Revised Evaluation of Hemodilution Response in the Semi-Closed Loop Infusion System

Vytautas Markevicius[1], Darius Cincikas[2], Narunas Porvaneckas[3], Edgaras Stankevicius[4], Dangirutis Navikas[1], Darius Andriukaitis[1], Jurate Sipylaite[2], Saule Svediene[2], Valentinas Uvarovas[3], Igoris Satkauskas[2], Giedrius Kvederas[3], Algimantas Valinevicius[1], Mindaugas Zilys[1], Audrius Andrijauskas[2]

[1]*Department of Electronics Engineering, Kaunas University of Technology, Studentu St. 50–418, LT-51368 Kaunas, Lithuania*

[2]*Vilnius University Faculty of Medicine, Clinic of Anaesthesiology and Intensive Care, Siltnamiu St. 29, LT-04130 Vilnius, Lithuania*

[3]*Vilnius University Faculty of Medicine, Clinic of Rheumatology, Orthopaedics-Traumatology and Reconstructive Surgery, Siltnamiu St. 29, LT-04130 Vilnius, Lithuania*

[4]*Institute of Physiology and Pharmacology, Lithuanian University of Health Sciences, A. Mickeviciaus St. 9, LT–44307 Kaunas, Lithuania*

audrius.andrijauskas@mf.vu.lt

***Abstract*—A mini volume loading test (mVLT) method is used for decision making in our prototype semi-closed loop infusion system (SCLIS). The mVLT fluid protocol consists of hemodilution response-guided mini fluid challenges. Each mini fluid challenge (MFC) consists of a 2.5 ml kg^{-1}–5 ml kg^{-1} crystalloid bolus infused over 2 min–5 min and followed by a 5 min period with no fluids. Arterial plasma dilution efficacy (aPDE) of a MFC is calculated from invasively measured hemoglobin (aHb) before and after each MFC. Capillary plasma dilution efficacy (*cPDE*) is calculated from non-invasively measured hemoglobin (SpHb). The zero or negative arterio-capillary plasmadilution efficacy difference (*acPED* ≤ 0 p.d.u.) is an indication of *hemodilution non-response* and *imminent edema*. However, it requires both invasive and non-invasive hemoglobin measurements. A non-invasive assessment of hemodilution response within the mVLT method would increase its practical application and reduce costs further enhancing its applicability in the SCLIS. This possibility exists if the *cPDE* could reliably predict the *acPED* value or the hemodilution *response* (the presence of *acPED* within a range of > 0) or *non-response* (*acPED* ≤ 0).**

We report a retrospective observational study in an elective total knee arthoplasty (TKA) setting. The 2.5 ml kg^{-1} boluses were used in six MFCs in both pre- and post-operative mVLT sessions. The primary objective was to assess the accuracy of *cPDE* in predicting the hemodilution *response* using the *receiver operating characteristic* (ROC) curve and *gray zone* approaches. Our secondary objective was to investigate the feasibility of a statistical optimization method (SOM) in predicting the *acPED*.

The analysis included 480 paired values of *cPDE* and *acPED*. The best cut-off value for *cPDE* was 0.015 p.d.u. (specificity = 0.84, sensitivity = 0.90). The *gray zone* identified a range of *cPDE* values between 0.013 and 0.028 (p.d.u.) for which the hemodilution response could not be indicated reliably. The 14 % of the *cPDE* values were in this range.

The non-invasive evaluation of hemodilution response is acceptably accurate in the perioperative TKA setting. The mVLT algorithm within our prototype SCLIS was upgraded by implementing the results of the present study.

***Index Terms*—ACDSS, SCLIS, mVLT, hemoglobin, fluids.**

I. INTRODUCTION

A mini volume loading test (mVLT) is used for decision making in a semi-closed loop infusion system (SCLIS) [1]–[5]. The mVLT fluid protocol implies hemodilution guided mini fluid challenges. These are 2.5 ml kg^{-1}–5 ml kg^{-1} boluses infused over 2 min–5 min, each followed by a 5 min period with no fluids. The assessment of hemodilution response requires hemoglobin measures before and after each mini fluid challenge (MFC). Hemoglobin in arteries (invasive, *aHb*) and capillaries (non-invasive, *SpHb*) are used to calculate the arterial and capillary plasma dilution efficacies (*aPDE* and *cPDE*, respectively) and arterio-capillary plasmadilution efficacy difference (*acPED*) [1], [3]. Based on observations in healthy volunteers [1] and patients [2], a *transcapillary reflux model* suggests that *acPED* ≤ 0 p.d.u. is an indication *hemodilution non-response* and *imminent edema*. This signifies that fluid loading should be stopped. However, the need for invasive measurements is a major drawback in the clinical implication of our novel automated clinical decision support system (ACDSS) and the SCLIS [3]–[5]. A solely non-invasive assessment of hemodilution response would be possible if the *cPDE* could reliably predict the *acPED* value or the hemodilution *response* (the presence of *acPED* value within a range of *acPED* > 0) or *non-response* (*acPED* ≤ 0).

The primary objective was to assess the accuracy of *cPDE* in predicting the hemodilution *responsiveness* using the *receiver operating characteristic* (ROC) curve and *gray*

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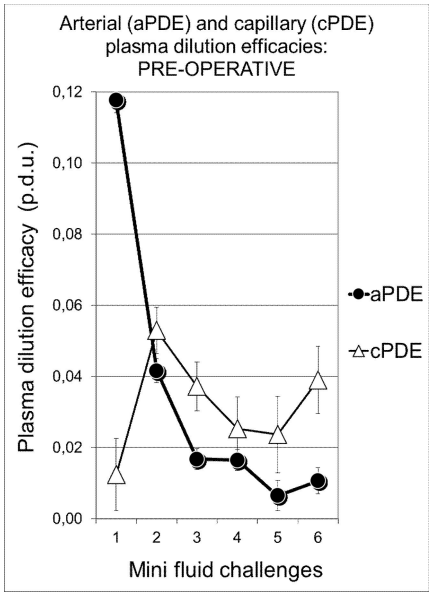
zone approaches [6]. The secondary objective was to investigate the feasibility of a statistical optimization method (SOM) in predicting the *acPED* using the measured *cPDE*.

II. MATERIALS AND METHODS

We retreived and retrospectively analysed data from our previous randomized controlled trial (Clinicaltrials.Gov, identifier: NCT01355900) in patients who had elective primary total knee arthroplasty (TKA) surgery [2], [7]. The adhesive spectrophotometric sensor (ReSposable R2-25a; Masimo Inc., Irvine, CA) connected to the Radical-7 Pulse CO-Oximeter (Masimo Inc.; software version 7.6.2.1) was used to measure *SpHb*. A radial artery cannula was placed in the same arm on which the sensor was attached. This line was used to extract blood for the analysis of *aHb* by CO-Oximetry (COULTER® LH750, Beckman Coulter Inc., Chicago, IL) with a coefficient of variation ≤ 0.8 %. An antecubital cannula for infusion was placed in the same arm.



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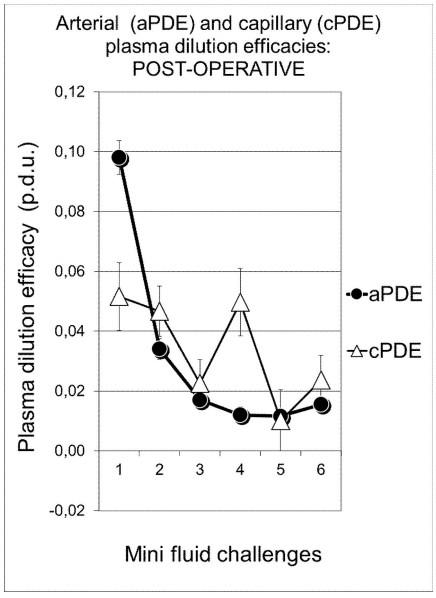


(b)

Fig. 1. The invasively (arterial, aPDE) and non-invasively (capillary, *cPDE*) measured plasma dilution efficacies of six mini fluid challenges. (a) Pre-operative mVLT session, and (b) post-operative mVLT session. Data are presented as means ± SEM.

The stepwise infusion was administered according to a *revised goal directed therapy* (revGDT) protocol consisting of conventional GDT supplemented by the mVLT [2]. The *cPDE* and *acPED* were obtained in 48 subjects who had two mVLT sessions – before the induction of anesthesia (pre-operative session) and again 24 hours later (post-operative). In each mVLT session they received six MFCs with 2.5 ml kg^{-1} boluses of Ringer's acetate solution. The *aHb* and *SpHb* were measured immediately before and after each MFC. These variables were used to calculate *aPDE*, *cPDE* (Fig. 1) and *acPED* (Fig. 2) using the Windows® platform-based software of our prototypes ACDSS and SCLIS [3]–[5].

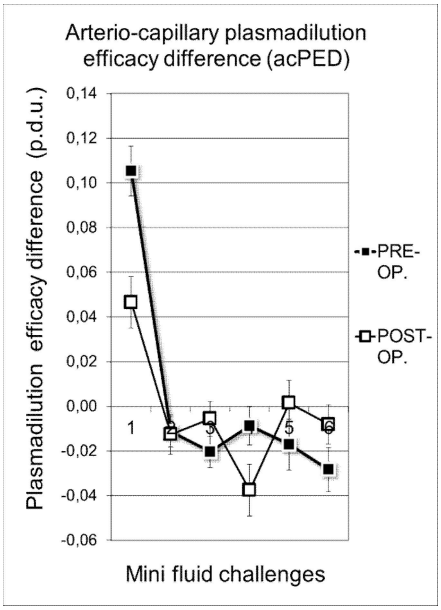


Fig. 2. Arterio-capillary plasmadilution efficacy difference (*acPED*). Differences between invasively (arterial) and non-invasively (capillary) determined plasma dilution efficacies of each of the six mini fluid challenges. Data are presented as means ± SEM.

III. STATISTICAL ANALYSIS

A. Sample Size

As previously suggested [8], assuming that 50 % of MFCs are likely to be hemodilution 'responder' cases, a total of 200 MFCs would be necessary for the reliable determination of the ROC curve and cut-off value. With an aim to perform bootstrapping, we included data from 480 MFCs, a number close to the previously used sample size [9]. We analysed the pooled data related to the last five MFCs in each of the two perioperative mVLT sessions in 48 subjects. Thus, there were 480 paired values of *cPDE* and *acPED* from 96 mVLT sessions. The MFCs were divided in 2 groups according to the *acPED*: the hemodilution responders were defined as *acPED* > 0 and non-responders as *acPED* ≤ 0.

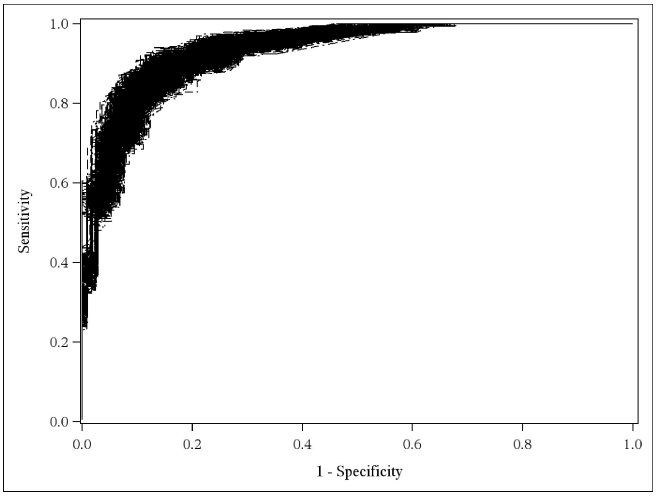
B. Receiver Operating Characteristic (ROC) Curve

A receiver operating characteristic (ROC) curve (Fig. 3) was created to assess the discriminative power of *cPDE* to predict the presence of the *acPED* value within a range of hemodilution non-response (*acPED* ≤ 0). The area under the ROC curve was also created by using bootstraping [9], [10]. It creates multiple samples (1,000) by randomly drawing instances from the study population. Since the unique best

cut-off *cPDE* value cannot be obtained by the bootstrap method, the best cut-off value with the ROC curve was obtained without bootstrap.

C. Threshold and Gray Zone Determination

The gray zone approach [6], [9], [11]–[13] was used to determine a range of *cPDE* for which no conclusion may be drawn concerning hemodilution response. We used a two-step procedure. In the 1st step, the best threshold for *cPDE* was determined in a bootstrapped population. The 95 % CI of the best threshold was defined using the distribution of the thresholds [2]. The best threshold for the ROC curve was defined as that which maximizes the Youden index (sensitivity + specificity −1).



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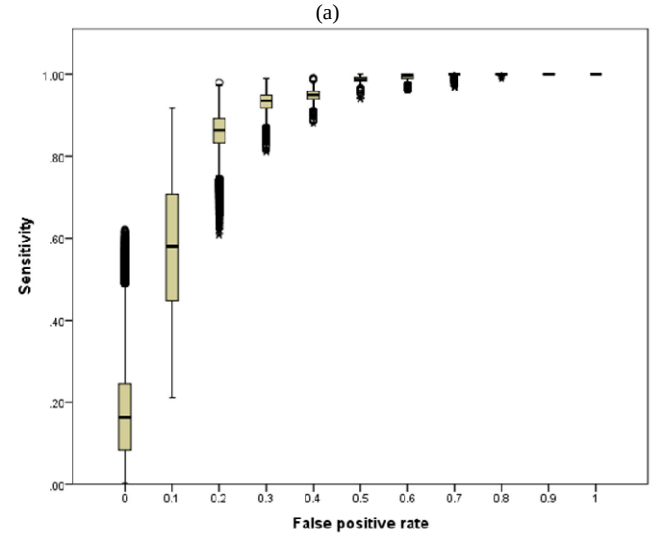
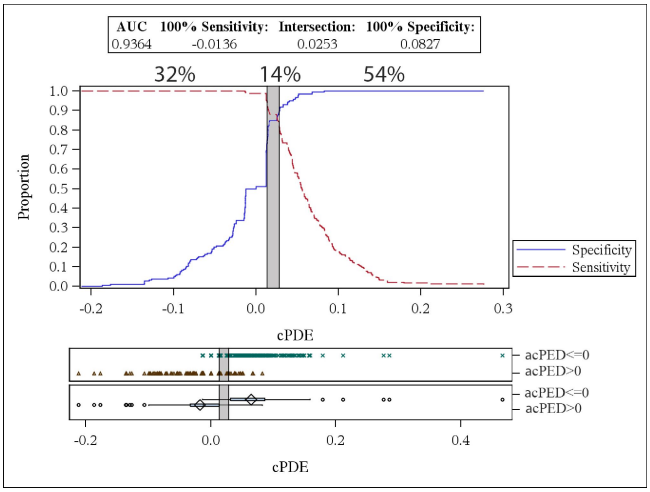


(b)

Fig. 3. Bootstrapping of the receiver operator characteristics (ROC) curves and gray zone determination for capillary plasma dilution efficacy (*cPDE*). (a) Bootstrapped ROC curves, (b) average ROC curves representing the discriminative power of *cPDE* to predict the hemodilution non-response specific arterio-capillary pasmadilution efficacy difference (*acPED* ≤ 0) of a mini fluid challenge. Box plots represent the distribution of the ROC curves for the 1,000 resampled populations.

The aim of the 2nd step was to determine the *cPDE* values for which no conclusive information could be provided. The two-curve representation illustrates this step (Fig. 4(a)). We defined inconclusive values with the sensitivity of < 90 % and specificity < 90 %. The gray zone was defined as the values that comply with a 10 % diagnostic tolerance. When the characteristics of the study population produced a 95 % CI of the best threshold and it is larger than the inconclusive zone, the values obtained during the first step were retained as the gray zone. The two-curve representation illustrates this step (Fig. 4(a)). As previously applied to prediction of fluid responsiveness for the flow-related dynamic target parameters in GDT [9], the optimal threshold for *cPDE* to predict the hemodilution non-response was then determined as the one that minimized the explicit cost ratio (R = 1), which is equivalent to maximizing the Youden's index. By determining this value for all the 1,000 resampled variables, a distribution for the optimal thresholds of the 1,000 samples was obtained. The optimal threshold was 0.015, and the 95 % CI of this distribution (the gray zone) was 0.013–0.027. Considering that the determination of the gray zone is prone to slightly different results between assessments [9], the results of the two approaches were merged as a gray zone from 0.013 to 0.028 (p.d.u.).



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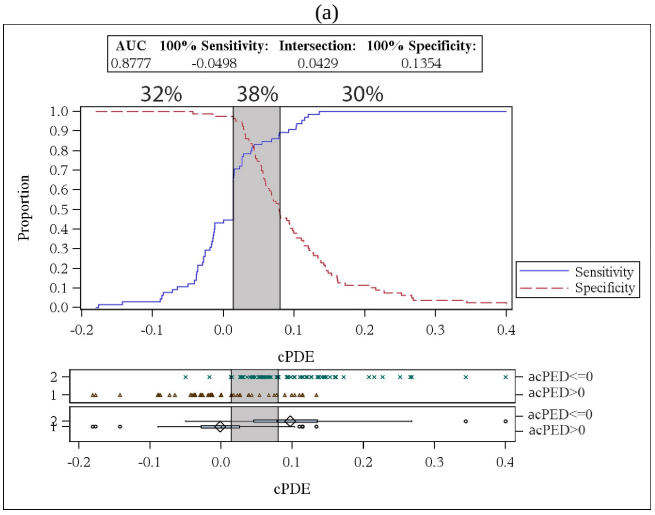

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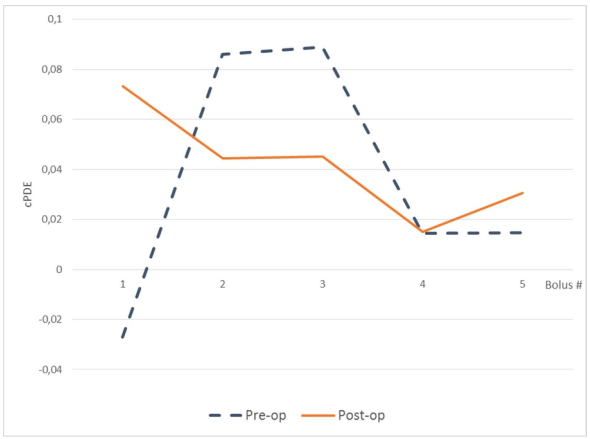
Fig. 4. Gray zone of the capillary plasma dilution efficacy (*cPDE*). Based on the data from (a) 480 mini fluid challenges using the 2.5 ml kg^{-1} boluses, and (b) 144 mini fluid challenges using the 5 ml kg^{-1} boluses of acetated Ringer's solution. Blue curve: sensitivity; red curve: specificity.

We used the SOM as an alternative method for predicting hemodilution response by calculating the predicted *acPED*.

IV. Statistical Optimization Method (SOM)

The SOM was based on the inverse relationship between

cPDE and *acPED* in individual patient's records (Fig. 5).



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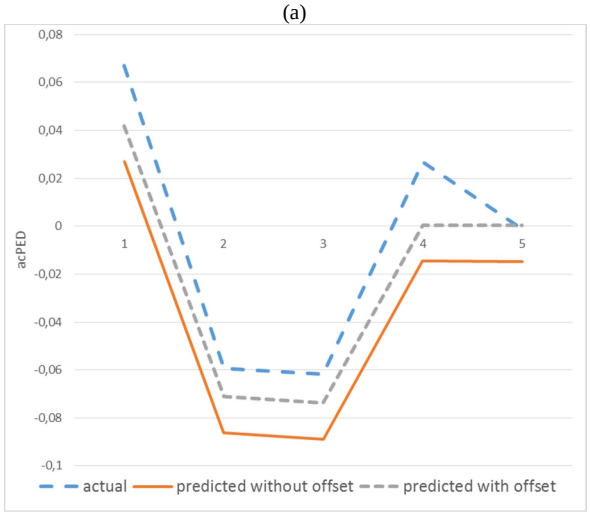

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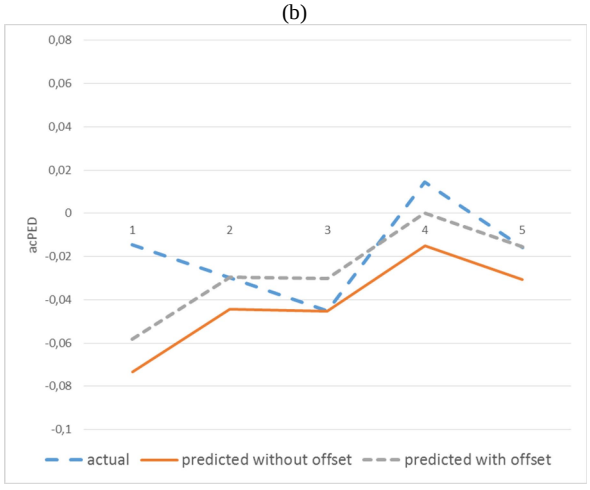


(c)

Fig. 5. One patient's (PID n. 26) trends of hemodilution response in five mini fluid challenges with 2.5 ml kg^{-1} boluses in two perioperative mVLT sessions. (a) The recorded (actual) pre- and post-operative capillary plasma dilution efficacy (*cPDE*), (b) pre-operative, and (c) post-operative actual and SOM predicted, with or without offset, arterio-capillary plasmadilution efficacy difference (*acPED*).

The SOM was applied to calculate the predicted *acPED* value ($acPED_{som}$) from the non-invasively measured (actual) *cPDE* by using two approaches:

1. Invertion of the *cPDE*

$$acPED_{som} = (-cPDE). \quad (1)$$

2. Applying an offset (coefficient)

$$acPED_{of} = K_{of} - cPDE = K_{of} + acPED_{som}, \quad (2)$$

where K_{of} – empiric coefficient determined by the brute-force search method.

The proportion of hemodilution response patterns was compared between the actual (based on the measured *acPED*) and the predicted (based on the calculated $acPED_{som}$ and $acPED_{of}$) hemodilution responses. Chi-square test was used to compare proportions of actual and predicted hemodilution responses in all approaches. The statistical analysis was performed with SAS 9.2 (SAS Institute Inc., Cary, NC). Results are expressed according to variable distributions (mean and 95 % CI) or median [25th; 75th percentiles] for quantitative variables.

V. RESULTS

Data from 48 TKA patients (41 women) were analysed. Subjects were 69.5 (6.0) years old, their height (m) was 1.62 [1.56 to 1.65], weight (kg) was 87.0 [75.5 to 97.5] and the body mass index (BMI, kg/m^2) was 33.5 [31.0 to 35.1]. We analyzed *cPDE* and *acPED* records, 480 values of each. The variables were recorded during five mini fluid challenges in each of the 48 pre- and 48 post-operative mVLT sessions.

A. The ROC Curve and Gray Zone Approaches

The area under the ROC curve with 95 % CI was 0.936 (CI: 0.915 to 0.958). The best cut-off value for *cPDE* was 0.015 (specificity = 0.84, sensitivity = 0.90, positive likelihood ratio = 8.34, negative likelihood ratio = 0.12). The 95 % CI for the best threshold value was 0.013 to 0.027 (p.d.u.). The results of the ROC curve and gray zone approaches were merged and suggested a range of inconclusive *cPDE* values from 0.013 to 0.028 (p.d.u.). The two-curve representation is used to illustrate this approach (Fig. 4(a)). There were 69 (14 %) *cPDE*s in this *gray zone*. There were 184 (38.3 %) *cPDE*s below this threshold. The previous version of mVLT algorithm [2] was then revised by implementing these findings (Fig. 5). The software of our prototype ACDSS within SCLIS [3], [4] was upgraded, accordingly (Fig. 7).

B. Actual Hemodilution Response

The actual *acPED* ≤ 0 (p.d.u.) was found in 296 (61.7 %) of the mini fluid challenges defined as non-responders. There were 82 (34.2 %) responders in pre-operative, and 102 (42.5 %) in post-operative mVLT sessions. There were 158 (65.8 %) non-responders in pre-operative, and 138 (57.5 %) in post-operative sessions.

There was no difference between the proportions of response patterns in pre- and post-operative mVLT sessions: there were 82 pre-operative MFCs with *acPED* ≤ 0 and 158 with *acPED* > 0 while there were 102 post-operative MFCs with *acPED* ≤ 0 and 138 with *acPED* > 0 ($P = 0.074$).

C. SOM Predicted Hemodilution Response

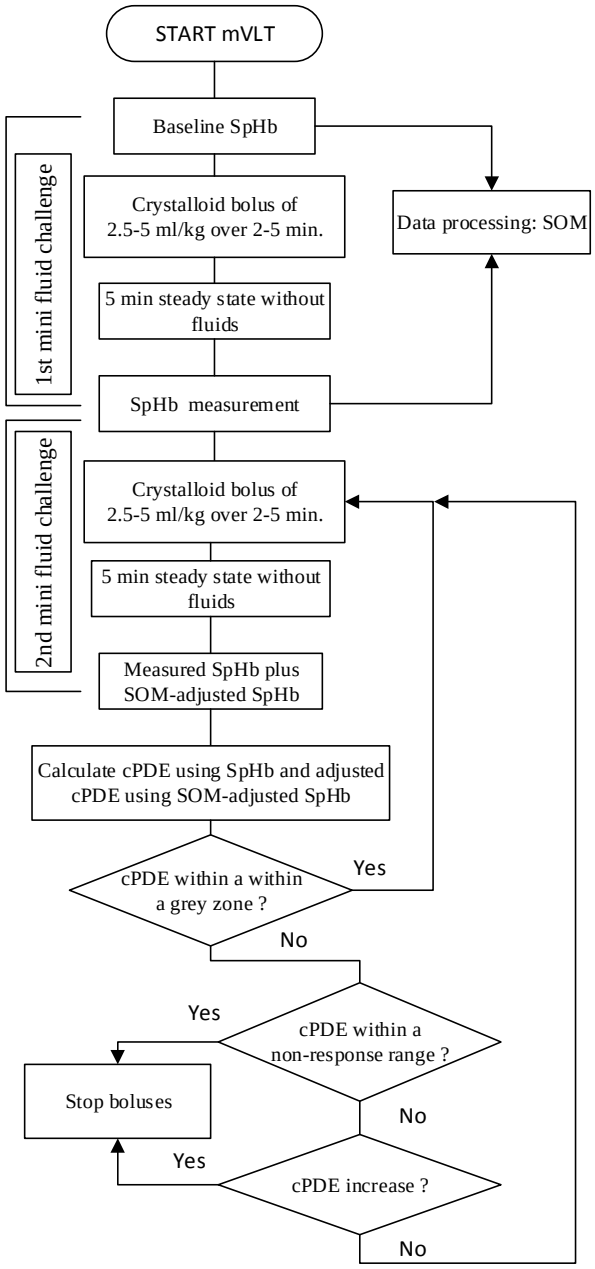
We found that 91 (18.9 %) $acPED_{som}$ was in the range of hemodilution 'response' ($acPED_{som}$ > 0 p.d.u.) and 389 (81.1 %) were in the range of 'non-response' ($acPED_{som}$ ≤ 0).

Also, 181 (37.7 %) $acPED_{of}$ was a responder ($acPED_{of}$ >

0 p.d.u.) and 299 (62.3 %) was non-responder ($acPED_{of} \leq 0$).

D. Actual vs. SOM Predicted Hemodilution Response

The number of actual and SOM predicted ($acPED_{som}$) was $n_1 = 480$ and $n_2 = 480$, and the proportion of response patterns was $p_1 = 184$ and $p_2 = 91$, respectively. There was a statistically significant difference ($P = 3.16*10^{-11}$).



SpHb - non-invasive total hemoglobin (Pulse CO-Oximetry),
cPDE - capillary plasma dilution efficacy,
SOM - statistical optimization method to ameliorate the SpHb-precision related fluctuations in cPDE.

Fig. 6. The mini volume loading test (mVLT) algorithm.

The 0.015 offset ($K_{of} = 0.015$) was used in the calculation of $acPED_{of}$ (2). The number of samples was $n_1 = 480$, $n_2 = 480$, and the proportions of hemodilution response patterns were $p_1 = 184$, $p_2 = 181$, respectively. There was no significant difference between the proportions ($P = 0.849$).

VI. DISCUSSION

This retrospective observational study used the ROC curve and gray zone approaches to examine the accuracy of *cPDE* in the evaluation of hemodilution response to mini fluid challenges with crystalloids in the mVLT protocol.

Our results show the three patterns of the *cPDE* predicted hemodilution responses: negative, inconclusive and positive. The gray zone approach has proposed two cut-offs: subjects with a *cPDE* > 0.028 p.d.u. exclude positive response with near certainty (negative response), whereas one with a *cPDE* < 0.013 p.d.u. will nearly always respond to a MFC (positive response). The *cPDE* between 0.013 and 0.028 (p.d.u.) cannot reliably predict the response (inconclusive response). There were 14 % MFCs with inconclusive *cPDE* predictions of response in two perioperative mVLT sessions.

The area under the ROC curve for *cPDE* (Fig. 3) was the *first approach* in our analysis. The ROC curve was created by using a bootstrap methodology which limits the impact of outliers [9], [10], but the best cut-off value (0.015 p.d.u.) was obtained without bootstrapping. The *second approach* was the *gray zone* method. This approach was proposed to avoid the binary constraint of a "black-or-white" decision of the ROC curve approach that often does not fit the reality of clinical practice [6].

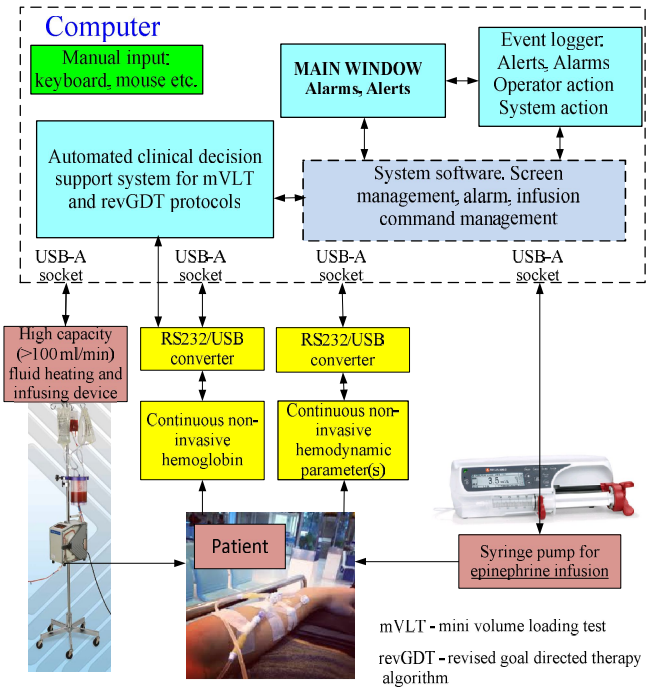


Fig. 7. Revised decision making in an automated clinical decision support system (ACDSS) within the semi-closed loop infusion system (SCLIS).

In this study, we also used a previously proposed ratio of costs (R) defined as R = false positive cost/false negative cost [9]. The R < 1 denotes that not treating a false-negative result is worse than treating a false-positive result which may lead to unnecessary fluid loading [potential risk/fluid overload]. The R > 1 denotes that to treat a false-positive result is worse than to miss a false-negative [9]. The results of both approaches were merged as a gray zone for *cPDE* from 0.013 to 0.028 (p.d.u.). The two-step procedure in the

gray zone approach was used with an aim to minimize the impact of potential outliers.

A difference between the *aPDE* and *cPDE*, the *acPED*, is dependent on the interaction between a transcapillary fluid filtration–absorption ratio (FAR) which affects hemodilution in capillaries, and net fluid elimination which affects the hemodilution in arteries. The *acPED* may decrease when the *aPDE* decreases, *e.g.*, due to activation of renal elimination, and/or when the *cPDE* increases due to an increase in fluid shift from tissues to capillaries (increase in FAR). Therefore, since activation of renal elimination requires about 20 min, and distribution of crystalloid throughout the extracellular fluid space requires about 30 min for completion [14], we have excluded the first mini fluid challenge related data from the present analysis.

Despite the obvious possibility of different combinations of the FAR and net fluid elimination rate, the revised mVLT algorithm (Fig. 6) implies that fluid loading is not indicated when hemodilution in capillaries is higher than in arteries as suggested by *cPDE* > 0.028 p.d.u., according to the results of the present study. The background concept of the mVLT is depicted on physiological basis in the transcapillary reflux model [1], [2]. It explains the changes in *acPED* during the incremental hemodilution in the the context of changes in viscoelastic properties of the tissues that surround capillaries and the rate of systemic fluid elimination from circulation. The phenomenon of negative *acPED* is explained by the *level* of tissue hydration in which interstitium releases excessive fluid into capillaries during the 5 min period with no fluids after a bolus. Our model, which is described in detail within previous reports [1], [2], is similar to the recently proposed 'physiological model' outlined within the 'Discussion' of the retrospective analysis of data from previous volume kinetic studies in healthy volunteers and patients [14]. The feasibility of the models needs evidence from the direct measurments of changes in pertinent tissues as they expand during the goal directed fluid infusion. Further research in this area is urgently required.

We used the findings of our present study to upgrade the mVLT algorithm (Fig. 6) in our Windows® platform-based software of the prototype SCLIS [3]-[5] (Fig. 7). We defined the positive *hemodilution response* as *cPDE* < 0.013 p.d.u. since it predicts the *acPED* > 0 p.d.u.. However, according to the mVLT method, both *cPDE* < 0.013 p.d.u. and *acPED* > 0 p.d.u. may be observed in both under- and over-hydration states. Thus, a static *cPDE* value is not a reliable factor when deciding on the need for additional MFCs. Meanwhile, a trend of *cPDE* can provide useful insights, *e.g.*, boluses are indicated if *cPDE* within that range decreases, but should be stopped if *cPDE* increases. Moreover, in cases when the *cPDE* is within the gray zone during several consecutive MFCs, it remains unclear as to how many MFCs are feasible. Theoretically, boluses could be indicated if the *cPDE* within the gray zone decreases, but should be stopped if it increases. Future research into this issue is needed.

The off-label use of Pulse CO-Oximetry for non-invasive measurement of capillary hemodilution remains an isue that has to be addressed in discussions with industry in the light of current evidence that non-invasive SpHb cannot reliably predict hemoglobin concentration in large vessels [15].

VII. Clinical Implications

When a given value of *cPDE* is in the gray zone, physicians cannot use this index as a factor in deciding whether to proceed with or to exclude the need for additional mini fluid challenges. Conversely, when a measured value is outside of the gray zone, the necessity of performing a fluid challenge can be confirmed (value above the upper limit of the grey zone) or excluded (value below the lower limit of the gray zone) with less than 10 % chance of error (specificity and sensitivity > 90 %). At the bedside, the gray zone appears to be more informative than the confidence interval of the best threshold value obtained using the ROC curve method.

The future implications of the mVLT within the revGDT protocol and SCLIS may include the evaluation of the body hydration levels and detection of imminent edema during infusion, as well as monitoring the redistribution of fluids following administration of a diuretic. These expectations are supported by previous reports that mVLT method was able to discriminate between differrent levels of hydration status in healthy volunteers who received 3 mini fluid challenges with the 2.5 ml kg^{-1} boluses of Ringer's acetate [1] and detect pre-operative dehydration in 36 TKA patients who received 3 mini fluid challenges with the 5 ml kg^{-1} boluses of the same crystalloid [2]. In 48 TKA patients, who received six 2.5 ml kg^{-1} boluses of Ringer's acetate in pre- and post-operative mVLTs, the positive 24-h fluid balance and higher arterio-capillary plasma dilution difference in pre-operative mVLT compared to post-operative suggested higher post-operative hydration level [16]. These results are consistent with the findings of our present study. We retrospectively analysed data that was obtained in 5 out of 6 mini fluid challenges in these 48 TKA patients and found that there was a trend towards lower number of negative hemodilution responses in pre-operative mVLT compared to post-operative: 82 pre- vs. 102 post-operative MFCs with the *acPED* ≤ 0 (P = 0.074).

VIII. Key Messages

– In 480 measurements, a gray zone approach showed that *cPDE* cannot reliably predict hemodilution response when its value is between 0.013 and 0.028 (p.d.u.).

– In the TKA surgery setting, about 14 % of mini fluid challenges with the 2.5 ml kg^{-1} boluses of a crystalloid had the *cPDE* values within a gray zone.

– An isolated value of *cPDE* should be considered as a tool rather than a target for titrating the fluid infusion. Future studies are necessary to evaluate the feasibility of targeting *cPDE* as a resuscitation endpoint.

IX. Conclusions

The non-invasive evaluation of hemodilution response is acceptably reliable in perioperative TKA setting. The mVLT algorithm within the prototype SCLIS was upgraded by implementing the results of the present study.

CONFLICT OF INTERESTS

A. A. has received a consultant's fee, travel funding and an honorarium for an expert report from Masimo Corp. (Irvine, CA, USA). A. A. is an inventor in US patent US 7,788,045 B2, US patent application US 61/470,224 and International application US 13/973,747.

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APPENDIX A

We have retrieved and pooled the data from the first part of the primary RCT [7] where 3 mini fluid challenges with the 5 ml kg^{-1} boluses of Ringer's acetate were used in each of the 36 pre- and 36 post-operative mVLT sessions [2]. Since we analysed only the data from the last two MFCs (second and third), a total of 144 measures were analysed. The cut-off *cPDE* value was 0.026 p.d.u. (specificity = 0.93, sensitivity = 0.77). The gray zone was a range of *cPDE* values between 0.015 and 0.080 (p.d.u.) (Fig. (b)). The difference in findings compared to the ones based on the 480 measures in 48 patients may be related to the use of a twice larger volume (doubled) but smaller number of boluses. However, the significantly smaller sample size (144 vs. 480) is probably the main source of discrepancy. Future research is needed for more conclusive results.

Previously, data from 36 subjects who received three 5 ml kg^{-1} boluses have been published addressing blood loss [7], accuracy of non-invasive SpHb measurements [3] and the use of the mVLT to detect pre-operative dehydration [2].

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