with 5 min intervals without

○ --- end of a brisk isoosmotic crystalloid infusion

□ --- after 5 min period without fluids that follows the end of a crystalloid infusion

● --- after 20 min period without fluids that follows the end of a crystalloid infusion (every infusion in VLT or last infusion in mVLT)

p.d.u. -- procedure defined unit (Confirmed minutes for the meeting in Uppsala 2008-10-23 – 25 (Report). Committee and Subcommittee on Nomenclature, Properties and Units (SC-C-NPU), IUPAC–IFCC. 2008.)

VOLUME LOADING TEST (**VLT**) - single relatively large test fluid load is followed by 20 min period without fluids
In VLT, dehydrated at initial baseline individuals present with more pronounced plasma dilution after 20 min period without fluid
Mini Volume Loading Test (**mVLT**) - consecutive mini fluid challenges (relatively small volume boluses followed by 5 min periods without fluid) are continued until plasma dilution does not increase any more, and may be followed by 20 min period without fluid.

Fig. 5 – Relationship between volume loading test (VLT) and mini volume loading test (mVLT). A fluid challenge is defined as a fluid bolus followed by its corresponding time without fluid. Thick lines are showing plasma dilution during bolus infusions and thin lines are showing plasma dilution during periods without fluid infusion. Solid lines reflect dehydrated subjects while broken lines reflect normohydrated subjects. The VLT test will show similar plasma dilution peaks at the end of infusion in both hydration states but show a difference twenty minutes after infusion. The mVLT test, however, will distinguish between these two states earlier, after two challenges in the dehydrated state and after three fluid challenges in the normohydrated state. The dilution plateau is a state where two dilutions after fluid challenges are equivalent.

infusion. This is achieved by detecting a "dilution plateau" where a mini fluid challenge does not induce any further increase in plasma dilution. For those subjects with a higher hydration level ("normally hydrated"), the dilution plateau will be detected earlier, in this figure during the second mini fluid challenge. For those subjects with a lower baseline hydration status ("dehydrated") this occurs during the third mini fluid challenge. There are several limitations to the use of PD. First, the dilution plateau can easily be missed due to the rapid transition scheme. Also, the detection of the plateau requires equivalent Hb values before and after a mini fluid challenge and this in turn requires a measuring device with very high accuracy and precision. That may theoretically explain why the dilution plateau was not observed during the mVLT in the present study, as well as in healthy volunteers [9]. The cPD was, however, higher than aPD and vPD after the 20 min period without infusion following the last bolus in patients (Figs. 3B and 4A) indicating the ongoing reflux of excessive fluid from the interstitium into capillaries.
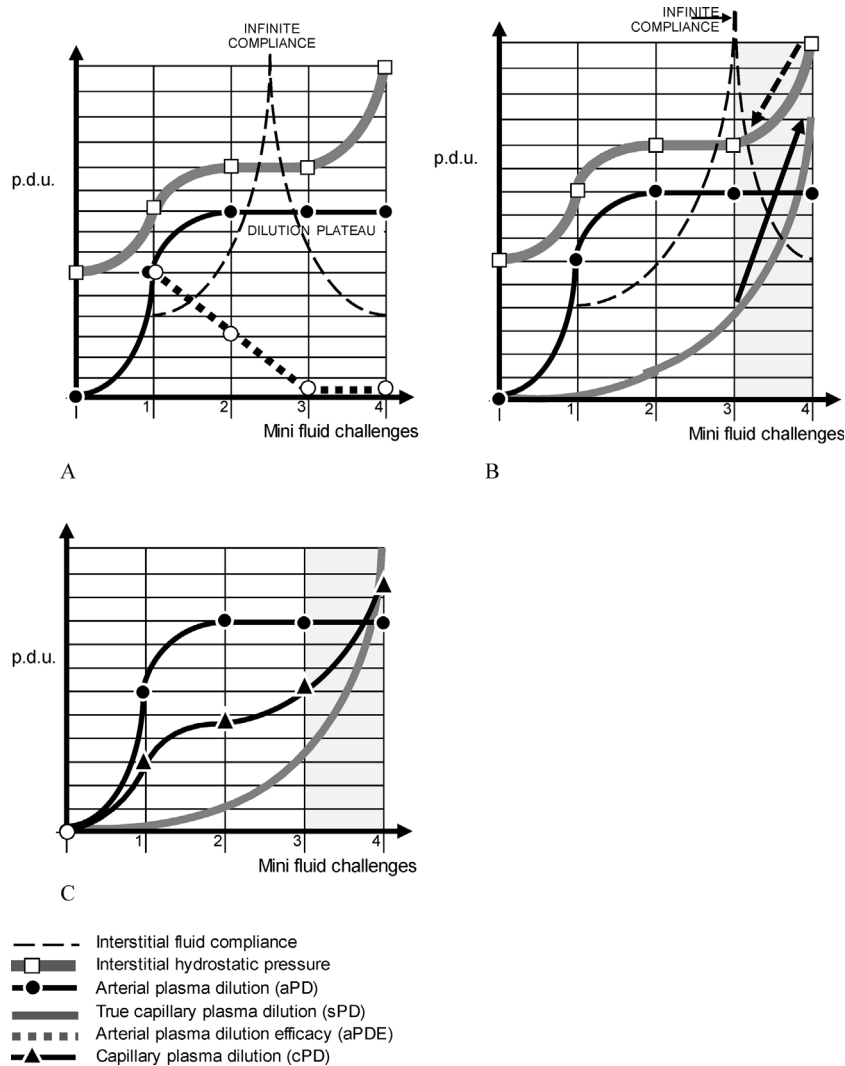
Aiming for a physiologic explanation of our results we suggested a "revised" transcapillary reflux model. The relationship between PD, the hydration status and renal fluid elimination is added to the previously proposed model [9]. Digested and infused fluids enter the veins through transcapillary fluid exchange between blood and tissues. The aPD is usually higher than vPD because transcapillary fluid filtration exceeds the rate of absorption to maintain the production of lymph (Fig. 5A). The interstitial fluid compliance and the hydrostatic pressure-dependent lymphatic flow from tissues into the central veins regulate the interstitial fluid volume [14,21]. This regulation has varying impacts on the PD in the central veins and, therefore, in arteries as well. A certain amount of fluid is eliminated by the kidneys. Obviously, the PD will differ from site to site within the circulation system. To investigate whether these differences in PD can be used for the evaluation of interstitial hydration status, the transcapillary reflux model could possibly explore the relationship between net arterio-venous (avDD), arterio-capillary (acDD) and veno-capillary (vcDD) dilution differences and the net interstitial fluid expansion during a bolus crystalloid infusion and the immediate time period after the infusion. Interstitial fluid compliance is defined as the interstitial fluid volume expansion divided by the corresponding shift in interstitial hydrostatic pressure. As shown in Fig. 5B, the transcapillary fluid filtration absorption ratio (FAR) and the interstitial fluid compliance are mutually dependent, i.e., an increase in the FAR causes an increase in compliance during rehydration, and vice versa. The absolute value of the acDD is always higher than the avDD because of arterio-venous shunting. This model demonstrates that acDD and avDD reflect the net direction of transcapillary fluid movement. Thus a positive avDD and acDD show that transcapillary filtration exceeds the rate of absorption, but they do not indicate the rate of interstitial fluid accumulation because the rate of lymphatic flux into the central veins is unknown. In contrast, negative avDD, acDD and vcDD values can be clinically relevant because these parameters show that transcapillary absorption exceeds the rate of filtration. The clinical interpretation of this observation can be derived from the context in which the observation is made. For instance, if negative avDD, acDD and vcDD values

are detected during the mVLT and they were preceded by positive values during the previous mini fluid challenges, then this would be a sign of excessive interstitial fluid being released into circulation. If these are detected after the administration of a diuretic, they can be used for monitoring the efficacy of the medication and the duration of its action. Such observations could be an important indicator that fluid is being eliminated from the blood stream before the blood returns to the same capillaries. Moreover, if the negative acDD and avDD values are associated with dilution non-responsiveness (aPDE ≈ vPDE ≈ 0) during mVLT, this confirms that optimization of the fluid status has been achieved. In contrast, the cPDE would not be that close to nil because capillary blood will be diluted by the reflux fluid from the interstitium. Thus, the cPDE would be minimized – the decrease of the cPDE would turn into an increase. We partially observed this after the third mini fluid challenge in the present study. The mean aPDE and vPDE values significantly decreased in the second and third mini fluid challenges and approached zero, while the decrease in cPDE that was seen after the second mini fluid challenge turned into an increase in the third challenge (Figs. 3C and 4B). However, in contrast to aPDE and vPDE, the changes in cPDE during the mVLT were not statistically significant. This limitation may be explained by the lack of precision in connection with noninvasive measures of SpHb or the higher number of required observations. However, the vPDE was higher than cPDE in the first mini fluid challenge, and that indicates that the accumulation in interstitium had hemoconcentratingly affected the cPD.

The FAR is indicative of the interstitial fluid accumulation rate. The periodic fluctuation of the FAR, known as vasomotion, meets the metabolic needs of tissues. A positive volume difference between filtration and absorption (FAR > 1.0) increases the lymph flow in the nonedematous tissues (Fig. 6A and B), but that difference will become negative (FAR < 1.0) during the transcapillary reflux of excessive interstitial fluid from edematous tissues. The lower increase in absorption compared to filtration will also result in the similar reflux, but FAR may be both >1.0 and <1.0. The lymphatic flux can also drain excessive interstitial fluid from edematous tissues (Fig. 6C), but this cannot be verified clinically. In contrast, the transcapillary reflux that results in a change from the prevailing filtration to absorption can be seen as positive values for both acDD and avDD turning into negative. Theoretically, the interstitial fluid compliance is the major homeostatic driving force leading to transcapillary reflux when the threshold for imminent interstitial edema is reached during mVLT. We postulate that the interstitium strives to maintain a state of maximum fluid compliance because in that state any changes of the interstitial fluid volume are associated with minimum deviations in the interstitial hydrostatic pressure which in turn results in a minimum amount of stress on the tissues. When the interstitium is dehydrated, the only way to increase the compliance is to expand the tissue by adding fluid. This can be accomplished through oral fluid intake or through a stepwise infusion of a crystalloid solution during the mVLT. As shown in the theoretical sketch (Fig. 7), an infinite interstitial fluid compliance is reached after the third mini fluid challenge. The plateaus of aPD and interstitial hydrostatic pressure indicate that the interstitial fluid accumulation rate and the

Fig. 6 – Transcapillary reflux model revised. It depicts the relationship between net arterio-venous, arterio-capillary and veno-capillary dilution differences and net interstitial fluid expansion. The arrows in the figure represent equal volumes of fluid. See ''Supplementary Material'' for whole disclosure. (A) The thirst-guided fluid intake is equal to the basal renal elimination; (B) the case of hydration non-responsiveness during mVLT; (C) the release of excessive fluid into the capillaries following the end of an infusion that causes interstitial edema.

FAR have reached a maximum. In contrast, if the interstitium is further expanded by fluid, the compliance starts to decrease and the pressure starts to increase. The fastest homeostatic way to return to the maximum compliance state and reduce the hydrostatic pressure is to release excessive fluid into the capillaries. The transcapillary reflux into the true capillaries (Fig. 6C) occurs during the 5-min period without fluids after a mini fluid challenge (see mini fluid challenge No. 4 in Fig. 7). Driven by the tendency of interstitial hydrostatic pressure to decrease and return to the value that was associated with infinite interstitial compliance (the pressure gradient is shown as a dashed arrow in Fig. 7B), the FAR decreases and the true capillary PD (sPD) increases sharply (the solid arrow in Fig. 7B). If the net pulmonary and renal fluid elimination match the net release of excessive interstitial fluid into the capillaries, there will be no increase in aPD (Fig. 6C) and this will lead to negative acDD and avDD values. According to the model, this would be the time point during stepwise crystalloid infusion when the reflux of excessive interstitial

fluid into capillaries starts. Thus, no more fluid should be given to prevent the interstitial tissue from being overfilled. Although calculation of avDD enables the detection of transcapillary reflux during the mVLT, there are several important limitations. The fluctuations of avDD are usually not significant because arterio-venous shunting ameliorates the impact that cPD has on aPD. That explains why the changes in avDD were not significant during the preoperative mVLT in the present study.

We defined the dilution of SpHb as the cPD, which is the mean of the aPD and sPD (Fig. 7B). It is important for the diagnosis of transcapillary reflux during the mVLT to be able to detect a negative acDD. However, aPD and sPD overlap in the cPD measurement because the cPD is the average of the two ($cPD = 0.5(aPD + sPD)$). Moreover, the aPD values of consecutive fluid challenges also overlap so aPDE is used instead of aPD. Thus, for the detection of transcapillary reflux, evaluating the acPED, which is the difference between the aPDE and cPDE, is more appropriate than evaluating the acDD. For the same

Fig. 7 – The role of interstitial fluid compliance in the revised transcapillary reflux model. See "Supplementary material" for whole disclosure. (A) The relationship between hemodilution related variables and interstitial fluid compliance; (B) the true capillary plasma dilution (sPD) exceeds aPD after the fourth mini fluid challenge as a result of transcapillary reflux-related decrease in the transcapillary fluid filtration absorption ratio; (C) the capillary plasma dilution (cPD) is the mean value of the aPD and the sPD. Theoretically, in a single capillary bed model the cPD is the dilution of the noninvasively measured hemoglobin (SpHb). The cPD exceeds aPD after the fourth mini fluid challenge because of an increase of sPD over aPD (see (B)).

reason the vcPED would be more appropriate than vcDD as well. A negative acPED and vcPED observed during the mVLT indicate that transcapillary reflux is active, and that interstitial fluids are being released in the vicinity of a single capillary bed under the fingernail and are being removed from circulation. The vcPED decreased significantly during the mVLT in the dehydrated healthy volunteers, while the changes were not significant in normohydrated [9]. We observed a similar pattern of dehydration signs in the present study where both acPED and ac PED decreased significantly during the preoperative mVLT in patients after an overnight fast.

The purpose of our extensive discussion of the underlying physiological model of transcapillary fluid movements is to help the reader understand our proposal to use PD as a target parameter for monitoring the whole-body fluid status.

Presumably, detection of transcapillary fluid reflux during the mVLT suggests that interstitial overfilling (edema) is imminent. Most importantly, the minimization of noninvasively determined cPDE seems to be associated with minimization of invasively determined aPDE and vPDE, and thus can be used in place of invasive measures for evaluation of hydration status. The mVLT technique could possibly be useful for perioperative fluid therapy protocols. Aiming to imitate the conventional clinical setting in our present study we used the gravity driven infusion system instead of high volume pump because the infusers capable of infusing 50–100 mL of preheated IV solution per minute are rarely available in everyday practice.

This study has several limitations. Primarily, it is based on physiological reasoning without any validation of what

actually happens in the pertinent tissues. Furthermore, the noninvasive signal is reflecting what is happening under the derma of a nail. However, we argue that because the derma and the skeletal muscles have similar interstitial fluid compliance [14,21] and constitute a major proportion of body tissue volume, the cPDE derived from SpHb readings may reflect the whole-body hydration status. This is similar to pharmacokinetic and volume kinetic models that are macro models based on arterial or venous samples from a specific site [22].

The strength of the study is that it is an attempt to link the clinical thinking and insights from clinical trials [4,7] with an advanced understanding of physiology and the pathology of a tissue fluid exchange [5,6,23] in a single model aiming to encourage interdisciplinary collaboration in its further development and validation. Recent development of an automated clinical decision support system for the mVLT application in a prototype semi-closed loop infusion system [24–26] serves as example.

5.   Conclusions

The signs of dehydration were observed in mVLT for patients after a preoperative overnight fast. The revised transcapillary reflux model was proposed for the explanation of the mVLT results. More studies are needed aiming to determine a "true" minimum effective volume for the bolus infusions during mVLT protocol.

Conflicts of interest

The authors state no conflicts of interest.

Acknowledgment

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.medici.2015.02.001.

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