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Article

Continuous Noninvasive Haemoglobin Monitoring in Vascular Surgery within the Goal-Directed Therapy Protocol

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Abstract: The optimisation of DO_2, within the Goal-Direct Therapy Protocol (GDTP) in high-risk surgical patients, improves their outcome. Haemodynamic and haemoglobin monitoring become crucial to achieve optimal DO_2. Our study compared Hb as measured by three methods: Coulter Counter (standard laboratory method) and CO-Oximetry (Masimo rainbow SET Radical 7 Pulse CO-Oximetry (SpHb) and Blood Gas Analysis) to establish the utility of the Hb continuous intraoperative monitoring, within the GDTP, in high-risk bleeding surgery. We studied 72 patients undergoing open abdominal aortic aneurysm repair. We compared the accuracy and the trending ability in measuring the haemoglobin concentration between the three methods (Coulter Counter, BGA and Masimo). We collected three simultaneous haemoglobin measurements: after induction of anaesthesia, pre- and post-aortic cross-clamping and at the end of the surgery. SpHb showed an excellent r-value for all samples (0.952, CI-95% (0.939, 0.961), *p*-value < 0.0001) compared to laboratory measurements. The results of the linear regression between SpHb and laboratory, for each time considered, demonstrated that SpHb showed excellent r and R^2 value. All data were statistically significant, with a *p*-value <0.0001. A Bland-Altmann analysis for SpHb vs. laboratory showed a bias of −1.45 g/dL (CI-95% −1.51 and −1.39 g/dL, LOA from −2.42 to −0.48 g/dL) with a precision of 0.49 g/dL. Four-quadrant plot trend analyses showed a high concordance rate ≥90%. During elective high-risk surgery, Masimo Pulse CO-Oximetry is not enough sufficiently accurate to assess the current value of haemoglobin but may be useful for the trend value ensuring DO_2 within intraoperative GDTP.

Keywords: haemoglobin; noninvasive monitoring; trend analysis; aortic surgery; goal-directed therapy

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Introduction

Anaemia during open aortic surgery represents a common condition due to acute intraoperative bleeding and iatrogenic hemodilution with alteration of oxygen delivery (DO_2) and the possibility of tissue hypoperfusion. Haemoglobin (Hb) is one of the elements of the DO_2-equation:

$$DO_2 = CO \times [1.39 \times [Hb] \times SaO_2 + (0.003 \times PaO_2)]$$

where

$$CO = SV \times HR$$

CO = Cardiac output, SV = Stroke Volume, HR = Heart Rate.

Thus, the Hb value becomes crucial in surgeries with bleeding and fluid shift, such as vascular surgery, because it influences the achievement and maintenance of optimal DO_2, especially for high-risk patients (mortality rate >10%) [1–3]. An optimisation of DO_2, by normalisation of SV, HR, and Hb, is the main target of the Goal-Directed-Therapy Protocol (GDTP), so haemodynamic and Hb monitoring are essential.

During aortic surgery, a rapid choice about red blood cells (RBC) transfusion is based on clinical judgment and the Hb value obtained with a Blood Gas Analysis (BGA) (CO-Oximetry).

The conventional haematological method (Coulter counter) is the gold standard for measuring the Hb value but is more time-consuming than BGA. However, both methods provide intermittent results that reflect just the value of Hb concentration at the time of sampling, losing reliability during an acute bleeding episode [4].

Consequently, ideal Hb monitoring should be non-invasive, rapid/continuous and easy. Radical 7 device (Masimo Corp, Irvine, CA, USA) pulse CO-Oximetry is the multiwavelength technology that continuously records and displays Hb concentration (SpHb), with a more dynamic picture [5]. These characteristics make this form of monitoring a valid tool to optimise DO_2 within a GDTP.

Given its non-invasiveness and ability to provide continuous real-time data at bedside, SpHb monitoring offers a new paradigm and opens up new possibilities for improved patient care.

SpHb technology has been tested in various clinical scenarios and two metanalyses concluded with an alert about clinical decision based on these devices [6,7]. However, there is a lack of data about the accuracy, precision and trending ability of SpHb in vascular surgery.

Our study is a comparison of Hb as measured by three methods (Coulter Counter, BGA and Masimo) to establish the utility of the Hb continuous intraoperative monitoring within the GDTP in high-risk bleeding surgery.

Methods

We conducted a prospective observational study at a single vascular surgery centre (AORN dei Colli, Monaldi Hospital, Naples, Italy), with approbation from the local ethical committee (University of Naples Luigi Vanvitelli, protocol number 544/2017). The study was completely intraoperative. We obtained written informed consent by patients scheduled for elective abdominal aortic open surgery. We recorded age, weight, height, sex, ASA status, and comorbidities preoperatively.

We used the Vascular-POSSUM score (V-POSSUM, http://www.riskprediction.org.uk/vasc-index.php) and ASA status to provide information on the risk of morbidity and mortality of all patients. Exclusion criteria were: age $\geq$ 85 years, emergency or urgency surgery, ASA status $\geq$ IV, NYHA $\geq$ III, a rate of predicted morbidity with V-POSSUM <15%, chronic and acute anaemia, haemoglobinopathies.

We studied, during a period of 30 months, 72 patients undergoing open abdominal (sub-renal) aortic aneurysm repair.

The primary endpoints of the study were to compare the accuracy in measuring Hb concentration using CO-oximetric methods (Masimo rainbow SET® Radical 7 Pulse CO-Oximetry ™ and BGA) with Hb values obtained using the standard laboratory method (Coulter counter) that is considered the gold standard.

The secondary endpoint was to analyse the trending ability between CO-Oximetry (Masimo and BGA) and Coulter counter (standard laboratory method).

Intraoperative standard monitoring consisted of ECG, SpO_2, end-tidal CO_2 ($EtCO_2$), non-invasive blood pressure and diuresis. In addition, we monitored invasive blood pressure, bispectral index (BIS™, Medtronic, Minneapolis, MN, USA), neuromuscular blockade (Tof Cuff®, RGB Medical, Madrid, Spain), skin temperature, and Central Venous Pressure (CVP).

For SpHb measurement, we used the Masimo Rainbow SET Radical 7® (Masimo Corporation, Irvine, CA, USA): the model was VKF-RAD7A, and the sensor was composed of a Disposable Optical Sensor (DOS-Rainbow R2-25a) and a Reusable Optical Sensor (ROS-Rainbow R2-25r). We applied the Masimo platform (with an optical shield to avoid interference) to the middle finger or the index of the patient's hand, free from venous and arterial lines or monitoring devices, in the absence of nail polish or acrylic nails.

All the patients, after premedication with intra-muscular Morphine (10 mg), received general anaesthesia. We used Propofol (0.7 mg/kg), Midazolam (0.07 mg/kg), Sufentanil (0.4 mcg/kg) for induction and Rocuronium (0.6 mg/kg) for neuromuscular blockade.

During the maintenance of anaesthesia, we used exhaled Desflurane 3%, keeping a BIS value between 40%–60%, Remifentanil infusion (0.15 mcg/kg/min), and next Rocuronium administration (0.2 mg/kg) guided by neuromuscular monitoring. We conducted mechanical ventilation (Dräger Zeus®, Drägerwerk, Lubeck, Germany) in volumetric mode (Tidal Volume 6 mL/kg ideal body weight, PEEP 5 cmH_2O, Respiratory Rate 12–16/min to obtain a PCO_2 35–40 mmHg and FiO_2 50% by a closed and Auto Flow system).

In a high-risk surgical population (mortality risk >10%) it is crucial to avoid hyper or hypovolemia. For a "tailored" use of fluids and drugs (vasoconstrictors, vasodilators, inotropes, beta-blockers), we followed a GDTP. We used EV 1000™ platform (Edwards Lifesciences, Irvine, CA, USA) as haemodynamic monitoring. We analysed the parameters with pulse-contour monitoring by FloTrac or Volume View. The target of our GDTP was the optimisation of the stroke volume index (SVI) [8].

We administered a basic crystalloid infusion of 1 mL/kg/h. After induction of general anaesthesia, in stable haemodynamic condition, we calculated maximal SVI following this protocol: we noted the first value of SVI as baseline, we practised a bolus of colloids (fluid challenge 3 mL/kg) and marked the new SVI value so that we calculated the variation with respect to the baseline value (ΔSVI%). In case of fluid responsiveness status (ΔSVI% > 10%), we repeated the fluid challenge after 10–15 min, up to a ΔSVI% < 10%.

The last SVI value with fluid responsiveness represented the SVI max, and the SVI trigger was SVI max − 10% SVmax. We provided a fluid challenge only if the SVI was under the SVI trigger.

We administered continuous infusion of Fenoldopam (0.1 mcg/kg/min) for renal protection.

If the mean arterial pressure was <65 mmHg (e.g., after declamping of the aorta) despite the optimisation of SVI, we used noradrenaline bolus iv (0.01–0.02 mg) to maintain adequate organ perfusion [9].

We used the HOTLINE® blood and fluid warmer (Smiths Medical, Minneapolis, MN, USA) to keep the temperature of infusions between 37 and 39 °C.

We recorded the total volumes of crystalloids, colloids and blood products, the percentage of patients receiving blood products and vasopressors drugs.

For each patient, we collected three simultaneous Hb measurements: laboratory (Lab), BGA (BGA) and Masimo (SpHb).

For invasive methods, BGA with the GEM Premier 4000 Blood Gas Analyzer (Werfen, Barcelona, Spain) and the conventional laboratory analysis with the COULTER® LH 780 (Beckman Coulter, Brea, CA, USA), we took a sample of 5 mL of blood from arterial line, after discarding 10 mL of blood. The arterial line was 44 cm in length with a dead volume of about 1 mL. At the same time, we registered the SpHb value.

We performed the synchronous measurements of Hb concentration at specific times: after the induction of anaesthesia (T_0), pre and post aortic cross-clamping (T_1 and T_2), and at the end of surgery (T_3). T_0 was also the start time of GDTP.

The volume of blood in the suction chambers represented an estimation of total blood loss. We adopted blood salvage. We performed blood transfusion if Hb value was $\leq$8 gr/dL in patients without comorbidities or $\leq$9 gr/dL in patients with cardiac disease or with active bleeding.

The anesthesiologist was the same in all the interventions, and the value obtained from BGA and not the value of SpHb was the parameter for intraoperative clinical decision.

We performed statistics with Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA) and XLSTAT 2019 (Addinsoft, XLSTAT statistical and data analysis solution, Paris, France).

We applied descriptive statistics for demographic and clinical data and reported as mean $\pm$ standard deviation (SD). We presented categorical variables as absolute numbers and percentages.

To study the relationship between the measurement methods (BGA vs. Lab and SpHb vs. Lab) we performed a regression analysis at each step (T_0, T_1, T_2 and T_3) and for all samples grouped (All). We calculated the Pearson correlation coefficient (r), the determination coefficient (R^2) and the regression coefficient. We considered a *p*-value < 0.05 with a significance level of alpha of 0.05 statistically significant and we calculated confidence intervals of 95% (CI-95%).

We performed a Bland–Altman analysis [10–12] to estimate the mean bias (accuracy), standard error (precision) and the limits of agreement (LOA, $\pm$1.96 SD) between data pairs of SpHb/BGA vs. lab measures at each step and for all the samples grouped. We considered a *p*-value < 0.05 with a significance level of alpha of 0.05 statistically significant and we calculated CI-95%. We presented the agreement between the assays by data plotting.

For the SpHb and BGA trend analysis, we calculated the variation of Hb concentration by CO-oximetry between consecutive times (T_1-T_0, T_2-T_1 and T_3-T_2) and between the end and the beginning of the surgery (T_3-T_0) and compared them with Lab-Hb variations at the same steps. We generated a four-quadrant plot to evaluate clinically significant directional changes. We performed a regression analysis to calculate r and CI-95%. As precision, we applied a central exclusion zone of 1 g/dL. We excluded data lying within this zone because they contain a high level of random variability (i.e., statistical noise). We calculated concordance rate as the ratio between the number of data located in the agreement regions (upper right and lower left quadrants) and the number of data located outside the exclusion region. The upper left and lower right quadrants represent the disagreement regions. The authors predefined a four-quadrant concordance rate $\geq$90% to be clinically acceptable.

Results

In the present study, we included seventy-two patients scheduled for open abdominal aortic elective surgery. We presented the main patients' characteristics, surgical and intraoperative data in Table 1.

Table 2 shows the haemodynamic parameters and blood gas analysis data for each time of surgery.

We obtained and analysed for each method 288 Hb concentration measurements. The Hb measurements ranged from 8.3 g/dL to 16.0 g/dL for Lab, from 7.5 g/dL to 16.5 g/dL for BGA and from 6.9 g/dL to 15.0 g/dL for SpHb. We report the mean (SD) of Hb measurements during the single times and for all times together in Table 3.

Table 1. Patients' characteristics, surgical and intraoperative data. Values expressed as number (proportion) and mean (SD). * Coronary Artery Bypass Graft. † Percutaneous transluminal coronary angioplasty. ‡ Chronic obstructive pulmonary disease. § Transient Ischemic Attack. ¶ Packed red blood cells. ** Fresh Frozen Plasma.

Patient Characteristics, Surgical and Intraoperative Data.	
Patients	72
Sex (M/F)	65/7 (90.3/9.7%)
Age (years)	68.8 (7.7)
Weight (kg)	75.9 (12.9)
Height (cm)	169.4 (6.8)
Coronary disease	28 (38.9%)
CABG */PTCA †	20 (27.8%)
Cardiomyophaty	15 (20.8%)
Hypertension	59 (81.9%)
Diabetes	16 (22.2%)
Chronic renal failure	11 (15.3%)
COPD ‡	32 (44.4%)
TIA §/Ictus	7 (9.7%)
ASA I	0 (0%)
ASA II	4 (5.5%)
ASA III	68 (94.5%)
Duration of surgery (min)	231 (61)
Crystalloids IV (mL)	647.2 (238.8)
Colloids IV (mL)	795.1 (282.5)
Vasopressors use in patients	42 (58.3%)
Patients transfused with PRBCs ¶	12 (16.7%)
PRBCs volume transfused (mL)	700 (432.8)
Patients transfused with intraoperative blood salvage	69 (95.8%)
Intraoperative blood salvage transfused (mL)	623.2 (276.2)
Patients transfused with FFP **	3 (4.2%)
FFP volume transfused (mL)	695 (335.9)
Total blood loss (mL)	1103.5 (498.8)
Diuresis (mL)	627.1 (257.4)
Final Fluid Balance (mL)	328.9 (372.8)

Table 2. Hemodynamic and blood gas analysis parameters for each time of surgery. Values expressed as mean (SD). * Stroke Volume Index. † Central venous oxygen saturation.

Hemodynamic and Blood Gas Analysis Parameters.				
	T_0	**T_1**	**T_2**	**T_3**
Heart Rate (bpm)	73.4 (5.8)	71.7 (5.4)	72.2 (5.1)	73.1 (5.0)
Mean arterial pressure (mmHg)	72.5 (6.8)	72.0 (2.6)	72.6 (5.5)	78.0 (3.6)
SVI * (mL/m^2)	35.4 (5.1)	41.6 (6.0)	37.1 (5.4)	42.1 (5.1)
Cardiac Index (L/min/m^2)	2.60 (0.39)	2.98 (0.49)	2.68 (0.43)	3.07 (0.41)
Central venous pressure (mmHg)	7.4 (1.6)	7.7 (1.9)	7.7 (1.9)	7.7 (1.7)
Temperature (Celsius degree)	36.2 (0.5)	35.8 (0.5)	35.3 (0.5)	35.8 (0.6)
$ScVO_2$ †(%)	81.8 (3.4)	80.9 (3.0)	80.4 (3.2)	80.2 (2.9)
pH	7.41 (0.03)	7.40 (0.03)	7.38 (0.03)	7.41 (0.02)
Base Excess (mmol/L)	0.32 (1.4)	−0.19 (1.12)	−1.30 (1.30)	0.19 (1.27)
Lactate (mmol/L)	0.7 (0.1)	0.8 (0.2)	1.6 (0.7)	1.5 (0.6)

We showed the results of linear regression analysis at each step (T_0, T_1, T_2, T_3) and for all the samples grouped between SpHb vs. Lab and BGA vs. Lab (All) in Figure 1.

Linear regression analysis at each step and for all the samples grouped.

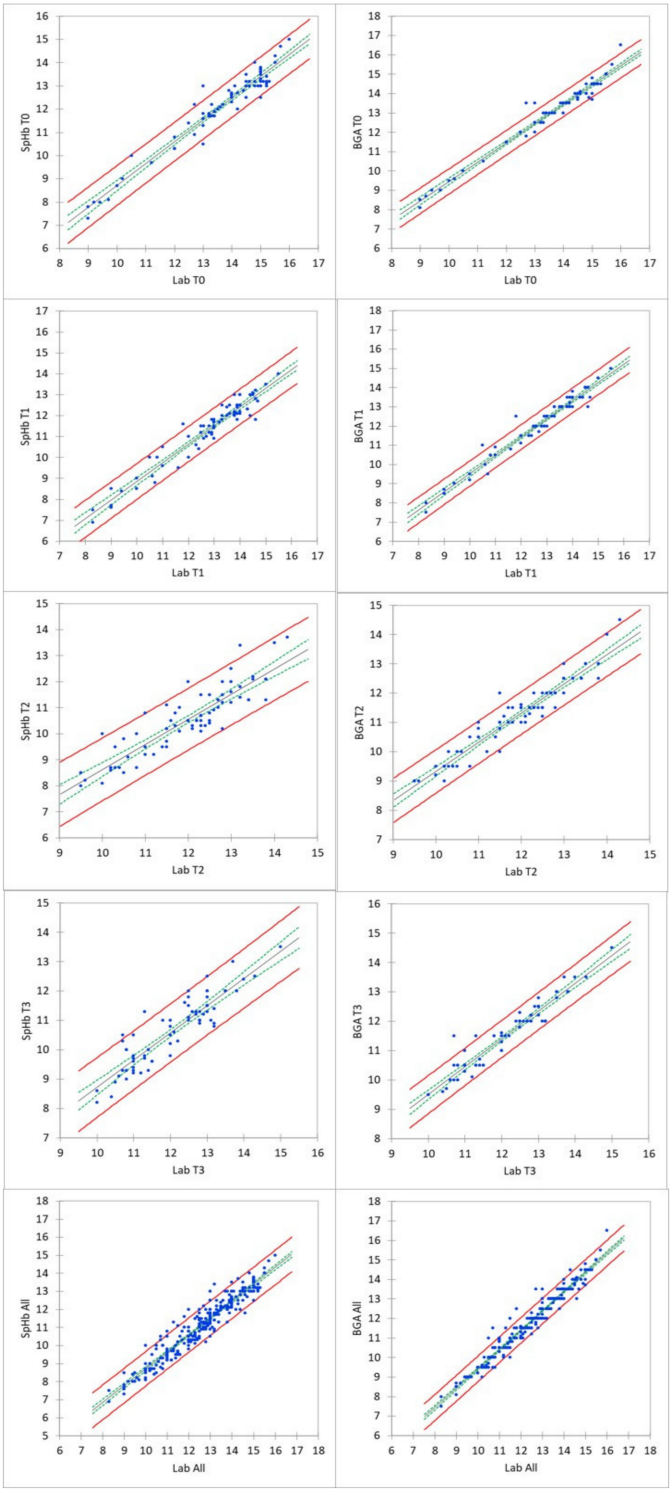

Figure 1. Results of linear regression analysis at each step (T_0, T_1, T_2, T_3) and for all samples grouped (All) between SpHb vs. Lab and BGA vs. Lab in g/dL. Hb value (blue dot). Model line regression (black line). Confidence Intervals 95% for the mean (dashed green line). Confidence Intervals 95% for observations (red line).

Table 3. Hb levels (g/dL) obtained from laboratory (Lab), co-oxymeter (BGA) and Masimo Radical 7 (SpHb) from T0 to T3 and during all the surgery (All). Values expressed as mean (SD).

Haemoglobin Concentration.			
	Lab	**BGA**	**SpHb**
T_0	13.63 (1.74)	13.08 (1.77)	12.13 (1.69)
T_1	12.75 (1.68)	12.15 (1.63)	11.32 (1.56)
T_2	11.92 (1.16)	11.25 (1.22)	10.49 (1.27)
T_3	12.16 (1.12)	11.55 (1.11)	10.72 (1.15)
All	12.62 (1.59)	12.01 (1.61)	11.16 (1.56)

We reported correlation coefficient (r), R^2 and regression coefficients in Table 4. SpHb showed an excellent r value for all the samples [0.952, CI-95% (0.939, 0.961), *p*-value < 0.0001] compared to laboratory measurements, such as BGA [0.979, CI-95% (0.973, 0.983), *p*-value < 0.0001]. We observed the lowest r value for SpHb at T_2 [0.888, CI-95% (0.826, 0.928), *p*-value < 0.0001], while for BGA r presented minimal variation during all the phases. R^2 of SpHb showed the same trend, indicating that the most variability is related to variation in Hb value measured by Lab.

Table 4. Results of regression analysis. Correlation, R^2 and regression coefficients between SpHb vs. Lab and BGA vs. Lab are reported, for each time of sampling and for all procedures (All). *p*-value < 0.0001.

Results of Linear Regression Analysis.						
	SpHb			**BGA**		
	r (95% CI)	**R^2**	**Regression Coefficient (CI-95%)**	**r (CI-95%)**	**R^2**	**Regression Coefficient (CI-95%)**
T_0	0.970 (0.952, 0.981)	0.941	0.941 (0.885–0.997)	0.984 (0.975, 0.990)	0.969	0.998 (0.956–1.041)
T_1	0.964 (0.942, 0.977)	0.929	0.892 (0.833–0.951)	0.981 (0.970, 0.988)	0.962	0.951 (0.906–0.996)
T_2	0.888 (0.826, 0.928)	0.788	0.966 (0.846–1.085)	0.956 (0.930, 0.972)	0.913	0.997 (0.924–1.070)
T_3	0.905 (0.852, 0.940)	0.819	0.929 (0.825–1.033)	0.959 (0.936, 0.975)	0.921	0.949 (0.882–1.015)
All	0.952 (0.939, 0.961)	0.905	0.934 (0.899–0.969)	0.979 (0.973, 0.983)	0.958	0.990 (0.966–1.014)

We show the data of the Bland−Altmann analysis for comparison of the accuracy of SpHb vs. Lab and BGA vs. Lab in Table 5 and scatter and Bland−Altman plots for SpHb vs. Lab and BGA vs. Lab in Figure 2. The Bland−Altmann analysis for SpHb vs. Lab showed a bias of −1.45 g/dL (CI-95% −1.51 and −1.39 g/dL, LOA from −2.42 to −0.48 g/dL) with a precision of 0.49 g/dL. The Bland−Altman analysis for BGA vs. Lab showed a bias of −0.61 g/dL (CI-95%, −0.65 and −0.57 g/dL, LOA from −1.26 to 0.04 g/dL) with a precision of 0.33 g/dL.

We show the four-quadrant plot trend analysis between SpHb vs. Lab in Figure 3. We report data points located in the exclusion zone of 1 g/dL, in the agreement regions, in the disagreement regions, with their respective percentages, and concordance rates in Table 6. Despite the high percentage of data ranged in the exclusion zone, the number of data located in the disagreement regions is very low (only two pairs registered in T_2-T_1 and T_3-T_2), with a high number of data located in the agreement regions (T_3-T_0, 60 pairs). The high concordance rates, $\geq$ 90%, suggest appropriate changes in SpHb and Lab values in the same direction.

Table 5. Bland−Altman analysis for comparison of the accuracy (Bias), precision, 95% limits of agreement of SpHb and BGA compared to Lab, for each time of sampling and for all procedures (All). *p*-value < 0.0001.

Results of Bland-Altman Analysis.				
Methods	**Time**	**Bias (g/dL) (CI-95%)**	**Precision (g/dL)**	**95% Limits of Agreement (g/dL)**
SpHb vs. Lab	**T_0**	−1.49 (−1.59; −1.39)	0.42	−2.32; −0.66
	T_1	−1.44 (−1.54; −1.33)	0.45	−2.33; −0.55
	T_2	−1.43 (−1.57; −1.29)	0.59	−2.58; −0.28
	T_3	−1.44 (−1.56; −1.32)	0.50	−2.41; −0.46
	All	−1.45 (−1.51; −1.39)	0.49	−2.41; −0.48
BGA vs. Lab	**T_0**	−0.54 (−0.62; −0.47)	0.31	−1.16; 0.07
	T_1	−0.60 (−0.68; −0.53)	0.33	−1.25; 0.04
	T_2	−0.67 (−0.76; −0.59)	0.36	−1.38; 0.03
	T_3	−0.61 (−0.68; −0.53)	0.32	−1.23; 0.02
	All	0.61 (−0.65; 0.57)	0.33	−1.26; 0.04

Scatter and Bland−Altmann plot.

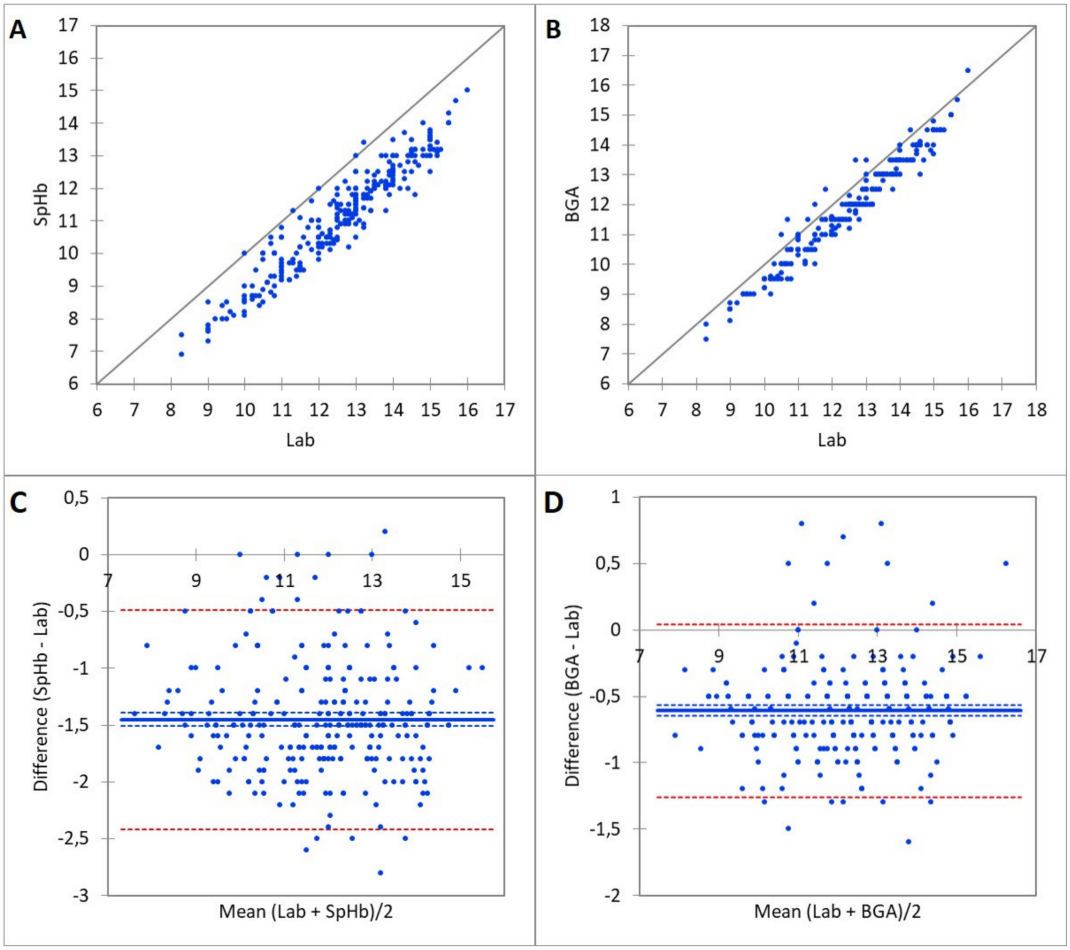

Figure 2. Scatter and Bland−Altmann plot. SpHb (**A**–**C**) underestimated the real value of Hb, obtained by Lab, with a mean difference of −1.45 g/dL (CI 95% [−1.51, −1.39]). BGA (**B**–**D**) underestimated the real value of Hb, obtained by Lab, with a mean difference of −0.61 g/dL (CI 95% [−0.65, −0.57]). Hb value (blue dot). Bias line (continued blue line). Confidence Intervals 95% for bias (dashed blue line). Confidence Intervals 95% (dashed red line).

Four-quadrant plot trends analysis between SpHb and Lab variation.

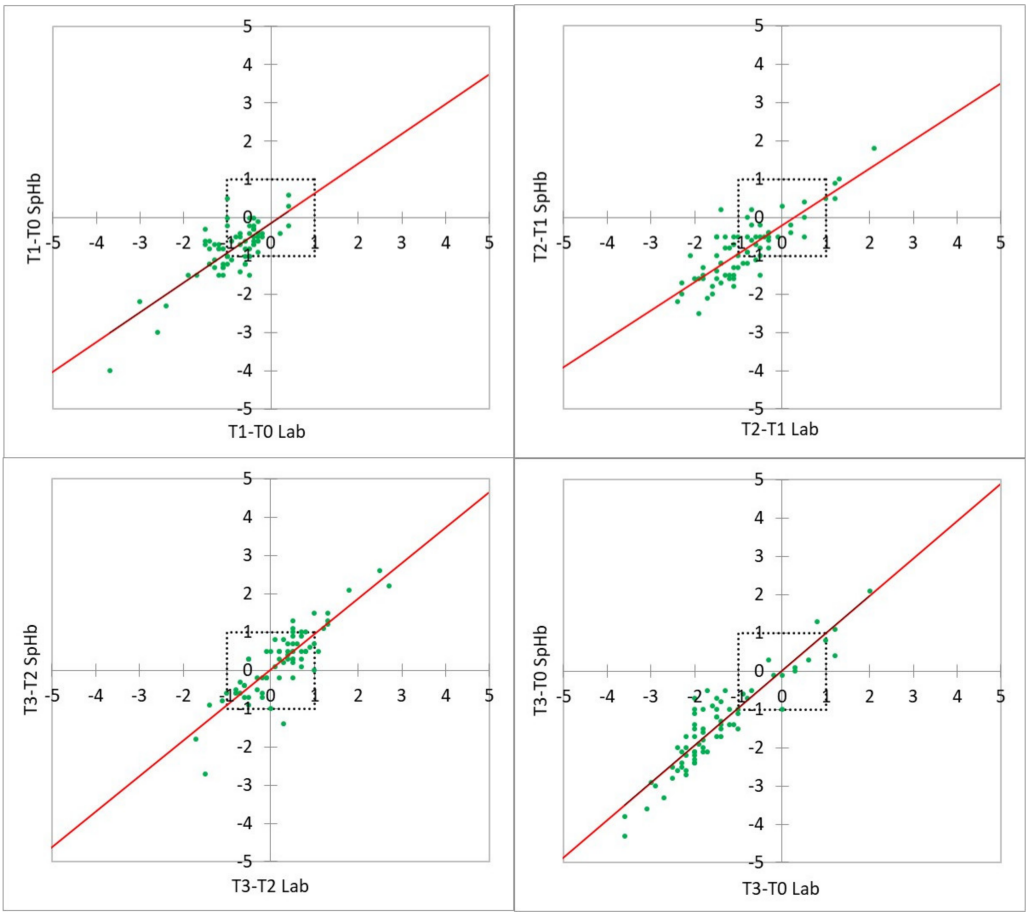

Figure 3. Four-quadrant plot trends analysis between SpHb and Lab variation (g/dL) during consecutive measurements and from T_3 to T_0. Hb value (green dot). Exclusion region (black dashed square). Model regression line (red line).

Table 6. The table shows data points located in the exclusion zone of 1 g/dL (Excluded), in the upper right and lower left quadrant (Agreement), in the upper left and lower right quadrant (Disagreement), with their respective percentages (%), and the concordance rate for SpHb vs. Lab.

Distribution of Data Points for SpHb vs. Lab.				
	Excluded	**Agreement (%)**	**Disagreement (%)**	**Concordance Rate**
T_1-T_0	41 (56.9%)	31 (43.1%)	0 (0%)	100%
T_2-T_1	29 (40.3%)	42 (58.3%)	1 (1.4%)	97.7%
T_3-T_2	56 (77.8%)	15 (20.8%)	1 (1.4%)	93.7%
T_3-T_0	12 (16.7%)	60 (83.3%)	0 (0%)	100%

We reported results of linear regression between SpHb and Lab trends in Table 7. For each trend considered, SpHb showed excellent r and R^2 value, especially for T_3-T_0. All data were statistically significant, with a *p*-value < 0.0001.

We show the four-quadrant plot trend analysis between BGA vs. Lab in Figure 4. We reported data located outside the exclusion zone of 1 g/dL, in the agreement regions, in the disagreement regions, with their respective percentages, and concordance rate in Table 8.

Table 7. Linear regression analysis results to determine the significant directional changes at each step (T_1-T_0, T_2-T_1, T_3-T_2 and T_3-T_0) between SpHb and Lab. *p*-value < 0.0001.

Results of Linear Regression Analysis for SpHb and Lab Trends.			
	r (CI-95%)	**R^2**	**Regression Coefficient (CI-95%)**
T_1-T_0	0.777 (0.665–0.855)	0.603	0.776 (0.626–0.926)
T_2-T_1	0.828 (0.738–0.889)	0.685	0.741 (0.621–0.861)
T_3-T_2	0.855 (0.778–0.907)	0.732	0.928 (0.794–1.062)
T_3-T_0	0.922 (0.877–0.950)	0.849	0.978 (0.880–1.076)

Four-quadrant plot trends analysis between BGA and Lab variation.

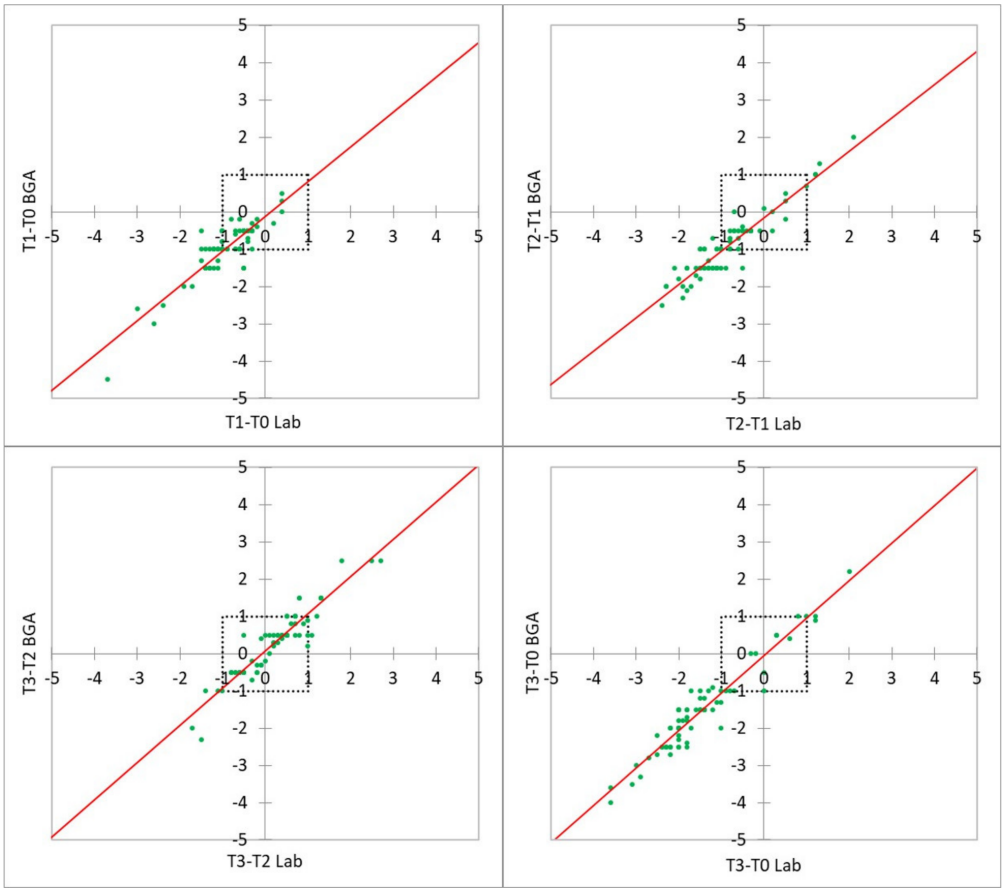

Figure 4. Four-quadrant plot trends analysis between BGA and Lab variation (g/dL) during consecutive measurements and from T_3 to T_0. Hb value (green dot). Exclusion region (black dashed square). Model regression line (red line).

Table 8. The table shows data points located in the exclusion zone of 1 g/dL (Excluded), in the upper right and lower left quadrant (Agreement), in the upper left and lower right quadrant (Disagreement), with their respective percentages (%), and the concordance rate of BGA vs. Lab.

Distribution of Data Points for BGA vs. Lab.				
	Excluded (%)	**Agreement (%)**	**Disagreement (%)**	**Concordance Rate**
T_1-T_0	45 (62.5%)	27 (37.5%)	0 (0%)	100%
T_2-T_1	31 (43.0%)	41 (57%)	0 (0%)	100%
T_3-T_2	58 (80.5%)	14 (19.5%)	0 (0%)	100%
T_3-T_0	13 (18.1%)	59 (81.9%)	0 (0%)	100%

Despite the high percentuage of data ranged in the exclusion zone, the ratio of disagreement was 0%. All the data were in the agreement regions, all above in T_3-T_0 (59 pairs). Basing on this data, the trend provided by BGA was reliable. We report the results of linear regression between BGA and Lab trends in Table 9. For each trend considered, BGA showed excellent r and R^2 value. All data were statistically significant, with a *p*-value <0.0001.

Table 9. Linear regression analysis results to determine the significant directional changes at each step (T_1-T_0, T_2-T_1, T_3-T_2 and T_3-T_0) between BGA and Lab. *p*-value < 0.0001.

Results of Linear Regression Analysis for BGA and Lab Trends.			
	r (CI-95%)	**R^2**	**Regression Coefficient (CI-95%)**
T_1-T_0	0.888 (0.827–0.929)	0.789	0.933 (0.818–1.048)
T_2-T_1	0.937 (0.901–0.960)	0.878	0.894 (0.814–0.973)
T_3-T_2	0.932 (0.893–0.957)	0.868	1.000 (0.907–1.093)
T_3-T_0	0.960 (0.936–0.975)	0.921	1.007 (0.937–1.078)

Discussion

The use of GDTP to optimise DO_2 in high-risk surgical patients improves their outcome [1,2]. DO_2 is the product between CO and arterial oxygen content, the last related to Hb concentration.

If CO monitoring is a routine tool in the operating room during complex surgery, we cannot affirm the same for Hb monitoring, even if it could offer many benefits and clinical advantages.

During high-risk bleeding surgery, the causes of anaemia are haemorrhage and haemodilution.

Dilutional anaemia, due to wrong fluid administration, may cause a paradoxical decrease in DO_2 [13]. Monnet et al. [14] reported that the administration of 500 mL of fluids might acutely decrease the Hb concentration by about 1 g/dL, or about 8%. This phenomenon should be considered as a potential unintended consequence of the administration of large amounts of fluids. In our study an appropriate protocol of fluid therapy (Goal-Directed Therapy Protocol) made the surgical population under examination homogeneous with a similar fluid balance.

Our fluid-therapy protocol provided electrolyte solution (1 mL/kg/h) as standard infusion and tetrastarch (3 mL/kg) as bolus. Our data reported 647.2 $\pm$ 238.8 mL, and 795.1 $\pm$ 282.5 mL (as mean $\pm$ SD) of crystalloids and colloids volume administrated, respectively.

The conventional haematological method (Coulter counter) and BGA (Co-oximetry) are the tools for measuring a Hb value. However, these methods are time-consuming, costly, invasive, intermittent. Instead, ideal Hb monitoring should be non-invasive, rapid/continuous and easy. Our device for non-invasive intraoperative Hb monitoring was Radical 7 device (Masimo Corp, Irvine, CA, USA) pulse CO-Oximetry. The transcutaneous spectrophotometry-based technology allows continuous Hb determination. Light received by the photodetector, after passing through the measurement site, generates electrical signals that, processed by advanced algorithms, provide an estimation of Hb based on its absorbance characteristics. An optical shield that covers the sensor prevents optical interference by other light sources.

In two literature metanalyses [6,7] about the accuracy and precision of SpHb, the authors concluded with an alert about clinical decision based on continuous non-invasive haemoglobin devices, with the lowest precision and wider 95% limits of agreement for Masimo.

However, most of the studies of these metanalyses assessed non-hemorrhagic patients and the accuracy of SpHb in shocked and/or bleeding patients was not investigated.

Our study, conducted during a high-bleeding risk surgery, showed that, despite the excellent r-value (0.952, CI-95% [0.939, 0.961], *p*-value < 0.0001), the SpHb was not

accurate enough in measuring the Hb concentration during general anaesthesia in vascular surgery. The data obtained with the Bland–Altman analysis demonstrate a large bias (−1.45 g/dL, CI-95% −1.51 and −1.39 g/dL) with broad limits of agreement (LOA from −2.41 to −0.48 g/dL), with a precision of 0.49 g/dL between the Hb values obtained with SpHb and conventional laboratory analysis. At the same time, the Bland–Altmann analysis demonstrated for BGA a bias of −0.61 g/dL (CI-95%, −0.65 and −0.57 g/dL, LOA from −1.26 to 0.04 g/dL) with a precision of 0.33 g/dL. Thus, our results show that the value of SpHb should not be considered as a replacement of more invasive haemoglobin monitoring methods.

Recently, Adel et al. [15] published a prospective observational study on the accuracy and trending of non-invasive haemoglobin measurement with a Radical-7 device in a surgical population with significant intraoperative bleeding (mean blood loss 1650 mL). They observed an excellent correlation between Lab-Hb and SpHb ($r = 0.938$, CI-95% [0.919–0.953]) and the Bland–Altman analysis showed low bias with moderate limits of agreement. Using a polar plot analysis, the angular bias (precision) was −4° (8.9°) denoting clinically acceptable trending.

This study excluded diabetic and vasculophatic patients, and none of them required the administration of vasopressor. These aspects can, in part, justify the different results of our study. Our study population showed a relatively high frequency of diabetes (22.2%) and, because the setting was vascular surgery, the presence of peripheral vascular disease represented a common clinical feature. Causey et al. [16] demonstrated that the correlation coefficient in vascular surgery is lower than other types of surgery.

Moreover, according to GDTP for the DO_2 optimisation, we optimised the volume first and then added vasopressors as needed: we used noradrenaline IV bolus in 42 patients (58.3%). Previous studies [17,18] have reported that noradrenaline administration caused a larger bias and limits of agreement but in our study, its effect was difficult to evaluate during blood sampling.

A large volume of blood loss and fluid shift characterise aortic surgery. In our population, the mean (SD) of blood loss was 1105.5 (498.8) mL. These characteristics are similar to liver surgery for transplantation.

In a prospective study on patients undergoing liver transplantation, Erdogan et al. [19] evaluated the accuracy of SpHb monitoring compared with conventional laboratory measurement. Moreover, they conducted subgroup analyses for distinct surgical phases that had special features and haemodynamic problems. The mean blood loss was 1017 ± 670.37 mL. The correlation coefficient between SpHb and laboratory Hb was highly significant (r coefficient of 0.73, CI-95% [0.67–0.78], $R^2 = 0.53$, $p < 0.001$). According to the same analyses performed for distinct phases of the surgical procedure (pre-anhepatic, anhepatic, neohepatic), similar correlations were in all the phases. Using a Bland–Altman plot, absolute bias, precision and limits of agreement of the 282 data pairs were 0.86 (CI-95% [0.50–1.21]), 1.58, and −2.25, and 3.96, respectively.

However, Huang et al. [20], in a study conducted in the same surgical population (blood loss 1982.50 ± 1470.54 mL), demonstrated that the correlation between SpHb and tHb was 0.59 ($p < 0.001$). The Bland–Altman analysis revealed that bias between SpHb and tHb was 2.28 g/dL, and limits of agreement were from −0.78 to 5.34 g/dL. A trending analysis showed that 87% of data were located within the acceptable trending area, indicating that the trending ability was not satisfied.

Regarding trend analysis, our results obtained with four-quadrant plot showed that despite the high percentuge of data ranged in the exclusion zone, the number located in disagreement regions was very low (only two pairs registered one in T_2-T_1 and one in T_3-T_2), with a high number located in agreement regions in T_3-T_0 (60 pairs). The high concordance

rates suggested appropriate changes in SpHb and Lab values in the same direction. For each time interval considered (T_1-T_0, T_2-T_1, T_3-T_2, T_3-T_0) SpHb showed excellent r and R^2 values.

Although questions regarding the absolute accuracy of SpHb have been raised, our data suggest that the trend analysis provided by Masimo may be a useful tool to detect severe perioperative bleeding and/or iatrogenic dilution. The benefits of SpHb are linked to the continuous real-time Hb measurements, which can alert the clinician when there is a dramatic change in Hb concentration requiring invasive methods for evaluation.

The trend accuracy provided by SpHb monitoring can allow: (a) the detection of decreasing Hb when it is assumed to be stable; (b) the identification of stable Hb values when they are assumed to be decreasing; and (c) the identification of increases in Hb when they are assumed not to be increasing. Thus, an acute downward SpHb trend may alert clinicians to consider an active bleeding phase and earlier needed RBC transfusion or other interventions. Likewise, a stable or increasing SpHb trend, together with other aspects of the patient assessment, can prevent an unnecessary RBC transfusion. Moreover, a gradual decrease in the SpHb in the absence of active bleeding should also prompt clinicians to re-examine their fluid management strategy.

In this regard, blood management within a GDTP should be employed to minimise RBC transfusions and related complications [21,22].

An analysis of 941,496 operations involving 15,186 transfused patients revealed a dose-dependent association of intraoperative RBC transfusion with the increased risk of mortality, wound problems, pulmonary complications, postoperative renal dysfunction, systemic sepsis, composite morbidity, and post-operative length of stay when compared with not-transfused patients [23]. Restrictive transfusion practices, with lower-than-usual Hb threshold, were safer with a 23% lower in-hospital mortality in multiple randomised controlled trials and meta-analysis [24].

In a prospective cohort study, Awada et al. [25] evaluated the impact of SpHb monitoring on blood transfusions in high-blood loss surgery. Compared to the control group (intraoperative haemoglobin monitoring by intermittent blood sampling), the SpHb-group had transfused with fewer units of blood (1.0 vs. 1.9 units for all patients; $p \leq 0.001$, and 2.3 vs. 3.9 units in patients receiving transfusions; $p \leq 0.001$), fewer patients receiving >3 units (32 vs. 73%; $p \leq 0.01$) and a shorter time to transfusion after the need was established (9.2 ± 1.7 vs. 50.2 ± 7.9 min; $p \leq 0.001$). Total blood loss for control and SpHb group were 1807 ± 794 mL and 1732 ± 804 mL, respectively (p-value 0.30). The absolute accuracy of SpHb was 0.0 ± 0.8 g/dL, and trend accuracy yielded a coefficient of determination of 0.93.

Conclusions

Our study demonstrates that in patients undergoing elective surgery with a high risk of bleeding, the Masimo Pulse CO-Oximetry is not sufficiently accurate in assessing the current value of Hb. However, this technology may be useful to assess the trending of the Hb concentration and thus to control an important factor of the DO_2 within the intraoperative GDTP.

The real-time ability of SpHb offers a “motion picture”, with a continuous trend that could allow right blood management with prompt recognition of acute bleeding and/or iatrogenic dilution.

Our study presents some limitations. We excluded patients scheduled for urgent and emergency surgery and patients with preoperative anaemia.

Further studies are needed to evaluate the clinical usefulness of the Pulse CO-Oximetry during acute haemorrhage, especially regarding the impact on decision-making about RBC transfusions.

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References

1. Cecconi, M.; Corredor, C.; Arulkumaran, N.; Abuella, G.; Ball, J.; Grounds, R.M.; Hamilton, M.; Rhodes, A. Clinical review: Goal-directed therapy-what is the evidence in surgical patients? The effect on different risk groups. *Crit. Care* **2013**, *17*, 209. [CrossRef] [PubMed]
2. Giglio, M.; Manca, F.; Dalfino, L.; Brienza, N. Perioperative hemodynamic goal-directed therapy and mortality: A systematic review and meta-analysis with meta-regression. *Minerva Anestesiol.* **2016**, *82*, 1199–1213. [PubMed]
3. Gupta, P.K.; Sundaram, A.; Mactaggart, J.N.; Johanning, J.M.; Gupta, H.; Fang, X.; Forse, R.A.; Balters, M.; Longo, G.M.; Sugimoto, J.T.; et al. Preoperative anemia is an independent predictor of postoperative mortality and adverse cardiac events in elderly patients undergoing elective vascular operations. *Ann. Surg.* **2013**, *258*, 1096–1102. [CrossRef] [PubMed]
4. Bourner, G.; Dhaliwal, J.; Sumner, J. Performance evaluation of the latest fully automated hematology analyzers in a large, commercial laboratory setting: A 4-way, side-by-side study. *Lab. Hematol.* **2005**, *11*, 285–297. [CrossRef] [PubMed]
5. Berkow, L.; Rotolo, S.; Mirski, E. Continuous noninvasive hemoglobin monitoring during complex spine surgery. *Anesth. Analg.* **2011**, *113*, 1396–1402. [CrossRef] [PubMed]
6. Kim, S.H.; Lilot, M.; Murphy, L.S.; Sidhu, K.S.; Yu, Z.; Rinehart, J.; Cannesson, M. Accuracy of continuous noninvasive hemoglobin monitoring: A systematic review and meta-analysis. *Anesth. Analg.* **2014**, *119*, 332–346. [CrossRef] [PubMed]
7. Hiscock, R.; Kumar, D.; Simmons, S.W. Systematic review and meta-analysis of method comparison studies of Masimo pulse co-oximeters (Radical-7 or Pronto-7) and HemoCue(R) absorption spectrometers (B-Hemoglobin or 201+) with laboratory haemoglobin estimation. *Anaesth. Intensive Care* **2015**, *43*, 341–350. [CrossRef] [PubMed]
8. Johnson, A.; Mohajer-Esfahani, M. Exploring hemodynamics: A review of current and emerging noninvasive monitoring techniques. *Crit. Care Nurs. Clin. N. Am.* **2014**, *26*, 357–375. [CrossRef] [PubMed]
9. Salmasi, V.; Maheshwari, K.; Yang, D.; Mascha, E.J.; Singh, A.; Sessler, D.I.; Kurz, A. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. *Anesthesiology* **2017**, *126*, 47–65. [CrossRef] [PubMed]
10. Bland, J.M.; Altman, D.G. Agreement between methods of measurement with multiple observations per individual. *J. Biopharm. Stat.* **2007**, *17*, 571–582. [CrossRef] [PubMed]
11. Bland, J.M.; Altman, D.G. Agreed statistics: Measurement method comparison. *Anesthesiology* **2012**, *116*, 182–185. [CrossRef]
12. Bland, J.M.; Altman, D.G. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* **1986**, *1*, 307–310. [CrossRef]

13. Lai, C.W.; Starkie, T.; Creanor, S.; Struthers, R.A.; Portch, D.; Erasmus, P.D.; Mellor, N.; Hosie, K.B.; Sneyd, J.R.; Minto, G. Randomized controlled trial of stroke volume optimization during elective major abdominal surgery in patients stratified by aerobic fitness. *Br. J. Anaesth.* **2015**, *115*, 578–589. [CrossRef]
14. Monnet, X.; Julien, F.; Ait-Hamou, N.; Lequoy, M.; Gosset, C.; Jozwiak, M.; Persichini, R.; Anguel, N.; Richard, C.; Teboul, J.L. Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. *Crit. Care Med.* **2013**, *41*, 1412–1420. [CrossRef]
15. Adel, A.; Awada, W.; Abdelhamid, B.; Omar, H.; Abd El Dayem, O.; Hasanin, A.; Rady, A. Accuracy and trending of non-invasive hemoglobin measurement during different volume and perfusion statuses. *J. Clin. Monit. Comput.* **2018**, *32*, 1025–1031. [CrossRef]
16. Causey, M.W.; Miller, S.; Foster, A.; Beekley, A.; Zenger, D.; Martin, M. Validation of noninvasive hemoglobin measurements using the Masimo Radical-7 SpHb Station. *Am. J. Surg.* **2011**, *201*, 592–598. [CrossRef]
17. Coquin, J.; Dewitte, A.; Manach, Y.L.; Caujolle, M.; Joannes-Boyau, O.; Fleureau, C.; Janvier, G.; Ouattara, A. Precision of noninvasive hemoglobin-level measurement by pulse co-oximetry in patients admitted to intensive care units for severe gastrointestinal bleeds. *Crit. Care Med.* **2012**, *40*, 2576–2582. [CrossRef]
18. Frasca, D.; Dahyot-Fizelier, C.; Catherine, K.; Levrat, Q.; Debaene, B.; Mimoz, O. Accuracy of a continuous noninvasive hemoglobin monitor in intensive care unit patients. *Crit. Care Med.* **2011**, *39*, 2277–2282. [CrossRef]
19. Erdogan Kayhan, G.; Colak, Y.Z.; Sanli, M.; Ucar, M.; Toprak, H.I. Accuracy of non-invasive hemoglobin monitoring by pulse CO-oximeter during liver transplantation. *Minerva Anestesiol.* **2017**, *83*, 485–492. [CrossRef]
20. Huang, P.H.; Shih, B.F.; Tsai, Y.F.; Chung, P.C.; Liu, F.C.; Yu, H.P.; Lee, W.C.; Chang, C.J.; Lin, C.C. Accuracy and Trending of Continuous Noninvasive Hemoglobin Monitoring in Patients Undergoing Liver Transplantation. *Transplant. Proc.* **2016**, *48*, 1067–1070. [CrossRef]
21. Meybohm, P.; Shander, A.; Zacharowski, K. Should we restrict erythrocyte transfusion in early goal directed protocols? *BMC Anesth.* **2015**, *15*, 75. [CrossRef]
22. Kozek-Langenecker, S.A.; Ahmed, A.B.; Afshari, A.; Albaladejo, P.; Aldecoa, C.; Barauskas, G.; De Robertis, E.; Faraoni, D.; Filipescu, D.C.; Fries, D.; et al. Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology: First update 2016. *Eur. J. Anaesthesiol.* **2017**, *34*, 332–395. [CrossRef]
23. Ferraris, V.A.; Davenport, D.L.; Saha, S.P.; Austin, P.C.; Zwischenberger, J.B. Surgical outcomes and transfusion of minimal amounts of blood in the operating room. *Arch. Surg.* **2012**, *147*, 49–55. [CrossRef]
24. Carson, J.L.; Carless, P.A.; Hebert, P.C. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst. Rev.* **2012**, *10*, CD002042.
25. Awada, W.N.; Mohmoued, M.F.; Radwan, T.M.; Hussien, G.Z.; Elkady, H.W. Continuous and noninvasive hemoglobin monitoring reduces red blood cell transfusion during neurosurgery: A prospective cohort study. *J. Clin. Monit. Comput.* **2015**, *29*, 733–740. [CrossRef]