Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/medici

Original Research Article

Evaluation of hydration status calculated from differences in venous and capillary plasma dilution during stepwise crystalloid infusions: A randomized crossover study in healthy volunteers

Christer H. Svensen[a,*], *Edgaras Stankevičius*[b], *Jacob Broms*[a], *Vytautas Markevičius*[c], *Audrius Andrijauskas*[d]

[a] *Section of Anaesthesiology and Intensive Care, Department of Clinical Science and Education, Karolinska Institutet, Stockholm, Sweden*
[b] *Institute of Physiology and Pharmacology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*
[c] *Department of Electronics Engineering, Kaunas University of Technology, Kaunas, Lithuania*
[d] *Clinic of Anaesthesiology and Intensive Care, Faculty of Medicine, Vilnius University, Vilnius, Lithuania*

ARTICLE INFO

Article history:
Received 11 April 2014
Accepted 7 August 2014
Available online 1 October 2014

Keywords:
Noninvasive hemoglobin
Hydration status
Crystalloid
Interstitial fluid
Mini volume loading test

ABSTRACT

Background and objective: A mini volume loading test (mVLT) was proposed for estimating hydration status and interstitial fluid accumulation during stepwise infusion of crystalloids. The method is based on both the transcapillary reflux model and the hypothesis that when subjects are dehydrated, venous plasma dilution induced by a fluid challenge is higher than in the capillaries, and that difference is diminished when the fluid challenge is given to more hydrated individuals. Our objective was to test that hypothesis by evaluating the veno-capillary dilution difference during mVLT in subjects with different hydration status.

Materials and methods: In a prospective randomized crossover study, three mini fluid challenges were given to 12 healthy volunteers on two occasions. The subjects were either dehydrated or hydrated before the experiments.

Results: In dehydrated subjects only, capillary plasma dilution was significantly lower than venous ($P = 0.015$, 0.005 and 0.006) after each mini fluid challenge.

Conclusions: Veno-capillary dilution difference during mVLT depends on the hydration status. The mVLT method could possibly discriminate between the different states of hydration.

* *Corresponding author at*: Section of Anaesthesiology and Intensive Care, Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset, SE-118 83 Stockholm, Sweden. Tel.: +46 706095763; fax: +46 86162202.
E-mail addresses: christer.svensen@sodersjukhuset.se, christer.svensen@ki.se

Peer review under responsibility of Lithuanian University of Health Sciences.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.medici.2014.09.007

1. Introduction

Intravenous fluid administration is a routine practice in anesthesia, surgery, and critical care. Crystalloid solutions are commonly used for rehydration and maintenance purposes. Such solutions are isotonic, have low molecular weight and are distributed throughout the extracellular volume. They can either rapidly be eliminated as urine in healthy, awake and normotensive subjects or accumulate in interstitial tissues, especially during anesthesia, surgery or inflammatory conditions [1–3]. Fluid retention in the circulatory system and fluid shift into tissues may differ because transcapillary fluid movement is affected by many factors such as volume status, integrity of the endothelial barrier or differences in interstitial compliance. This has been investigated in laboratory and animal work [4]. An effort to evaluate the compliance capacity of interstitial tissues has been investigated in human volunteers [5]. Currently, there is no clinically useful method for detecting and quantifying interstitial accumulation of fluid.

As a development of the volume loading test (VLT) [6], we introduce a mini volume loading test (mVLT). It implies calculation of plasma dilution (PD) induced by small volume (mini) fluid challenges to evaluate the state of hydration and possibly detect imminent interstitial edema. The method is based on the transcapillary reflux model that points to differences between PD in different sites of circulation during fluid loading. The transcapillary fluid filtration absorption ratio (FAR) is dependent on multiple factors such as Starling forces, the integrity of the glycocalix layer, the volume status and the expansion of interstitium by fluids (hydration status). The model states that the difference between venous and capillary PD is higher due to a higher FAR when subjects are dehydrated.

The objective of this study was to test the hypothesis that veno-capillary dilution difference, determined both invasively and noninvasively, is higher when the healthy individuals are dehydrated before fluid loading.

2. Materials and methods

2.1. Explanation of the mini volume loading test

A mVLT method consists of mini fluid challenges. These usually consist of 2.5 mL kg^{-1} boluses of crystalloid solutions infused over 5 min followed by 5 min periods without fluid. Hemoglobin samples are used for determining venous (vHb), arterial (aHb) and capillary (cHb) before and after each mini fluid challenge. Hb is used for calculation of plasma dilution – venous (vPD), arterial (aPD) and capillary (cPD). The PDs are further used to calculate the plasma dilution efficacy (PDE) from a single mini fluid challenge – venous (vPDE), arterial (aPDE) and capillary (cPDE). Finally, the plasma dilution efficacy difference (PED) among the Hb measuring sites – arterio-venous (avPED), veno-capillary (vcPED) and arterio-capillary (acPED) – is calculated.

2.1.1. Mathematical equations

The PD is calculated from a mini fluid challenge induced by a change in Hb. Since we are considering the dilution of plasma, we need to adjust for the hematocrit (Hct):

$$PD_i = (Hb \cdot Hbi_i^{-1} - 1) \cdot (1 - Hct)^{-1} \quad (1)$$

where PD_i is the plasma dilution after the mini fluid challenge with the number i, Hb is the initial hemoglobin concentration value obtained before the first mini fluid challenge, Hb_i is the hemoglobin concentration value obtained after the mini fluid challenge number i, and Hct is the initial hematocrit value obtained before the first mini fluid challenge (since the noninvasive hematocrit is not available during the noninvasive determination of PD, the initial hematocrit value is derived by dividing the noninvasive initial hemoglobin concentration by 330, which is the mean value of the normal range for the mean cell hemoglobin concentration).

However, comparison of the PD after repetitive fluid boluses that are only separated by a few minutes cannot fully reflect the differences in intravascular fluid retention because the dilutions overlap. Thus, PDE is used to evaluate the ability of a mini fluid challenge to increase the PD from a preceding mini fluid challenge. The PDE can be calculated as follows:

$$PDE_i = (PD_i + 1) \cdot (PD_{i-1} + 1)^{-1} - 1 \quad (2)$$

where PDE_i is the plasma dilution efficacy of the mini fluid challenge number i, PD_i is the plasma dilution at the end of the mini fluid challenge number i, and PD_{i-1} is the plasma dilution at the end of the preceding mini fluid challenge.

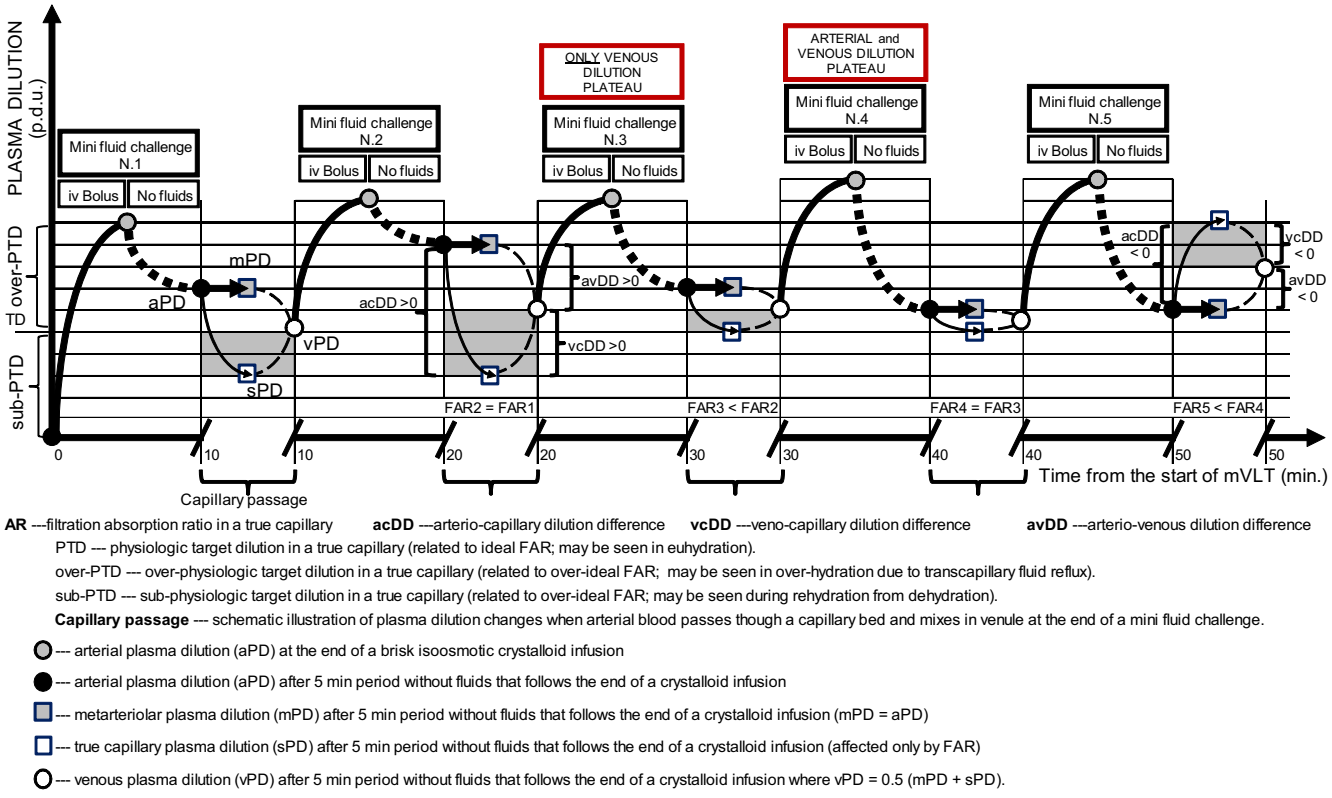
The PED between the Hb measuring can be calculated as follows:

$$vcPED_i = vPDE_i - cPDE_i \quad (3)$$

where $vcPED_i$ is the veno-capillary plasma dilution efficacy difference of the mini fluid challenge number i, $vPDE_i$ is the venous plasma dilution efficacy of the mini fluid challenge number i, and $cPDE_i$ is the capillary plasma dilution efficacy of the mini fluid challenge number i. The avPED and acPED are calculated in a similar way.

2.1.2. Transcapillary reflux model

Transcapillary reflux model explains the differences between PD during mVLT at various sites of circulation by relating them to different states of hydration. According to this model, a difference between vHb and cHb (here called the gap) could be explained in two ways. The Fahraeus effect [7] related constituent is constant because it is related to changes of blood viscosity when it enters vessels with a lower inner radius. However, it applies only to metarteriole because the inner radii of true capillaries allow the passage of only one erythrocyte at a time. Hence, the hematocrit cannot be influenced by the Fahraeus effect. However, the Hb in true capillaries (sHb) is affected by the transcapillary fluid exchange. Thus, another constituent of the gap is dependent on the FAR. It changes due to the shifts of transcapillary fluid movement. The Hb in metarteriole (mHb) is not affected by the FAR since these capillaries are simply connections between arteries and veins (arterio-venous shunts). Thus, the PD induced by a mini fluid challenge is equal in a large artery and a metarteriole, but it may be different in corresponding veins due to the influx of blood from true capillaries. Fig. 1 shows a simplified outline of PD trends during a simulated five mini fluid challenges. The aPD and vPD induced by the mini fluid challenge decrease and reach



AR ---filtration absorption ratio in a true capillary **acDD** ---arterio-capillary dilution difference **vcDD** ---veno-capillary dilution difference **avDD** ---arterio-venous dilution difference

PTD --- physiologic target dilution in a true capillary (related to ideal FAR; may be seen in euhydration).

over-PTD --- over-physiologic target dilution in a true capillary (related to over-ideal FAR; may be seen in over-hydration due to transcapillary fluid reflux).

sub-PTD --- sub-physiologic target dilution in a true capillary (related to over-ideal FAR; may be seen during rehydration from dehydration).

Capillary passage --- schematic illustration of plasma dilution changes when arterial blood passes though a capillary bed and mixes in venule at the end of a mini fluid challenge.

--- arterial plasma dilution (aPD) at the end of a brisk isoosmotic crystalloid infusion

--- arterial plasma dilution (aPD) after 5 min period without fluids that follows the end of a crystalloid infusion

--- metarteriolar plasma dilution (mPD) after 5 min period without fluids that follows the end of a crystalloid infusion (mPD = aPD)

--- true capillary plasma dilution (sPD) after 5 min period without fluids that follows the end of a crystalloid infusion (affected only by FAR)

--- venous plasma dilution (vPD) after 5 min period without fluids that follows the end of a crystalloid infusion where vPD = 0.5 (mPD + sPD).

Fig. 1 – A model of the dilution plateau observed during the mVLT fluid protocol. The graph shows a theoretical relationship between changes of transcapillary fluid filtration absorption ratio (FAR) and plasma dilution (PD), as well as its derivative variables during the five mini fluid challenges. The 3rd mini fluid challenge indicates venous dilution non-responsiveness (venous plateau) because only vPD is equal to the values seen after the preceding (2nd) mini fluid challenge. The 4th mini fluid challenge indicates total dilution non-responsiveness (arterial and venous plateaus) because both aPD and vPD are equal to the values seen after the preceding (3rd) mini fluid challenge. The net fluid extravasation is equal to the infused volume. This may indicate imminent interstitial edema. The fifth mini fluid challenge is an indication of transcapillary reflux where venous blood is more diluted than arterial because of an influx of more diluted blood from true capillaries. Thus, in contrast to the first four mini fluid challenges, the avDD, acDD and vcDD values are negative. (See Appendix A for the more detailed explanation of this figure).

a value close to nil (a dilution plateau) after the third and fourth mini fluid challenges. This is an indication that the net fluid extravasation is equal to the net volume of the infused fluid. The vPD is lower than the aPD because of an influx of less diluted blood from the true capillaries. Thus, the fluid infusion is no longer contributing (not any longer efficacious) in diluting the blood at this point. The fifth mini fluid challenge is equivalent to the first two challenges. The increase of aPD, however, is lower than the increase of vPD because of an increased flux of interstitial fluid into capillaries (a transcapillary reflux). This in turn is dependent on a significant decrease in FAR. This may be a first indication of a release of edema. Most importantly, the avDD, acDD and vcDD values have changed from positive to negative during the mVLT. The PED variables are more indicative for monitoring of these trends. Fig. 2 shows an outline of PED trends during the corresponding five mini fluid challenges. The related equation $0 < vcPED < acPED$ is associated with rehydration during recovery from dehydration, $vcPED = acPED = 0$ is associated with imminent interstitial edema and $0 > vcPED > acPED < 0$ is associated with transcapillary reflux. It may appear during edema release in overhydration, or after administration of a diuretic medication. The trend of PED is therefore very important for the mVLT.

2.2. *The protocol*

This was a prospective randomized crossover study in healthy young volunteers conducted at the Department of Anaesthesiology and Intensive Care at Södersjukhuset, Stockholm, Sweden. Ethical permit (no. 2009/1187-31/1) was granted by the Regional Ethical Board of Stockholm. Twelve healthy young volunteers were enrolled in 2009 and followed the CONSORT diagram for studies (CONSORT Fig. 3). The subjects were 11 females and one male with mean age 29 (SEM 1.5). They were on the average 71 kg (SEM 3). Each of them, in a random order, underwent two fluid experiments separated by at least 14 days. They were allocated to two groups. The experiment started at 07:00 in the morning. The subjects had no breakfast in the morning of the experiments. One group was considered

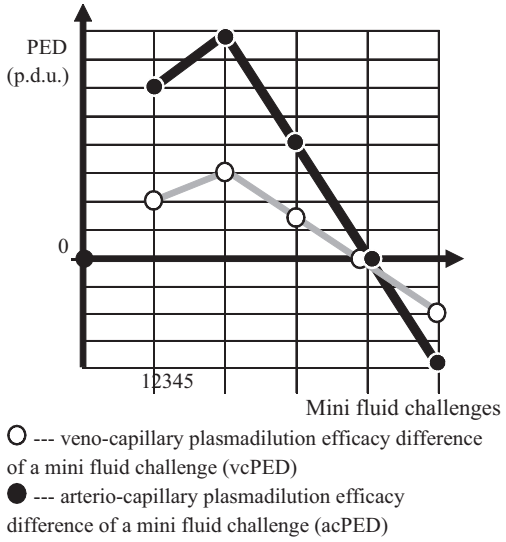


Fig. 2 – Plasma dilution efficacy difference (PED) for the detection of transcapillary reflux during mVLT: the model. The graph shows theoretical PED trends during five mini fluid challenges. The arterio-capillary and veno-capillary PED were derived from arterial, venous and capillary PD variables depicted in Fig. 1. The PED changes from positive to negative when transcapillary fluid reflux occurs, presumably signaling of imminent edema. The veno-capillary PED is lower than arterio-capillary PED only until the transcapillary reflux occurs.

dehydrated (DEH) due to an overnight fast and the other group was considered hydrated (HYD) after drinking 5 mL kg^{-1} of water 45 min before the 1st fluid bolus.

On arrival monitors for ECG, pulse-oximetry and non-invasive blood pressure measurement were applied. In addition, the measuring of cardiac stroke volume by means of bioimpedance based noninvasive (PhysioFlow™, Bristol, PA) technique was applied. A spectrophotometric adhesive sensor R2-25 (Masimo Inc., Irvine, CA) was used for non-invasive measurements of Hb (SpHb®, Masimo Inc., Irvine, CA). It was placed on the nail of a middle finger and connected to a Radical-7 Pulse CO-Oximeter (Masimo Inc., Irvine, CA). The averaging time for SpHb was set to ''short'', and then switched to ''venous'' mode. Intravenous line for blood sampling was set in the same arm. An intravenous line was placed in an independent arm. Oxygen was provided through a facemask.

Subjects were closely observed while remaining still in a supine position for 45 min before the start of infusion. An mVLT was provided to both groups. This test consisted of three 2.5 mL kg^{-1} boluses of acetated Ringer's followed by the 5 min periods without fluids (3 steady states) during the mVLT. The vHb was immediately determined before the first bolus and after each of the three mini fluid challenges. The first blood samples were analyzed in a laboratory by a CO-Oximetry analyzer (COULTER®, Brea, CA) and the rest were analyzed with a bed-side hemoglobinometer (HemoCue®, Ängelholm, Sweden). Noninvasive SpHb values were simultaneously recorded manually along with the blood sampling. In this study, the SpHb is labeled as *capillary hemoglobin* (cHb) because it is measured in the capillaries under a fingernail.

2.2.1. *Statistical methods*

A Kolmogorov–Smirnov test was used to evaluate the pooled data for normality, and the data is presented as the mean ± SEM for the normally distributed data and as the median, 25th and 75th percentiles for the nonnormally distributed data. The mean values were compared using paired *t* test. The Wilcoxon signed rank test was applied to nonnormally distributed data when appropriate. 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).

3. Results

All subjects completed the study. In the dehydrated subjects the three observations of vPD (0.058 [0.039–0.105], 0.079 [0.056–0.114] and 0.097 [0.068–0.116]) induced by the three mini fluid challenges was higher than cPD (0.006 [0.000–0.037], –0.006 [–0.486 to 0.036], and 0.032 [–0.019 to 0.079], $P = 0.015$, 0.005 and 0.006, respectively) (Fig. 4). An important observation was that the mean vcPED became negative in the 2nd mini fluid challenge for the hydrated group, while this occurred in the 3rd mini fluid challenge dehydrated group (Fig. 5). The vcPED decreased significantly during the mVLT only in the dehydrated subjects (from 0.069 ± 0.021 (SEM) in the 1st mini fluid challenge to –0.019 ± 0.013 (SEM) in the 3rd ($P = 0.015$). There was no change in vcPED during the mVLT in hydrated subjects. We used the procedure defined unit (p.d.u.) for the estimates of PD and its derivatives because there are no consensus units for these variables.

4. Discussion

The aim of this paper was to investigate the differences between invasive venous and noninvasive capillary plasma dilutions induced by the stepwise crystalloid infusion in healthy individuals with different baseline hydration status. As shown in Fig. 4, the mVLT used three relatively small (mini) fluid challenges, each consisting of a 2.5 mL kg^{-1} crystalloid bolus followed by 5-min period without fluid. The hypothesis suggested by the physiology-based transcapillary reflux model was confirmed. Venous plasma dilution was significantly higher than the corresponding capillary plasma dilution in dehydrated subjects only.

We have tried to quantify the level of hydration status by determining the change in plasma dilution induced by a stepwise crystalloid infusion. Our transcapillary reflux model has also introduced a new concept to indicate where the administered fluid is no longer efficacious but instead starts to contribute to interstitial edema. This occurs when net fluid extravasation is equal to the net volume that enters circulation. Thus, the invasively and noninvasively measured plasma dilution induced by a mini fluid challenge becomes negligible in the part of the PD trend which is labeled as dilution plateau

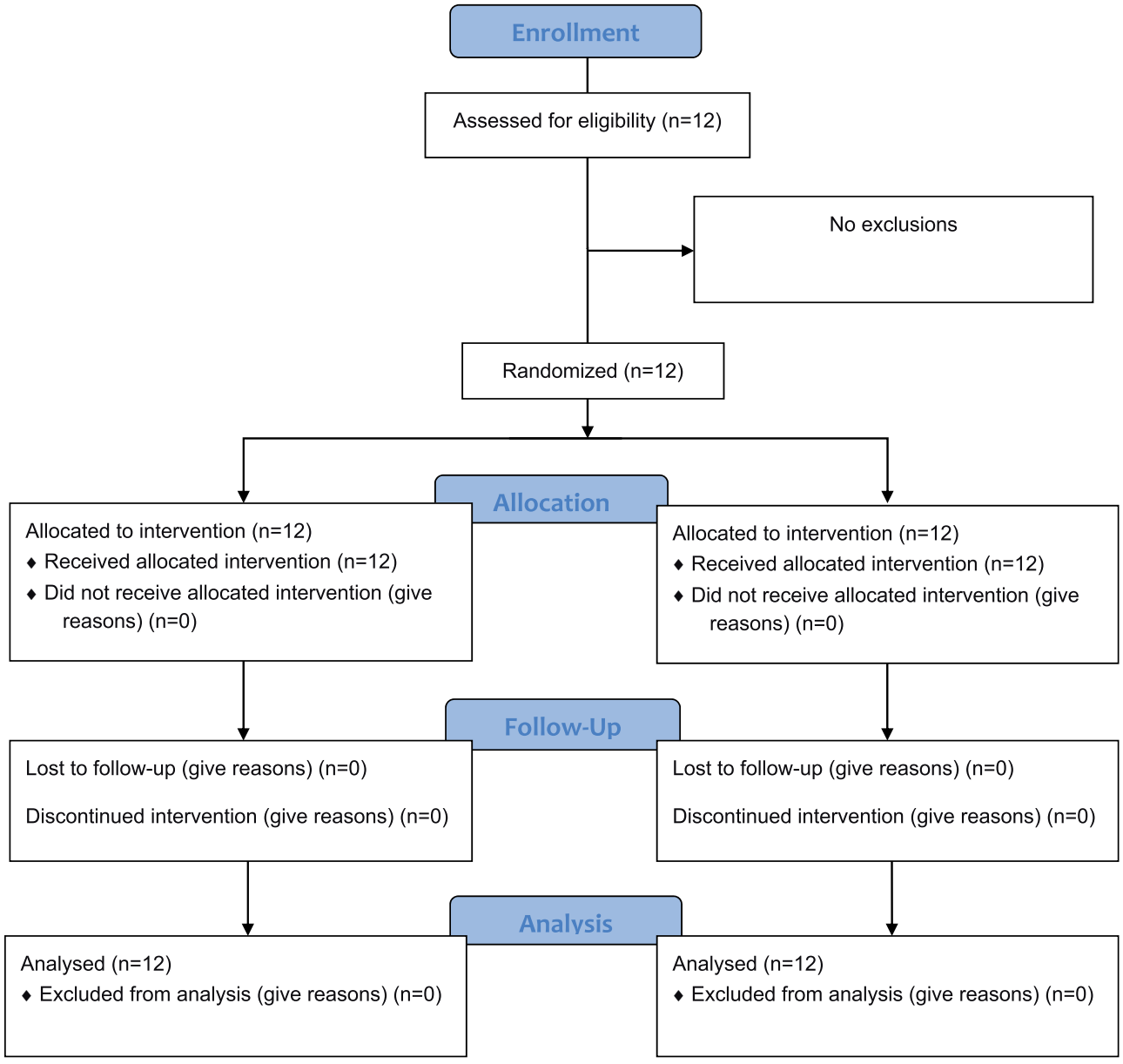


Fig. 3 – CONSORT diagram.

(Fig. 1; see Appendix A). According to the model, this would be a time point when no more fluid should be given to prevent interstitial tissue from being unnecessarily overfilled. The increasing absorption of excessive interstitial fluid into capillaries in that situation leads to capillary PD becoming higher than arterial or venous PD. The calculated arterio-capillary and veno-capillary plasma dilution efficacy differences will then be negative (Fig. 2). Our findings indicate that during a stepwise administration of a crystalloid, this occurred after the 2nd mini fluid challenge in hydrated while it occurred only after the 3rd challenge in dehydrated subjects (Fig. 5).

Venous plasma dilution plateau per se is not fully indicative of fluid status. The reason is that many factors affect the rate of intravascular fluid retention. The increase of transcapillary fluid filtration absorption ratio and an increase in renal elimination would therefore have an important and similar impact on venous plasma dilution during mVLT. Thus, an ''optimized'' hydration status (optimal interstitial fluid expansion) is not necessarily equivalent to the hydration nonresponsiveness presenting as a dilution plateau. Changes of transcapillary fluid equilibration would therefore be more specific to changes of interstitial fluid accumulation. The transcapillary fluid exchange between blood and tissues is regulated by several factors such as the integrity of the endothelial glycocalyx, the net transcapillary pressure, the interstitial fluid compliance, and the lymphatic flow [1–3,8,9]. It would be an overwhelming task to monitor all of these in a model with such high complexity. Therefore, a reasonable approximation of changes in transcapillary fluid equilibration can be obtained from evaluating changes of capillary plasma dilution, which presumably can be derived from non-invasively measured total hemoglobin [10]. In this study, we used a

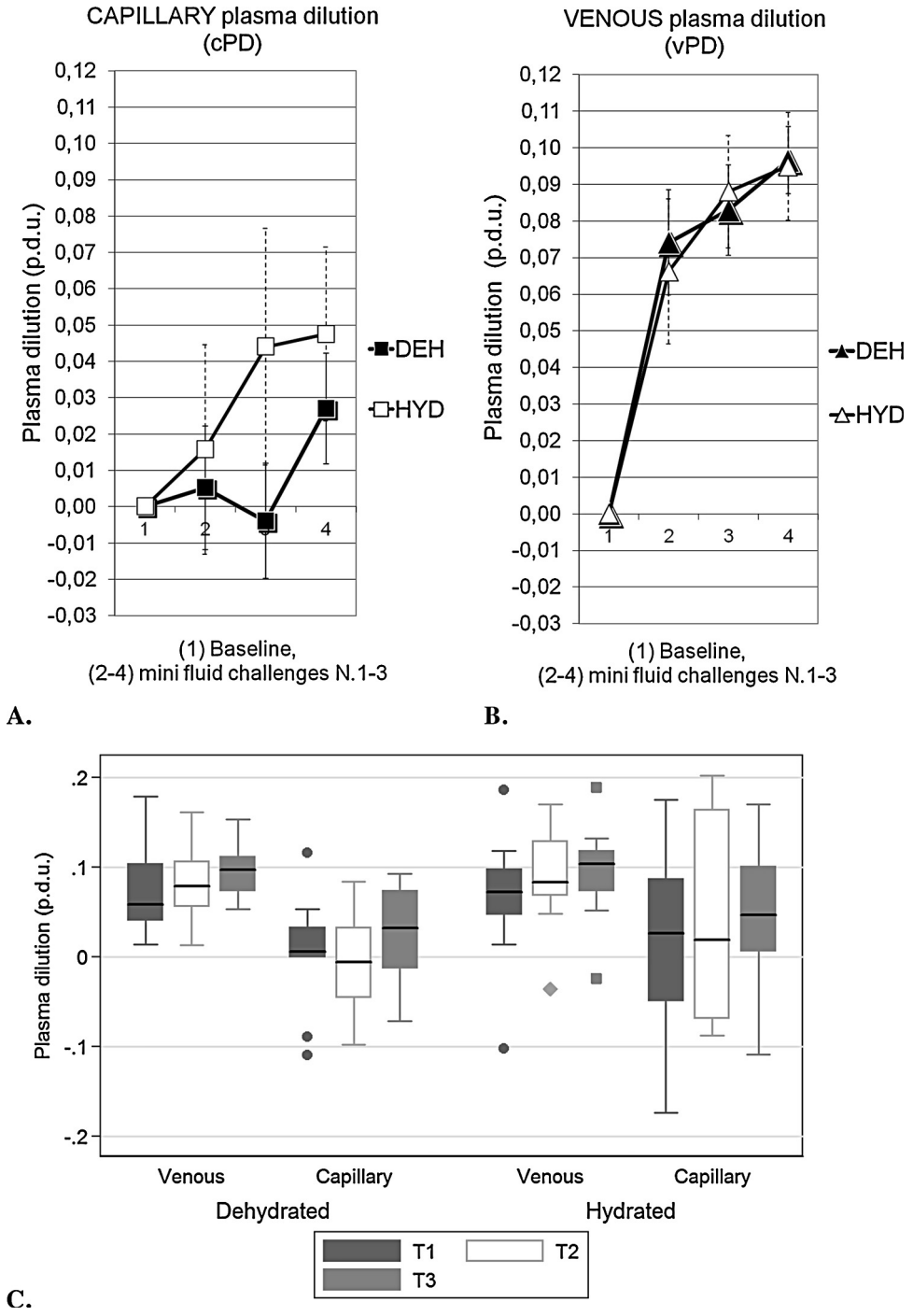


Fig. 4 – The plasma dilution trends during mVLT on two occasions in healthy volunteers. The figure shows non-invasively (capillary) and invasively (venous) determined plasma dilution (cPD and vPD, respectively) at four data points in hydrated (HYD) and dehydrated (DEH) healthy volunteers. Data point 1 is at the baseline before the first bolus, and data points 2–4 are after the 5 min periods without fluids that followed each of the three 2.5 mL kg^{-1} crystalloid boluses in the three mini fluid challenges. (A) The non-invasive capillary PD (cPD). (B) The invasive venous PD (vPD) in HYD and DEH groups. The data are presented as the means ± SEM. (C) The PD variables in the boxplot for the comparison of cHb and vPD that are nonnormally distributed.

noninvasive hemoglobinometer, the Radical 7 device that calculates SpHb in the capillaries of derma from under the finger nail. We hypothesized that the SpHb is equivalent to the cHb suitable for the mVLT method. This is because SpHb is not a conventional directly measured hemoglobin concentration but a variable which is calculated from the net light absorbance in a segment of a capillary bed. According to the anatomy of microcirculation in derma under the finger nail, the true

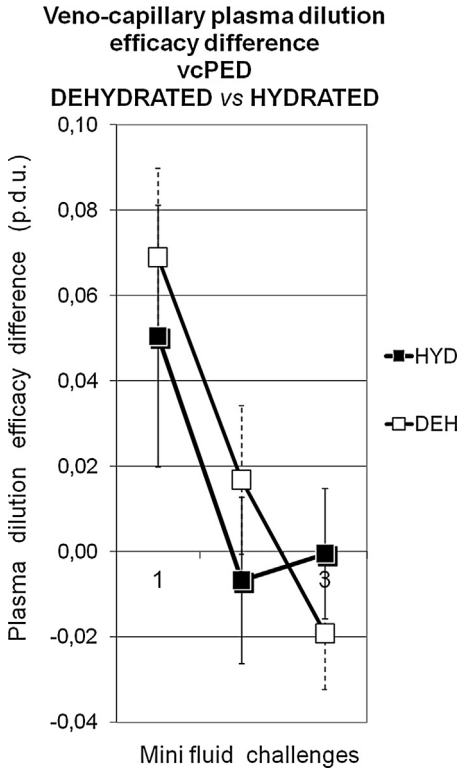


Fig. 5 – The difference between venous and capillary plasma dilution efficacy during mVLT on two occasions in healthy volunteers. The figure shows veno-capillary plasma dilution efficacy difference (vcPED) of the three mini fluid challenges in hydrated (HYD) and dehydrated (DEH) healthy volunteers. Data points 1–3 were after the 5 minute periods without fluids that followed each of the three 2.5 mL kg^{-1} crystalloid boluses in the three mini fluid challenges. The vcPED became negative earlier in better hydrated individuals. The negative vcPED presumably signifies transcapillary reflux and imminent edema. The data are presented as the means ± SEM.

capillary flow is prevailing over metarteriolar. Thus, hemoglobin in true capillaries is the main determinant of SpHb value. We used SpHb as a surrogate for the cHb in calculating the cPD, cPDE and vcPED. By evaluating and comparing the capillary and venous variables in a stepwise fluid loading protocol, it was possible to determine which subjects were less hydrated before the mVLT. The negative vcPED indicates 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.

However, the present study has several limitations. The arterial variables were not obtained. The method and the transcapillary reflux model are based on physiological reasoning without any validation of what actually happens in the pertinent tissues because we did not measure either interstitial pressure or volume. However, the interstitial fluid compliance of the derma is similar to that of skeletal muscles [9], and taken together these tissues account for the largest part of expandable tissues in the body. Thus, a local release of the interstitial fluid into the circulation can be considered as fairly equivalent to the function of the entire interstitium in the body. The previously reported negative arterio-venous dilution difference observed soon after a brisk crystalloid infusion [11] supports our concept of transcapillary reflux. Presumably, detection of transcapillary fluid reflux (where vcPED < 0) or hydration non-responsiveness (dilution plateau) during the mVLT (Figs. 1 and 2) suggests that the whole-body fluid status could possibly be optimized.

The mathematical model deploys variables that are derived from Hb measures, and thus evaluation of their trends may be challenged by measurement errors, especially noninvasive. The error is assumed to be normally distributed with a mean of 0 and an SD of 1% of the error-free vHb values. The vHb measurements with errors may be generally not far from the error-free measurements. The resulting vPD line, however, may have a swinging appearance, but it will still be suitable for trending. In contrast, the vPDE curve may look more noisy by random. The small measurement errors may result in large errors when the vPDE is calculated from repetitive vHb measurements. The same sort of errors would occur for noninvasively measured Hb and its derivatives (cPD and cPDE). Obviously, the calculated curve of vcPED would show minimal resemblance to the error-free curves shown in Figs. 2 and 4. Polynomial trend lines however can solve that problem.

Our results encourage further validation of this method in animal studies and clinical trials.

5. Conclusions

Veno-capillary dilution difference during mVLT depends on the hydration status. The mVLT method allows discrimination between the different states of hydration.

Conflict of interest

C.S. receives lecture fees from Fresenius KABI, Uppsala, Sweden, and has intermittently been a member of the Masimo Inc. Advisory Board.

A.A. has received a consultant's fee and travel funding from Masimo Corporation (Irvine, CA, USA). Also, A.A. received an honorarium from Masimo Corporation for an expert witness report.

Acknowledgement

We are thankful to Mona-Britt Divander, RN, for her input in data collection.

Appendix A

The extended explanation of the transcapillary reflux model and Fig. 1

During mVLT fluid protocol the aPD is measured at the initial baseline and after the 5 min period without fluid that

follows each fluid bolus (Fig. 1). Since arterial and venous plasma dilutions (aPD and vPD) increase in the first two fluid challenges, it is an indication that the body responds to fluid (hydration responsiveness). The vPD increases less than aPD because venous blood is a mixture of metarteriolar and true capillary flows. The PD in metarteriole (mPD) is equal to aPD, but the true capillary PD (sPD) is independent from aPD. The sPD changes are solely FAR dependent. Thus, since FAR is equal after the first two mini fluid challenges, the fluid influx into the true capillaries makes the vPD increase lower than arterial because vPD = 0.5 (mPD + sPD). The arterio-venous, arterio-capillary and veno-capillary dilution differences (avDD, acDD and vcDD) have therefore increased in the second mini fluid challenge. Thus, avDD, acDD and vcDD values are positive. If a state of dehydration is apparent, the FAR is increased in respect to individual physiologic target value which is present in the state of normohydration. The sPD in the first two mini fluid challenges is therefore lower than optimal leading to a subphysiologic target dilution (sub-PTD) in true capillaries. The third mini fluid challenge indicates a partially nonresponsive situation (partial hydration non-responsiveness) because aPD has increased but vPD is equal to the value seen after the preceding mini fluid challenge (venous dilution plateau). The FAR, however, has increased to the physiologic target value, and sPD has therefore reached its optimal value – the physiologic target dilution (PTD) in true capillaries. The avDD, acDD and vcDD values have decreased but remain positive. The fourth mini fluid challenge indicates a totally non-responsive situation (total hydration non-responsiveness) because aPD and vPD are equal to the values seen after the preceding mini fluid challenge (arterial and venous dilution plateau). This means that the net fluid extravasation is equal to the infused volume. The FAR and sPD remain at their physiologic target values. That state may signify imminent interstitial edema. The fifth mini fluid challenge is an indication of hydration responsiveness similar to the first two mini fluid challenges, but the increase of aPD is, however, lower than an increase of vPD. This is because the sPD and FAR have significantly increased above the physiologic target values, and thus venous blood becomes more diluted than arterial because of an influx of more diluted blood from true capillaries. Thus, in contrast to first four mini fluid challenges, the avDD, acDD and vcDD values are negative.

REFERENCES

[1] Huxley VH, Scallan J. Lymphatic fluid: exchange mechanisms and regulation. J Physiol 2011;589(Pt 12):2935–43.

[2] Negrini D, Moriondo A. Lymphatic anatomy and biomechanics. J Physiol 2011;589(Pt 12):2927–34.

[3] Wiig H. Pathophysiology of tissue fluid accumulation in inflammation. J Physiol 2011;589(Pt 12):2945–53.

[4] Oien AH, Justad SR, Tenstad O, Wiig H. Effects of hydration on steric and electric charge-induced interstitial volume exclusion – a model. Biophys J 2013;105(5):1276–84.

[5] Svensen C, Drobin D, Olsson J, Hahn RG. Stability of the interstitial matrix after crystalloid fluid loading studied by volume kinetic analysis. Br J Anaesth 1999;82(4):496–502.

[6] Hahn RG, Andrijauskas A, Drobin D, Svensen C, Ivaskevicius J. A volume loading test for the detection of hypovolemia and dehydration. Medicina (Kaunas) 2008;44(12):953–9.

[7] Fåhræus R, Lindqvist T. The viscosity of the blood in narrow capillary tubes. Am J Physiol – Legacy Content 1931;96 (3):562–8.

[8] Aukland K, Reed RK. Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. Physiol Rev 1993;73(1):1–78.

[9] Wiig H, Rubin K, Reed RK. New and active role of the interstitium in control of interstitial fluid pressure: potential therapeutic consequences. Acta Anaesth Scand 2003;47 (2):111–21.

[10] Sjötrand F, Rodhe P, Berglund E, Lundström N, Svensen C. The use of a noninvasive hemoglobin monitor for volume kinetic analysis in an emergency room setting. Anesth Analg 2013;116(2):337–42.

[11] Svensen CH, Rodhe PM, Olsson J, Borsheim E, Aarsland A, Hahn RG. Arteriovenous differences in plasma dilution and the distribution kinetics of lactated Ringer's solution. Anesth Analg 2009;108(1):128–33.