Statistically Biased Calibration Method for the Real-time Adjustment of Noninvasive Haemoglobin Measurements in a Semi-automated Infusion System

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***Abstract*—Closed loop systems are the ultimate solution to ensure that optimal therapies are delivered in a timely manner. A concept of a semi-closed loop infusion system for perioperative semi-automated optimisation of blood pressure and haemodilution is proposed. The key variable for the latter objective is the noninvasively and continuously measured blood haemoglobin concentration. However, it lacks reliability in predicting the haemoglobin in large blood vessels. Our proposed statistically biased calibration method for the adjustment of noninvasively measured Hb enabled better prediction of arterial Hb when it was applied to data from our ongoing clinical trial.**

***Index Terms*—Haemoglobin concentration, noninvasive haemoglobin measurements, perfusion index, haemodilution, closed loop system, control equipment, centralised control.**

I. INTRODUCTION

Intravenous fluid administration and maintaining the safe limits of arterial blood pressure is part of perioperative treatment. Rational perioperative management is estimated to contribute to annual prevention of 3,000,000 post-operative complications and 800,000 deaths worldwide for high-risk surgical patients [1].

Goal-directed fluid therapy (GDT) has been shown to improve outcome but is only used in 16% of high-risk surgeries [2]. This is mainly because it requires administration of mini-fluid challenges followed by evaluation of the target parameter's deviation (response), which is labour-intensive, time-inefficient and stressful to personnel. Thus, there is an obvious need for a semi-closed loop, if not a closed-loop fluid infusion and vasopresor drug injection system consisting of devices that measure vital parameters, analyse them and propose treatment on the basis of the preprogrammed clinical algorithms.

Development of closed-loop fluid infusion systems is also not new [3], [4]. Increasing concerns related to colloids [5] are shifting priority to the use of crystalloid solutions in GDT. However, interstitial accumulation of crystalloids may cause the swelling of tissues (oedema). In the meantime no clinically useful technique for monitoring tissue fluid accumulation is available, and there is no validated methodology to detect an imminent oedema. The minimal volume loading test (mVLT) was recently proposed for the detection of imminent oedema during a stepwise crystalloid infusion [6]. The mVLT fluid protocol implies administration of mini- fluid challenges. These are 2.5 – 5.0 ml kg^{-1} crystalloid boluses infused over 3-5 min and followed by 5 min periods without fluids. Evaluation of plasma dilution is performed by measuring haemoglobin concentration (Hb) before and after each mini fluid challenge. Imminent oedema is suspected when the ability of a mini fluid challenge to advance haemodilution is minimised (approaches zero) [6].

The mVLT algorithm may be used in a closed or semi-closed loop fluid infusion system on condition that a reliable and preferably noninvasive continuous measurement of Hb is applied for estimating plasma dilution. *Arterial* and

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venous Hb (aHb and vHb) can still only be reliably measured invasively [7]. The CO-oximetry technique is usually employed in portable devices and laboratory equipment. The noninvasive measurements are attributable to *capillary* Hb (cHb) because these measurements are performed in microvessels under a finger nail [6], [8], [9]. Probably the most advanced and continuously updated device for cHb measurements is the Radical-7 (Masimo Corp., USA). This employs the *pulse* CO-oximetry technique, which uses more than 7 wavelengths of light to acquire cHb (labelled as SpHb^{TM}) data based on light absorption. The SpHb is usually reliable in predicting the invasive arterial and venous Hb in relatively stable physiological conditions such as screening the pre-donation Hb and anemia [10]. However, SpHb can lack accuracy and especially precision in predicting invasively measured Hb in physiologically unstable conditions such as intravenous fluid infusion [11], major surgery and haemorrhage [7]–[9].

Aiming to increase accuracy and especially precision in predicting arterial and venous Hb from cHb measurements, the focus has recently shifted from improving measuring techniques to the mathematical adjustment of cHb measurements. Following this objective, we developed a *statistically biased calibration method* for the real-time adjustment of cHb measurements. It is expected to increase the reliability and applicability of noninvasive haemoglobin measurements for our proposed semi-closed loop infusion system.

The statistically biased calibration method was put to the test by applying it to data from our ongoing randomised clinical trial in total knee athroplasty surgery patients undergoing perioperative optimisation procedures [12].

II. METHODS

A. Statistically biased calibration method

The statistically biased calibration method employs three steps: (1) *calculating statistical bias,* (2) *performing in vivo calibration*, and (3) *predicting invasive Hb.* Deviations of aHb, SpHb and PI (*key variables* later in the text) induced by mini fluid challenges are used to demonstrate how the method works. In equations below, the venous Hb can be used instead of arterial, and the arterio-venous gap can be used instead of the arterio-capillary gap. Also, the SpHb represents capillary Hb measured by any technique.

1) Calculating statistical bias

This implies statistical analysis and mathematical processing of the key variables obtained from a group of individuals under similar observation conditions (a pool), e.g. the key variables were obtained simultaneously before and after each of the six mini fluid challenges in 25 subjects during the mVLT protocol. The statistical bias of SpHb in respect to aHb is determined by calculating the *coefficients* of the *polynomial* as follows.

A. Calculating the normalised acGAP at baseline

$$acGAP_{ib} = \frac{aHb_{ib} - SpHb_{ib}}{aHb_{ib}}, \quad (1)$$

where acGAP – arterio-capillary gap, aHb – arterial Hb, and $SpHb_b$ – capillary Hb; $_i$ – identification number of an individual in the pool, $_b$ – baseline.

B. Calculation of normalised acGAP is performed in each individual from a pool after the first mini fluid challenge

$$acGAP_{i1} = \frac{aHb_{i1} - SpHb_{i1}}{aHb_{ib}}, \quad (2)$$

where acGAP – arterio-capillary gap, aHb – arterial Hb, and SpHb – capillary Hb; $_i$ – identification number of an individual in the pool, $_1$ – data point after first mini fluid challenge, $_b$ – baseline.

C. Calculating the coefficients of the polynomials. These are (1) G - coefficient of acGAP impact, (2) C – offset and (3) iPI - coefficient of PI impact at baseline. These are calculated by mathematical optimisation which implies the following steps and equations simultaneously applied by a computer to individual data obtained from all individuals in a pool of subjects involved in calculating the statistical bias.

Step 1. Calculating the modified acGAP after 1st mini fluid challenge

$$acGAP_{mi} = acGAP_{ib} \times G_b + acGAP_{i1} \times G_1 + \\ + \frac{C}{aHb_{ib} + iPI * PI_{ib} * aHb_{ib}}, \quad (3)$$

where $acGAP_m$ – modified arterio-capillary gap, acGAP – arterio-capillary gap, G – coefficient of acGAP impact, C – an offset, iPI – coefficient of the PI impact at baseline, PI – perfusion index, and aHb – arterial Hb; $_i$ – identification number of an individual in the pool, $_b$ – baseline, $_1$ – data point after first mini fluid challenge. The coefficients of the polynomials G, C and iPI are arbitrarily chosen and equal, same for all individuals and all mini fluid challenges. Initially they can all be set to zero.

Step 2. Calculating the predicted arterial heaemoglobin concentration (paHb) after each mini fluid challenge starting from the 2nd challenge

$$paHb_{ij} = \frac{SpHb_{ij}}{aHb_b} + acGAP_{mi} \times aHb_{ib} + \\ +0.01 \times PI_{ij} \times SpHb_{ij} \times C_{PI}, \quad (4)$$

where paHb – predicted arterial Hb, SpHb – capillary Hb, aHb –arterial Hb, $acGAP_m$ – modified arterio-capillary gap (the value obtained form equation N.3), PI –perfusion index, C_{PI} – coefficient of combined PI and SpHb impact on the predicted aHb (PI multiplied by SpHb); $_i$ – identification number of an individual in the pool, $_j$ – number of a mini fluid challenge (starts from N.2), $_b$ – baseline. The coefficient of the polynomial C_{PI} is arbitrarily chosen and same for all individuals and all mini fluid challenges. Initially the C_{PI} can be set to zero.

Step 3. Calculate difference between aHb and paHb after

each mini fluid challenge starting from the 2nd challenge

$$\Delta_{ij} = aHb_{ij} - paHb_{ij}, \quad (5)$$

where Δ – difference between the measured and the predicted arterial Hb, aHb – arterial Hb, paHb – predicted arterial Hb, $_i$ – identification number of an individual in the pool, $_j$ – number of a mini fluid challenge (starts from N.2).

Step 4. Calculate the standard deviation (σ) and average of a pool (Δ_{ij}) obtained by equation N.5.

Step 5. Computer searches for the best-fit coefficients of the polynomials by randomly changing the intially set value, e.g. zero (equations N.3 and N.4), by ±0.05. It is continued until Δσ in each mini fluid challenge starting from the 2nd becomes less than a threshold value, e.g. $\Delta\sigma < 0.05$.

2) Performing in vivo calibration

The *in vivo* calibration enables the use of the statistical bias to calculate the paHb from SpHb measurements for a single individual. It requires measurement of simultaneous deviations in aHb, PI and SpHb that occur spontaneously or are induced, e.g. by a mini fluid challenge. Measurements of key variables are performed immediately before and after a deviation in key variables.

3) Predicting invasive Hb

This applies to individuals that were not among subjects involved in the previously described calculation of statistical bias. Individual key variables measured during the above decribed *in vivo* calibration are entered into formula N.4, but the coefficients of the polynomials are those predetermined in the process of calculating the statistical bias. It was applied to detemine the efficacy of the method in reducing individual cGAP by applying it retrospectively to the data from our previous clinical observations.

B. Retrospective clinical investigation

The key variables from periopertive mVLT sessions in patients undergoing total knee arthroplasty surgery were analysed. Each patient participated in two mVLT sessions. The preoperative (Pre-op) mVLT was performed immediately before anaesthesia and surgery, while the postoperative (Post-op) mVLT commenced 24 hrs later. In Group 1 (n=25) six mini fluid challenges employed 2.5 ml kg^{-1} boluses in both mVLT sessions. In contrast, only three mini fluid challenges but with larger boluses (5.0 ml kg^{-1}) were used in both mVLT sessions for Group 2 (n=36).

Arterial blood samples were obtained to determine aHb immediately before the 1st bolus (T0), and after the 5 min period following each fluid bolus (T1-T6 in Group 1, and T1-T3 in Group 2). The key variables were also obtained after the 20 min period without fluids that followed the last bolus in all mVLT sessions, that data point being referred to as EQ. Arterial blood samples were analysed in a laboratory by the haematology analyser COULTER® LH750 (Beckman Coulter Inc., MI, USA). The SpHb measurements were manually recorded simultaneously at the data points stated above.

To detemine the statistical bias, we used the data obtained at data points T0 - T6 during a Pre-op mVLT in twenty five patients. The key variables obtained at these data points (at baseline and after each of the six mini fluid challenges) were used in equations numbered 1 to 5 and the coefficients of the polynomials were calculated. These were G_b = 0.3, G_1 = 0.65; C = 3.5; C_{PI} = -1.75 and iPI = 1.5. The *in vivo* callibration was performed in each mVLT session, and the individual key variables measured during the 1st mini fluid challenge in each session were entered into formula N.4 along with the predetermined coefficients of the polynomials stated above. The paHb was then calculated from individual SpHb values measured at data points T2-T6 and EQ in Group 1, also at T2-T3 and EQ in Group 2.

III. RESULTS

The Bland-Altman plot was used to demonstrate agreement between the paired SpHb and aHb values from both mVLT sessions in both groups (Fig. 1 and Table I).

The overall peri-operative bias, lower and upper limits of agreement were -0.8 g l^{-1} (SD 8.4 g l^{-1}), -17.5 g l^{-1} and 15.9 g l^{-1}, respectively. Also, there was moderate correlation (R = -0.47, P = 0.000). The T0, T1 and EQ data points were excluded from the Bland-Altman plot, because the T0 and T1 related key variables were used for the *in vivo* calibration, and EQ related data were analysed separately (Table II). The non-adjusted acGAP is the difference between the paired SpHb and aHb, while the adjusted acGAP is the difference between the paired paHb and aHb. The number of outliers is defined in Table I and Table II as a percentage of acGAP outside the ±10 gl^{-1} accuracy limits.

Overall percentage of outliers was significantly lower when the paHb values are used instead of SpHb in T2-6 and EQ points separately (Table I and II). The statistically biased calibration method was calculated for preoperative Group 1 data in T2-6 points of measurements, moreover it was equal significance in both Group 1 and Group 2. The proportion of outliers was not reduced significantly (P=0.078) just in Group 1 in EQ points. It could be caused by small number of measurements.

TABLE I. THE ACGAP AT DATA POINTS T2-6.

Data points T1-T6	**Non-adjusted gap**	**Adjusted gap**	
	acGAP >10 gl^{-1} % (of measurements)	**acGAP >10 gl^{-1} % (of measurements)**	***P* value χ^2 test**
Pre-op Gr. 1	16.8	0	0.000
Post-op Gr. 1	20.8	8.0	
Pre-op Gr. 2	15.3	9,7	0.002
Post-op Gr. 2	36,1	12.5	
Total	21.3	6.6	0.000

Similarly, the Bland-Altman plot was used to demonstrate an agreement between the 394 paired SpHb and paHb values (Fig. 2 and Table I). The peri-operative bias, lower and upper limits of agreement were -1.7 g l^{-1} (SD 5.3 g l^{-1}), -12.3 g l^{-1} and 8.8 g l^{-1}, respectively. Also, there was a weak correlation (R = -0.14, P = 0.004).

As shown in Table II, the similar efficacy of a statistically biased calibration method in reducing the acGAP is also seen at data point EQ.

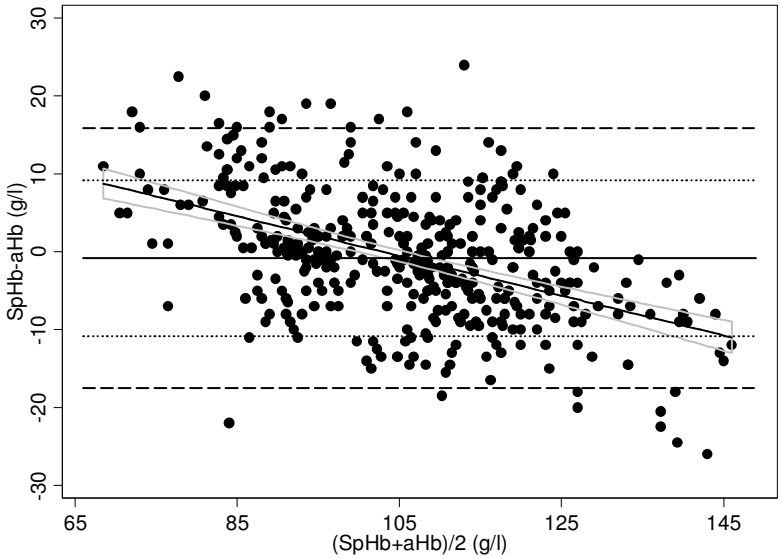

Fig. 1. Bland-Altman plot showing the agreement between 394 paired values of SpHb and aHb (197 Pre-op + 197 Post-op). The accuracy ±10 g l^{-1} limits are defined by dotted lines.

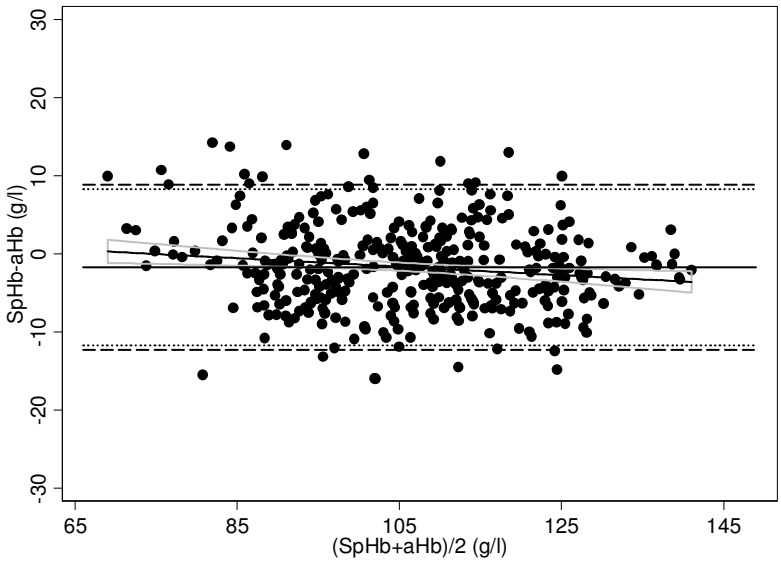

Fig. 2. Bland-Altman plot showing the agreement between 394 paired values of paHb (adjusted SpHb) and aHb (197 Pre-op + 197 Post-op). The accuracy ±10 g l^{-1} limits are defined by dotted lines.

TABLE II. THE ACGAP AT DATA POINT EQ

Data points EQ	Non-adjusted gap	Adjusted gap	
	acGAP >10 gl^{-1} % (of measurementes)	acGAP >10 gl^{-1} % (of measurements)	*P* value χ^2 test
Pre-op Gr. 1	24.0	8.0	0.078
Post-op Gr. 1	32.0	16.0	
Pre-op Gr. 2	36.9	16.7	0.000
Post-op Gr. 2	63.9	13.9	
Total	49.2	13.9	0.000

IV. SEMI-CLOSED-LOOP INFUSION SYSTEM

Despite improvements in techniques and skills, the outcome of treatment after major surgery remains partly dependent on the overall perioperative optimisation of the patient. Optimisation procedures are labour-intensive, stressful to care providers and require simultaneous monitoring of multiple parameters. Nevertheless, optimisation targets may still be missed.

Typical risk reduction measures are not sufficient to reduce the probability of errors resulting from operator errors. Improvement of the device software and hardware, adding more alerts and alarms is not enough to significantly reduce the risk of such types of hazards, so there is a need for new methods to improve the safety of medical devices.

Closed loop systems are the ultimate solution to ensure that optimal therapies are delivered in a timely manner [3], [13], [14]. The objectives such as keeping the perioperative ABP and optimised haemodilution in the preset safe limits can be achieved semi-automatically. The mathematical modelling cannot account for all the environmental factors, but it may be helpful for clinicians in dealing with the complexity of decision-making and applying treatment in a timely manner. Integrating patient monitoring, fluid and drug infusion devices into one system and using a controller, which would be able to assess the requirements for a specific treatment according to patients' vital signs can make it possible to reduce the probability of hazards arising from the lack of appropriate timely reaction. Controllers such as PID, Fuzzy logic, Artificial neural networks, Rule-based, Model-based and others can be used to fit the specific

requirements.

Perioperative patient optimisation at minimum requires maintenence of normal arterial blood pressure (ABP). This can be achieved by applying continuous ABP monitoring and administration of fluid infusion and medication in case of arterial hypotension. A semi-closed loop system could enable administration of treatment in a timely manner and reduce the stress levels of care-givers. We developed the semi-closed loop system infusion system consisting of ABP and Hb measuring devices, algorithmic data analysis and generating the commands for the pumps to perform the vasopressor injection and infuse fluids and blood (Fig. 3).

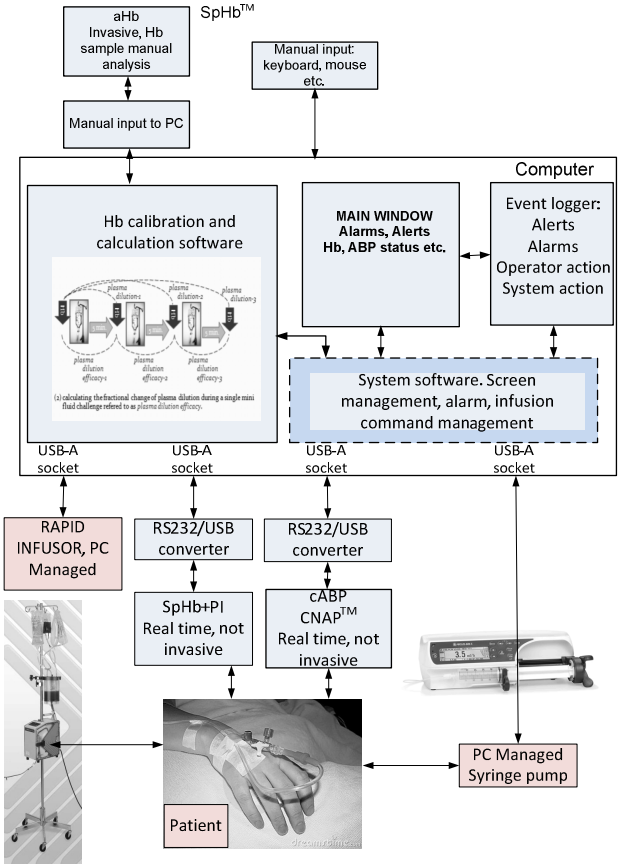

Fig. 3. Semi-closed-loop infusion system with noninvasive statistical evaluation of arterial hemoglobin concentration.

One of the system components – a closed loop vasopressor drug injection system - has been recently put to the test [5]. It used a continuous noninvasive arterial pressure measurement device (CNAP™; Draeger Medical, Germany) connected to a laptop computer. When CNAP fell below a pre-set limit, the computer automatically delivered injection commands to the two syringe pumps pre-filled with vasopressors. The software in a computer of our semi-closed loop system implements the extended clinical algorithm for generating the following commands: (1) administer the vasopressor injection (automated, but can be objected), (2) perform the mVLT fluid protocol (semi-automated, requires physician's approval), (3) administer maintenance crystalloid infusion (semi-automated, requires physicians approval), (4) perform the red cell transfusion (semi-automated, requires physician's approval). According to the mVLT methodology, when fluid infusion reaches the point where the ability of an infusion to advance haemodilution is minimised, it functions as confirmation of optimised haemodilution. Fluid boluses are not justified for ABP management after that point. The transfusion is considered if signs of anemia intolerance persist after the optimisation of haemodilution and ABP. To enable the more reliable noninvasive monitoring of anemia, our system implements a calibration protocol according to the statistically biased calibration method (Fig. 4).

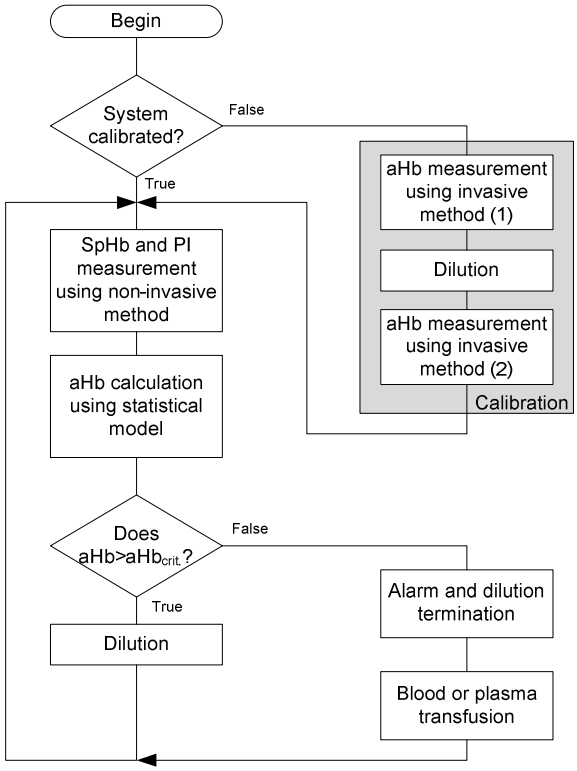

Fig. 4. Algorithm for the implication of statistically biased calibration method in the semi-closed-loop infusion system.

Graphic displays will also help clinicians to better capture and integrate the multivariable clinical information. This may lead to faster and more accurate diagnosis and therapeutic decision-making. Our designed semi-closed loop infusion system will soon be put into the test by our research team by applying it in the perioperative setting for patients undergoing major orthopaedic surgery.

V. DISCUSSION

The results of the present study show that the statistically biased calibration method effectively reduced the gap between the invasively measured arterial Hb and the noninvasively measured SpHb. Its involvement in the semi-closed loop infusion systeem has been proposed. However, equations used for calculating the coefficients of the polynamials are far from being optimal. In the future, it should be possible to design more efficient methods by applying different equations, e.g. with non-linear variations of coefficients of the polynamials (applying multiplication, division, etc.) and also using a different number of coefficients, but the process of mathematical optimisation would be similar to the approach we have presented. Importantly, as large as possible a pool of key variables obtained in as large as possible a pool of observation periods and number of individuals should be used to calculate the

coefficients of the polynamials so that they become more 'universal'. However, although such mathematical optimisation reduces the individually occuring gap between the invasive and noninvasive Hb measurements, there will always remain a space for individual incompliance with the established statistical behaviour. This can probably be minimised by applying the mathematics to the physiological modelling rather than statistical adjustment of individual measurements. It could be based on the mathematical modelling of the anatomically and physiologically determined difference between Hb in a larger and a smaller blood vessel labelled as a GAP [6]–[8]. Theoretically, the GAP is mainly caused by the Fahraeus effect [6]. This means that blood viscosity is reduced, the cHb decreases and the GAP increases when the internal radius of a blood vessel decreases [6] [9] [15]. The Fahraeus effect-related systemic GAP depends on the difference between the internal radius of a large vessel (artery or vein), and the mean radius of multiple capillaries under the sensor for cHb measurements. Arteries and veins are common blood sampling sites for Hb measurements by the CO-oximetry technique. Thus, cHb tends to be lower than arterial and venous Hb due to the Fahraeus effect, leading to positive arterio-capillary and arterio-venous GAPs.

Aiming to minimise the Fahraeus effect related GAP, the *in vivo* adjustment of SpHb value was installed in a Radical-7 device [16]. This implies an automatic adjustment of SpHb values after the measured GAP value is manually entered into the device. This feature does not alter the measuring technique, but just adds (or subtracts) a constant value to the measurements. Preliminary reports stated that *in vivo* adjustment efficiently reduced the GAP [17]. However, there are drawbacks in the background concept of *in vivo* adjustment. First, it is based on an assumption that the initially measured arterio capillary and arterio-venous GAPs remain stable during the upcoming period of SpHb observation. Meanwhile, aside from the theoretical speculations [6], there is some evidence that changes of tissue perfusion index (PI) affect the GAP [11]. Obviously, this is because PI reflects changes in the internal radius of capillaries, leading to changes of radius difference between lage vessels and capillaries, which in turn affects the Fahraeus effect-related GAP. Next, the *in vivo* adjustment of SpHb does not eliminate the impact of changes in transcapillary fluid movement that affect the SpHb and consequently the GAP. The transcapillary fluid equilibration is an extremely intense and dynamic process, because about 95% of fluid exchange between the blood and body tissues takes part in capillaries while only about 3 - 5% of the body blood volume is in capillaries. The related hardly predictable changes of haemodilution in capillaries affect the arterio-capillary and veno-capillary GAPs, and also the difference between arterial and venous Hb, e.g. the latter can shift from positive to negative during intravenous fluid therapy [18]. Thus, a difference of haemodilution in arteries and capillaries during mVLT is used to evaluate transcapillary fluid balance and the body's response to fluid infusion. Consequently, only the changes in PI can be reliably used to reduce fluctuations in arterio-capillary GAP. Theoretically, it can be achieved by determining the individual relationship between the simultaneous changes of PI (ΔPI) and cHb (ΔcHb) during a callibration procedure. The latter would imply evaluation of a single simultaneous change in PI and cHb that occurs spontaneously or is induced, e.g. by a mini fluid challenge. However, the Radical 7 device currently applies different averaging times for SpHb and PI measurements. That makes evaluation of relationship between simultaneous ΔPI and ΔSpHb impossible. Presuming that this drawback is eliminated, the PI-related adjustment of SpHb could be implemented as an addition to the currently used *in vivo* adjustment. The background concept would be as follows.

The PI is calculated by expressing the pulsatile signal as a percentage of the non-pulsatile signal. Theoretically, the relatively frequent pleth oscillations (vasomotion) in micro-capillaries (smallest capillaries) overlap the less frequent heart rate dependent oscillations in macro-capillaries (largest capillaries). Consequently, the infrared light absorption by haemoglobin in the overlapping zone determines the non-pulsatile part of extracted signal. Thus, as shown in Fig. 5, the PI increases when the blood flow in micro-capillaries decreases in respect of macro-capillaries and leads to the lower infrared light absorption therein.

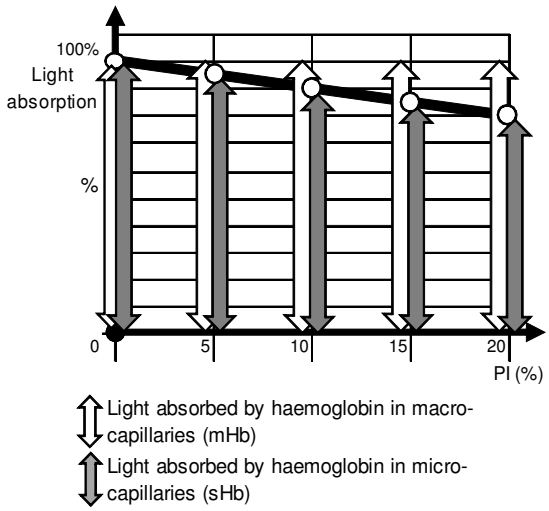

Fig. 5. Relationship between the tissue perfusion index and the light absorption in micro- and macro-capillaries. PI – perfusion index.

Obviously, the arterio-capillary GAP decreases when PI increases simply because cHb decreases more than aHb, which is not affected by changes in PI. This explains why the noninvasively measured haemodilution was more pronounced than invasively measured haemodilution when the PI decreased during crystalloid infusion [11]. The transcapillary fluid filtration absorption ratio (FAR) will also affect the capillary Hb and Hct, but FAR cannot be measured in a clinical setting.

Thus, theoretically, most efficient individual adjustment of cHb values aiming to reliably predict the invasive Hb could be developed on the backgound concept presented below. The ΔGAP is a result of an interferring affect of ΔFAR and ΔPI. However, since units of measure for the GAP (g l^{-1}), PI (%) and FAR (ratio) are different, equation [ΔGAP = ΔPI – ΔFAR] for negative GAP and equation [ΔGAP = (-ΔPI) – ΔFAR] for positive GAP cannot be used. However, to avoid the conflict of units, the ratios of these variables can be used to determine their relationship. Both invasive and noninvasive Hb and PI measures during the

calibration are required to determine the deviation in FAR expressed as Ratio of Filtration (ROF).

These are equations used for the calibration

$$ROG_1 = GAP_1 \times GAP_0^{-1}, \quad (6)$$

where ROG_1 is the ratio of GAPs, which is the ratio between GAP_1 (the GAP value determined after a deviation of parameters in the calibration protocol) and GAP_0 (baseline GAP value in the calibration protocol)

$$ROP_1 = PI_1 \times PI_0^{-1}, \quad (7)$$

where ROP_1 is ratio of perfusion indexes, which is the ratio between PI_1 (the PI value after a deviation of parameters in the calibration protocol) and PI_0 (baseline PI value in the calibration protocol)

$$ROF_1 = FAR_1 \times FAR_0^{-1}, \quad (8)$$

where ROF_1 is ratio of FARs, which is the ratio between FAR_1 (the FAR value after a deviation of parameters in the calibration protocol) and FAR_0 (baseline FAR value in the calibration protocol).

Since the discrepancy between the ΔGAP and ΔPI are related to ΔFAR, the latter equation can be applied

$$ROF_1 = ABS\left(ROG_1\right) - ABS(ROP_1). \quad (9)$$

Modification of software in the noninvasive capillary Hb measuring devices is therefore required to provide the synchronised averaging of PI and cHb variables..

VI. CONCLUSIONS

Applying the statistically biased calibration method for the adjustment of noninvasively measured Hb enables better prediction of arterial Hb. Since both capillary and aterial Hb are important for a clinician, bothe values could therefore be displayed on the screen of the devices for noninvasive Hb measures. Both Hb values are very important for the use of mVLT method, also reliability of our proposed semi-closed-loop infusion system. Its clinical implication is expected to provide more efficient perioperative optimisation of a patient with an improvement in the overall outcomes of treatment. It would also relieve clinicians of relatively simple and repetitive tasks.

VII. ACKNOWLEDGEMENTS

Conflicts of interest:

– Audrius Andrijauskas received a consultant's fee from Masimo Corp., Irvine, USA. A.A. is also an author of the US Patent US 7,788,045 B2, Non-provisional US Patent application Dkt. No. 81281-A-PCT and International Provisional Patent application Dkt. No. 5975/84428-PRO;

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

REFERENCES

[1] M. Cannesson, G. Pestel, C. Ricks, A. Hoeft, A. Perel, "Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists", *Crit Care*, vol. 15, no. 5, 2011, R197. [Online]. Available: http://dx.doi.org/10.1186/cc10364

[2] M. A. Hamilton, M. Cecconi, A. Rhodes, "A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients", *Anesth Analg*, vol. 112, pp. 1392–1402, 2011. [Online]. Available: http://dx.doi.org/10.1213/ANE.0b013e3181eeaae5

[3] J. Rinehart, N. Liu, B. Alexander, M. Cannesson, "Closed-Loop Systems in Anesthesia: Is There a Potential for Closed-Loop Fluid Management and Hemodynamic Optimization?", *Anesth Analg.,* vol. 114, pp. 130–143, Jan. 2012. [Online]. Available: http://dx.doi.org/10.1213/ANE.0b013e318230e9e0

[4] F. Michard, "Decision Support for Hemodynamic Management: From Graphical Displays to Closed Loop Systems", *Anesth Analg.*, submitted for publication.

[5] A. T. Sia, H. S. Tan, B. L. Sng, "Closed-loop double-vasopressor automated system to treat hypotension during spinal anaesthesia for caesarean section: a preliminary study", *Anaesthesia,* vol. 67, no. 12, pp. 1348–1355, 2012. [Online]. Available: http://dx.doi.org/10.1111/anae.12000

[6] A. Andrijauskas, C. Svensen, J. Ivaskevicius, N. Porvaneckas, G. Kvederas, U. Marmaite, "Goal directed fluid therapy revised: indirect monitoring of interstitial fluid accumulation during mini fluid challenges with crystalloids" *The Open Conference Proceedings Journal,* vol. 3, pp. 42–51, 2012.

[7] T. Isosu, S. Obara, A. Hosono, S. Ohashi, Y. Nakano, T. Imaizumi, M. Mogami, M. Murakawa, "Validation of Continuous and Noninvasive Hemoglobin Monitoring by Pulse CO-Oximetry in Japanese Surgical Patients", *J Clin Monit Comput.*, vol. 27, no. 1, pp. 55–60, 2013. [Online]. Available: http://dx.doi.org/10.1007/s10877-012-9397-2

[8] A. Andrijauskas, C. Svensen, J. Ivaskevicius, N. Porvaneckas, G. Kvederas, P. Andrijauskas, "Clinical Interpretation of Noninvasive Hemoglobin (SpHb). Revised: Single Capillary-Bed rather than Arterial Hemoglobin", *European Journal of Anaesthesiology,* vol. 29, suppl. 50, pp. 47-48, 2012. [Online]. Available: http://dx.doi.org/10.1097/00003643-201206001-00153

[9] R. Naftalovich, D. Naftalovich, "Error in noninvasive spectrophotometric measurement of blood hemoglobin concentration under conditions of blood loss", *Med Hypotheses*, vol. 77, no. 4, pp. 665–667, 2011. [Online]. Available: http://dx.doi.org/10.1016/j.mehy.2011.07.010

[10] M. Raikhel, "Accuracy of Noninvasive and Invasive Point-Of-Care Total Blood Hemoglobin Measurement in an Outpatient Setting", *Postgrad Med.*, vol. 124, no. 4, pp. 250–255, 2012. [Online]. Available: http://dx.doi.org/10.3810/pgm.2012.07.2584

[11] C. Bergek, J. H. Zdolsek R. G. Hahn, "Accuracy of noninvasive haemoglobin measurement by pulse oximetry depends on the type of infusion fluid", *Eur J Anaesthesiol,* vol. 29, pp. 586–592, 2012.

[12] G. Kvederas, N. Porvaneckas, A. Andrijauskas, C. H. Svensen, J. Ivaskevicius, J. Mazunaitis, U. Marmaite, P. Andrijauskas, "A randomized double-blind clinical trial of tourniquet application strategies for total knee arthroplasty", *Knee Surg Sports Traumatol Arthrosc.*, submitted for publication. [Online]. Available: [Online]. Available: http://dx.doi.org/10.1007/s00167-012-2221-1

[13] N. Dubauskiene, V. Markevicius, A. Faktorovicius, "Challenges of Close Loop Electronic Medical Systems", *Elektronika ir Elektrotechnika (Electronics and Electrical Engineering),* no. 5, pp. 95–98, 2010.

[14] N. Dubauskiene, V. Markevicius, A. Valinevicius, D. Navikas, "Automated Blood Pressure Control with Closed Loop System", *Elektronika ir elektrotechnika (Electronics and Electrical Engineering)*, vol. 18, no. 9, pp. 35–38, 2012.

[15] R. Fåhreus, T. Lindqvist, "The viscosity of blood in narrow capillary tubes", *Am J of Physiology,* vol. 96, pp. 562–568, 1931.

[16] M. O'Reilly, "Response to Gayat et al.", *Ann Emerg Med*, vol. 58, no. 1, pp. 106–107, 2011. [Online]. Available: http://dx.doi.org/10.1016/j.annemergmed.2011.02.028

[17] K. Torp, S. Aniskevich, S. Pai, T. Shine, P. Peiris, C. Crawford, "In-Vivo Calibration Improves Accuracy of Non-Invasive Hemoglobin Measurements", in *Proc. of the American Society of Anesthesiologists,* Washington, Oct. 2012.

[18] C. H. Svensen, P. M. Rodhe, J. Olsson, E. Borsheim, A. Aarsland, R. G. Hahn, "Arteriovenous differences in plasma dilution and the distribution kinetics of lactated ringer's solution", *Anesth Analg.*, vol. 108, pp. 128–133, 2009. [Online]. Available: http://dx.doi.org/10.1213/ane.0b013e31818c95e1