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Detection of hypovolemia by non-invasive hemodynamic monitoring during major surgery using Ringer´s solution, 5% albumin, or 20% albumin as infusion fluid: a post-hoc analysis of a randomized clinical trial

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Abstract

Background Fluid loading with crystalloids is the conventional treatment of major hemorrhage but might tend to create fluid overload. We studied hemodynamic profiles of fluid replacement therapies during major surgical hemorrhage and compared the ability of pulse pressure variation (PPV), plethysmographic variation index (PVI), cardiac output (CO) and Guyton´s approach to detect hypovolemia.

Methods In this single center randomized controlled trial, fluid replacement therapy to treat hemorrhage in 42 patients was randomized to consist of either 5% albumin (12 mL/kg) or 20% albumin (3 mL/kg) over 30 min, both completed by Ringer lactate replacing blood loss in a 1:1 ratio, or Ringer solution alone in a 3:1 ratio. Measurements included CO, PPV, PVI, arterial and central venous pressures, heart rate (HR) and subsequent calculation of Guyton´s physiological parameters. CO was measured by an esophageal Doppler probe.

Results The Ringer-only fluid program resulted in slight hypovolemia (mean, 313 mL), decreased mean arterial pressure (MAP), increased HR, PPV values and vasopressor requirement. The 5% and 20% albumin programs were more effective in filling the vascular system, as evidenced by higher mean circulatory filling pressure and unchanged or decreased PPV over the 5 h observation period. The 20% albumin increased the systemic vascular resistance and the resistance to venous return. Receiver operating characteristics curves indicated that hypovolemia > 500 mL could only be accurately detected by PPV when 5% albumin was used, that PVI was reliable when Ringer was infused, and that CO indicated the hypovolemia when 20% albumin was administered.

Conclusions The trends in PPV, PVI, and CO reflected the changes in intravascular volume, but how well they indicated hypovolemia > 500 mL may differ depending on the choice of infusion fluid. Identifying hypovolemia using non-invasive hemodynamic monitors remains challenging and associated with low predictive values.

Trial registration number: NCT05391607, May 26, 2022.

Keywords Hypovolemia, Hemorrhage, 5% albumin, 20% albumin, Ringer-lactate, Circulatory filling pressure, Pulse pressure variation

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Background

Treatment of major hemorrhage during surgery is challenging for the clinician as the goal is to provide enough infusion fluid to restore, maintain, or improve tissue perfusion and adequate hemodynamics while avoiding fluid overload. This requires knowledge about both the hemorrhaged volume and blood volume expansion (BVE) properties of available fluids. Very large volumes may be needed if only crystalloid fluid is used, which increases the risk of tissue edema (lung, gastrointestinal tract), rebleeding, and poor wound healing. In contrast, lower volumes can be sufficient when colloid fluids are used due to their different pharmacokinetic profile. Hence, the BVE capacities of used fluids are important to have in mind when striving to maintain normovolemia, and the subsequent hemodynamic evolution is essential to evaluate the impact and the quality of the treatment.

Open radical cystectomy is a lengthy operation that involves a rapid blood loss of around 800 mL during the approximately 30 min when the bladder is removed [1]. The patient typically requires very large intravenous fluid volumes if only crystalloid is used. Therefore, in a recent clinical trial, we randomized patients undergoing this operation to receive alternative volume replacement programs with 5% or 20% albumin and compared their BVE to that of Ringer lactate (RL) [2]. The blood volume was calculated by a mass balance method based on comparison between measured blood losses and the hemodilution.

Identifying hypovolemia using non-invasive hemodynamic monitors would greatly help the anesthesiologist when facing a major hemorrhage. Many parameters can be measured by everyday used monitoring. However, how effective these methods are in detecting hypovolemia during major surgery with rapid hemorrhage need to be precise.

In this secondary analysis of a three-group parallel randomized clinical trial [2], we performed an observation study of the hemodynamic parameters, the relationships between the degree of hypovolemia and the clinically used methods to detect hypovolemia, namely pulse pressure variation (PPV), plethysmography variability index (PVI), and cardiac output (CO), between different fluid therapies to combat major hemorrhages.

We analyzed the evolution of the Guyton´s parameters for each fluid regimen. Guyton's formulas allow analysis of the interaction between the heart and the blood vessels to determine cardiac output at the equilibrium. They bring a useful assessment of the vascular filling pressure, systemic vascular resistance and can help to evaluate the clinical efficacy of fluid therapies [3].

The aim of the present study is to examine how well different hemodynamic measures reacts to plasma volume expansion or hypovolemia when a fluid therapy is given to maintain normovolemia and find some non-invasive hemodynamic tools to detect hypovolemia.

Methods

Ethics approval

The study was approved by the Swiss government's local ethics committee (cantonal ethics committee KEK Bern, Switzerland, KEKBE ID 2022–00209, chairperson Prof C. Seiler, May 11, 2022); prospectively registered at ClinicalTrials.gov (NCT05391607, principal investigator P.Y. Wuethrich, May 26, 2022) and conducted in compliance with the Declaration of Helsinki and good clinical practice. The full trial protocol can be accessed on request. All patients gave preoperative written informed consent to participate.

Study design, inclusion and exclusion criteria

This is a planned secondary analysis of a study primarily designed to analyze differences in BVE of RL vs 5% albumin vs 20% albumin solutions administered to 42 patients during major hemorrhage. This was an investigator-initiated, open-label, three-arm, active controlled single-center trial conducted at the Department of Urology University Hospital Bern, Switzerland, between May 26, 2022 and April 13**,** 2023. Reporting complied with the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statements. The number of included patients was based on the power calculation of the original trial. These results have been published elsewhere [2]. Consecutive patients planned for pelvic lymph node dissection, open radical cystectomy, and urinary diversion were screened for inclusion. Inclusion criteria were age > 18 y and non-emergency surgery. Exclusion criteria were renal dysfunction (eGFR < 60 $mLmin^{-1}1{,}73\ m^{-2}$), heart failure, hypersensitivity or allergy to exogenous albumin, pregnancy, breastfeeding, known or suspected drug or alcohol abuse.

Anesthesia and preparations

All patients were encouraged to drink 800 mL of a carboloading solution (Preload, Nestlé Health Science, Vevey, Switzerland) the evening before and 400 mL up to 2 h before arrival at the operating theater. No i.v. fluids were administered within 12 h before surgery.

Thoracic epidural analgesia was maintained during the surgery with bupivacaine 0.25% infused at a rate of 6 to 8 mL/h. Anesthesia induction was performed with fentanyl 2 µg/kg, propofol 2 mg/kg and rocuronium 0.6–0.9 mg/kg intravenously to facilitate endotracheal intubation and maintained with sevoflurane 0.6 MAC (age corrected) and dexmedetomidine at a rate of 0.3 $\mu g\ kg^{-1}\ h^{-1}$. Ventilation with an inspired oxygen fraction of 60% was mechanically

controlled to maintain $P_{Et}CO_2$ between 35 to 40 mmHg, with a positive end-expiratory pressure of 5 mmHg and tidal volume of 8 mL/kg. Supportive administration of norepinephrine (NE) to maintain a target mean arterial blood pressure (MAP) of > 65 mmHg was initiated at a rate of 0.03 µg kg^{-1} min^{-1}.

Allocated fluid management

Patients were randomly allocated to one of three volume replacement groups: RL (Group "Ringer"), 5% albumin (Group "5% albumin"), 20% albumin (Group "20% albumin").

1. RL (Fresenius Kabi AG, Kriens, Switzerland) was administered in the active control group "Ringer". RL solution was administered at a 3:1 ratio of the blood loss [4, 5].
2. 5% albumin (Albumin CSL 5%, CSL Behring, Bern, Switzerland) was given at a volume of 12 mL/kg (ideal body weight) was started and continued over 30 min at a constant rate constant rate during removal of the bladder [6].
3. 20% albumin (Albumin CSL 20%, CSL Behring, Bern, Switzerland) 3 mL/kg (ideal body weight) was started and continued over 30 min at a constant rate during removal of the bladder [7].

Both albumin infusions were complemented by a RL matching blood loss in a 1:1 ratio [6].

Baseline intravenous fluid administration was performed using 1 mL kg^{-1} h^{-1} of RL solution during the pelvic lymph node dissection and hemorrhagic phase, respectively, and then 3 mL kg^{-1} h^{-1} until the end of surgery [8, 9].

Fresh frozen plasma transfusion was administrated based on the senior surgeons' observations and packed red blood cells were transfused to maintain a blood hemoglobin (Hb) value > 80 g/L.

Blood loss was assessed by accounting for the aspirated blood and the weight difference of the gauzes before and after-use at regular intervals (15 min) [10].

Blood volume

BVE was calculated as follows: the initial blood volume (BV) was first obtained using Nadler's formula (BV_0), where the total BV prior to the infusion of 20% or 5% albumin (BV_0) was derived from the height (h) in meters, body weight (w) in kilograms, and sex [11].

$$\text{Male}: \ BV_0 = 0.3669h^3 + 0.03219w + 0.6041$$

$$\text{Female}: \ BV_0 = 0.3561h^3 + 0.03308w + 0.1833$$

The BV at a later time 1 was calculated by first estimating the total hemoglobin mass in the circulation at baseline [$Hb_{mass(0)}$] as being equal to the product of BV_0 and the blood Hb concentration at baseline, Hb_o. Losses from Hb_{mass} were then subtracted for each measurement, and the BV_1 obtained by dividing this difference by a freshly taken Hb [12, 13].

$$Hb_{mass(0)} = BV_o Hb_o$$

$$Hb_{mass(1)} = Hb_{mass(0)} - \text{Blood loss}_{(0-1)}[(Hb_0 + Hb_1)/2]$$

$$BV_1 = {Hb_{mass(1)}}/{Hb_1}$$

$$\text{Blood volume expansion (BVE)} = BV_1 - BV_o$$

Hemodynamics

Data on central hemodynamics were collected at regular intervals during the 30-min colloid-infusions and up to 300 min after the infusion was initiated. Reporting was truncated at 240 min as some surgeries were completed earlier which left missing data.

CO was recorded with a CardioQ esophageal probe (Deltex Medical, Chichester, UK) and PVI with a Radical-7 Pulse CO-Oximeter (Masimo International, Neuchâtel, Switzerland) at the same time as the blood samples were collected.

The radial artery was cannulated for measurement of the MAP, PPV, and heart rate (HR).

The central venous pressure (CVP) was measured via a cannula placed in the right internal jugular vein after calibration against the atmospheric pressure after the induction of anesthesia.

Endpoints

The primary outcome of this study, already published in a dedicated paper was to monitor the plasma volume expansion to compare the efficacy of RL solution from those of 5% albumin and 20% albumin when used to combat hypovolemia during removal of the bladder (hemorrhagic phase of cystectomy) [2].

The secondary endpoints are the evaluation of the longitudinal hemodynamic parameters evolution over 300 min (NE, MAP, CO, HR, PPV, PVI) during different fluid therapies, also presenting Guyton's hemodynamic parameters. The primary analysis of this secondary study aims to compare the parameters PPV, PVI and CO explicitly between the 3 intervention groups, evaluating their relation with hypovolemia.

Hemodynamics calculations

The static hemodynamic parameters CO, MAP, HR and the dynamic parameters PPV and PVI were reported as crude data, but the static parameters were also integrated and reported as "Guyton´s hemodynamic parameters". Here, the mean circulatory filling pressure (P_{msa}) has been derived from the static hemodynamic parameters,

assuming a constant veno-arterial compliance of 24:1:[14, 15].

$$P_{msa} = aCVP + bMAP + cCO,$$

where $a = 0.96$, $b = 0.04$ $(a + b = 1)$, and $c = 0.96 \times 1/26 \times$ systemic vascular resistance at rest. However, c is commonly derived from anthropometric data. The value of c varies between 0.3 and 1.2 depending on age and body constitution (average 0.6) and is calculated as follows [3]:

$c = 0.038\ (94.17 + 0.193\ \text{age})\ /\ [4.5\ (0.99^{\text{age}-15}\ 0.007184\ (\text{height}^{0.725})\ \text{weight}^{0.425}]$.

The global pumping efficiency $Eh = (P_{msa} - CVP) / P_{msa}$; Systemic vascular resistance (SVR) = (MAP–CVP)/CO; Pressure gradient for venous return, $dVR = P_{msa} - CVP$; Resistance to venous return, RVR = dVR / CO.

Statistics

In terms of summary measures, data are presented with mean and standard deviation in case of normally distributed variables and with median and interquartile range otherwise. Categorical variables are summarized with counts and frequencies.

To account for the repeated measure design of the study, the time evolution of longitudinally measured variables is analyzed with a linear mixed-effect model featuring the time point—treatment group interaction as fixed effects and a random offset for each patient. Based on these models, time averages as well as pairwise contrasts among groups (e.g., RL versus 5% albumin) were computed by means of marginal means and are presented with mean and 95%-confidence intervals. Tukey's method is employed to adjust the post-hoc pairwise contrasts for multiple comparisons.

Time-dependent area under the receiver operating characteristic curves (AUROCs) were computed using the method presented by Blanche and colleagues [16]. Time-dependent AUROCs relating PPV, PVI and CO individually with hypovolemia were computed for each treatment group separately. Hypovolemia was defined as blood loss larger than 500 mL. Associated 95%-confidence intervals were computed by means of bootstrap sampling (N = 1′000).

The sample size is based on the primary publication. A p-value < 0.05 was considered statistically significant and all analyses were performed R version 4.0.2.

Results

The pre-operative baseline characteristics were similar between groups, age averaged 65 ± 11 y, BMI 25 ± 5 kg/m (mean ± SD), and 30% of the included patients had an ASA physical status classification ≥ 3. Intraoperative fluid variables are presented in Table 1. The infused volume of 5% albumin was 884 ± 215 mL while the administered amount of 20% albumin was 239 ± 48 mL. The Ringer group received significantly more RL than each of the 5% and 20% albumin groups (2800 mL vs 2200 mL vs 2000 mL, respectively, $P = 0.003$). The blood loss averaged 848 mL [615–1145] (median, [IQR]). Three patients received blood components.

Hemodynamics

Figure 1 presents the hemodynamic variables of our patients during their fluid programs. Patients in the Ringer group had MAPs dropping and higher HRs in comparison to the other groups, especially around the end of the bleeding phase, when blood loss occurred at its highest rate (T = 60 min). These patients required more NE (Fig. 1E), specially during the first 120 min of observation. Moreover, the patients in the Ringer group featured lower CO ($P = 0.014$) and higher SVR ($P = 0.026$) (Fig. 1A and C). In the albumin groups, MAP was lower in patients receiving 5% albumin as compared to those receiving 20% albumin ($P = 0.017$) (Fig. 1B). The systemic vascular resistance (SVR) increased when administering 20% albumin but decreased or was unchanged from the 5% albumin and RL solutions (Fig. 1C).

Table 1 Fluid balance variables during surgery. Data are given as the median [IQR], mean ± SD, or counts and frequencies (%)

	Ringer	5% albumin	20% albumin	P-value
Duration of surgery (min)	325 [302, 377]	347 [336, 404]	343 [321, 373]	0.487
Hemorrhagic phase (min)	64 [51, 80]	56 [45, 69]	58 [50, 75]	0.836
Blood loss (mL)	694 [601, 1306]	862 [600, 1095]	832 [749, 1165]	0.900
Crystalloids (mL)	2800 [2350, 4200]	2182 [1500, 2400]*	2000 [1700, 2300] *	0.003
Colloids (mL)	0	884 ± 215	239 ± 48*	< 0.001
PRBC (yes)	2/11 (15%/85%)	0/14 (0%/100%)	0/14 (0%/100%)	0.339
FFP (yes)	1/13 (8%/92%)	0/14 (0%/100%)	1/13 (7%/93%)	0.338
Norepinephrine (mg/kg)	0.020 [0.013;0.028]	0.014 [0.011;0.017]	0.013 [0.010;0.015]	0.114

PRBC packed red blood cell; *FFP* fresh frozen plasma, *$P < 0.002$ compared to Ringer group; $^{+}P < 0.002$ compared to 5% albumin

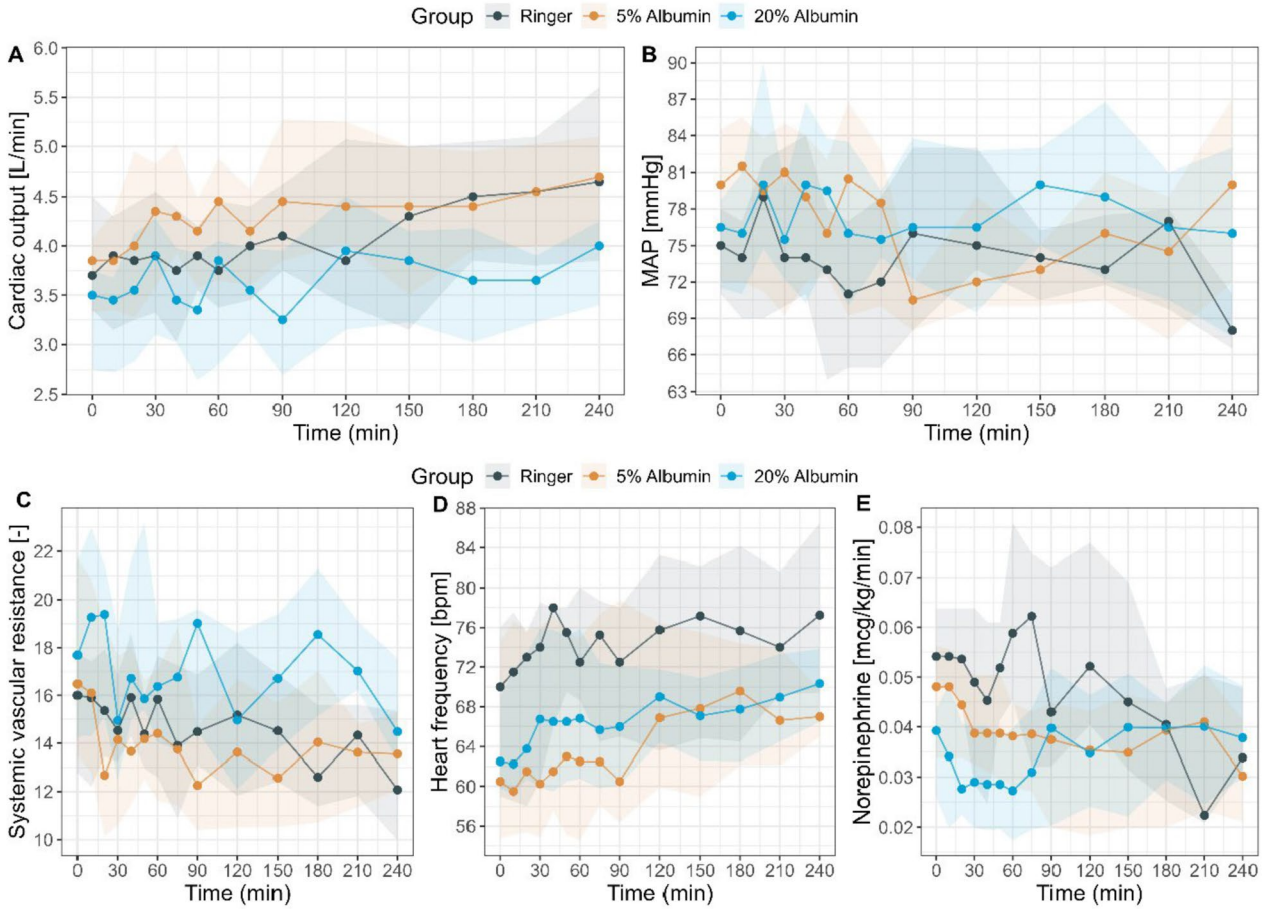

Fig. 1 Cardiac output, MAP (mean arterial pressure), systemic vascular resistance, heart frequency, norepinephrine as values over the time. Data are presented with median and interquartile range (shaded bands)

Overall, patients in the Ringer group had higher PPV values ($P=0.056$) and PVI ($P=0.046$) (Fig. 2) than the patients in the albumin groups. Moreover, the patients in the RL group featured higher relative PPV ($P=0.003$).

When the intervention started, the median PPV averaged 8 (95% CI: 6 to 10) with no statistically significant difference between the groups. PPV decreased during the surgery in the 5% albumin group (all time points compared to baseline, $P<0.0001$) and the 20% albumin group (all $P=0.01$) but not in the RL group ($P=0.42$).

We found lower PPV and PVI in the 5% albumin group.

Guyton's parameters

Intraoperative averaged values over 240 min and changes relative to baseline of Guyton's variables are presented in Supplementary Table 1.

The global pumping efficiency (Eh) was higher for RL than for both albumin solutions to which the higher CVP for the albumin solutions contributed greatly (Supplementary Fig. 1A). The pressure gradient for venous return (dVR) was lower for 20% albumin than for the other fluids, but the changes during surgery did not differ significantly (Supplementary Fig. 1B). The resistance to venous return (RVR) increased most from 20% albumin and least with 5% albumin ($P=0.033$) (Supplementary Fig. 1C).

Figure 3 presents the mean circulatory filling pressure (P_{msa}) which initially increased when 5% or 20% albumin was infused but not when RL was administered, showing better vascular filling with the albumin solutions.

Hypovolemia

CO displays these predictive capacities which are measured by the AUC for each time point whilst accounting for the repeated measure design of the study. The threshold for clinically relevant hypovolemia was set to 500 mL and relative values of the hemodynamic parameters (T = +0 min was the baseline) were chosen. Note that AUC values are only available for those time points for which there are some hypovolemic patients. High AUC

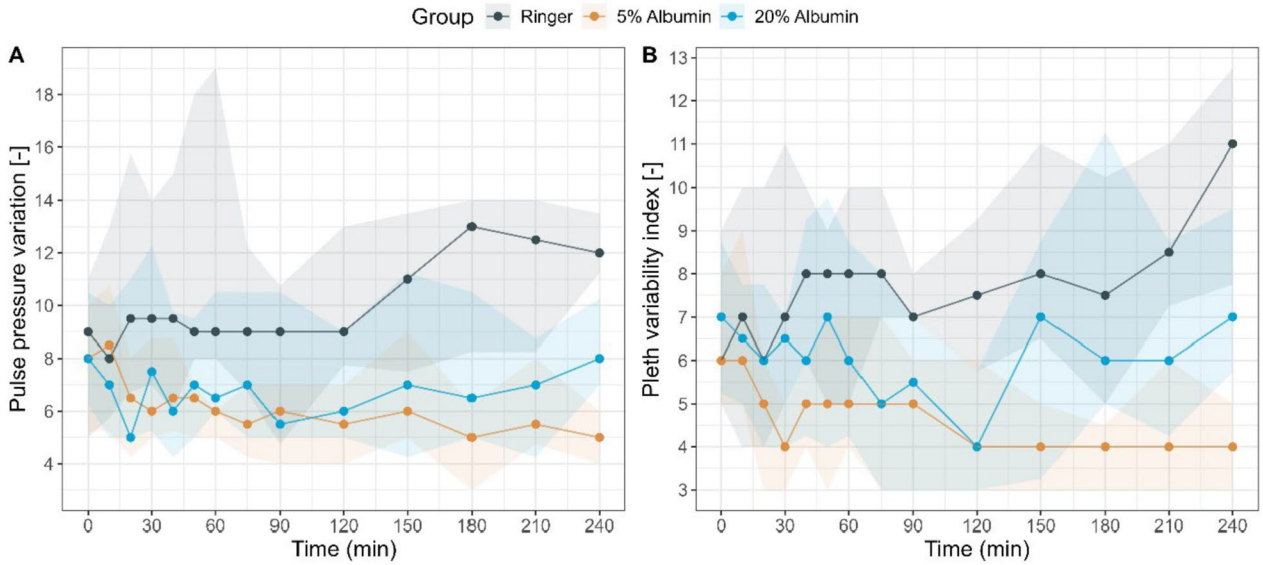

Fig. 2 Hemodynamic parameters **A** PPV (pulse pressure variation), **B** PVI (plethysmographic variation index). Data are presented with median and interquartile range (shaded bands)

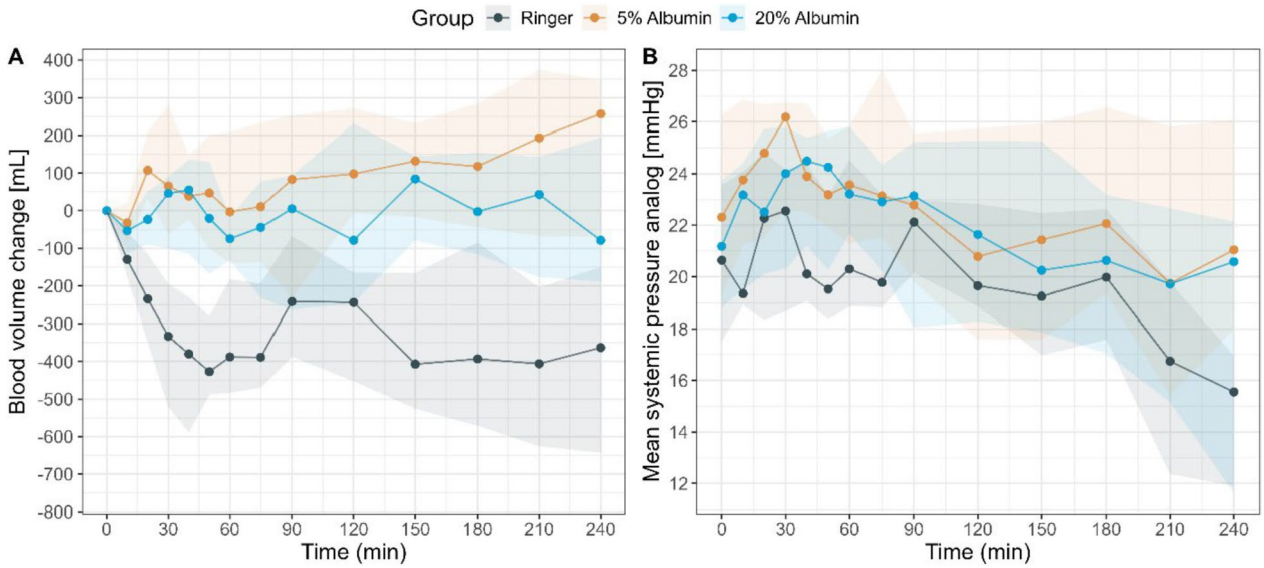

Fig. 3 Relation between blood volume change and mean systemic pressure analog (Pmsa). Data are presented with median and interquartile range (shaded bands)

values (0.91, 95%-CI 0.80–0.99) are found for the relative PPV values in the 5% albumin group. Moderate AUC values (0.71, 95%-CI 0.34–0.98) are found for the relative PVI values in the RL treatment group and low AUC values (0.61, 95%-CI 0.33–0.85) are found for the relative CO values in the 20% albumin group (Supplementary Fig. 2).

Figure 4 shows PPV, PVI and CO for different degrees of hypovolemia. The distribution of the hemodynamic parameters strongly depends on the treatment group: for example, hypovolemia greater than 500 mL were associated with high PPV values only in the RL group, whereas we find the opposite for the patients treated with 5% albumin (Fig. 4B). Overall, Fig. 4 highlights that the choice of plasma volume expander (RL or albumin) has a significant impact on the relationship between the hemodynamic parameters and hypovolemia: pooling the three treatment groups would mask (or confound) this impact,

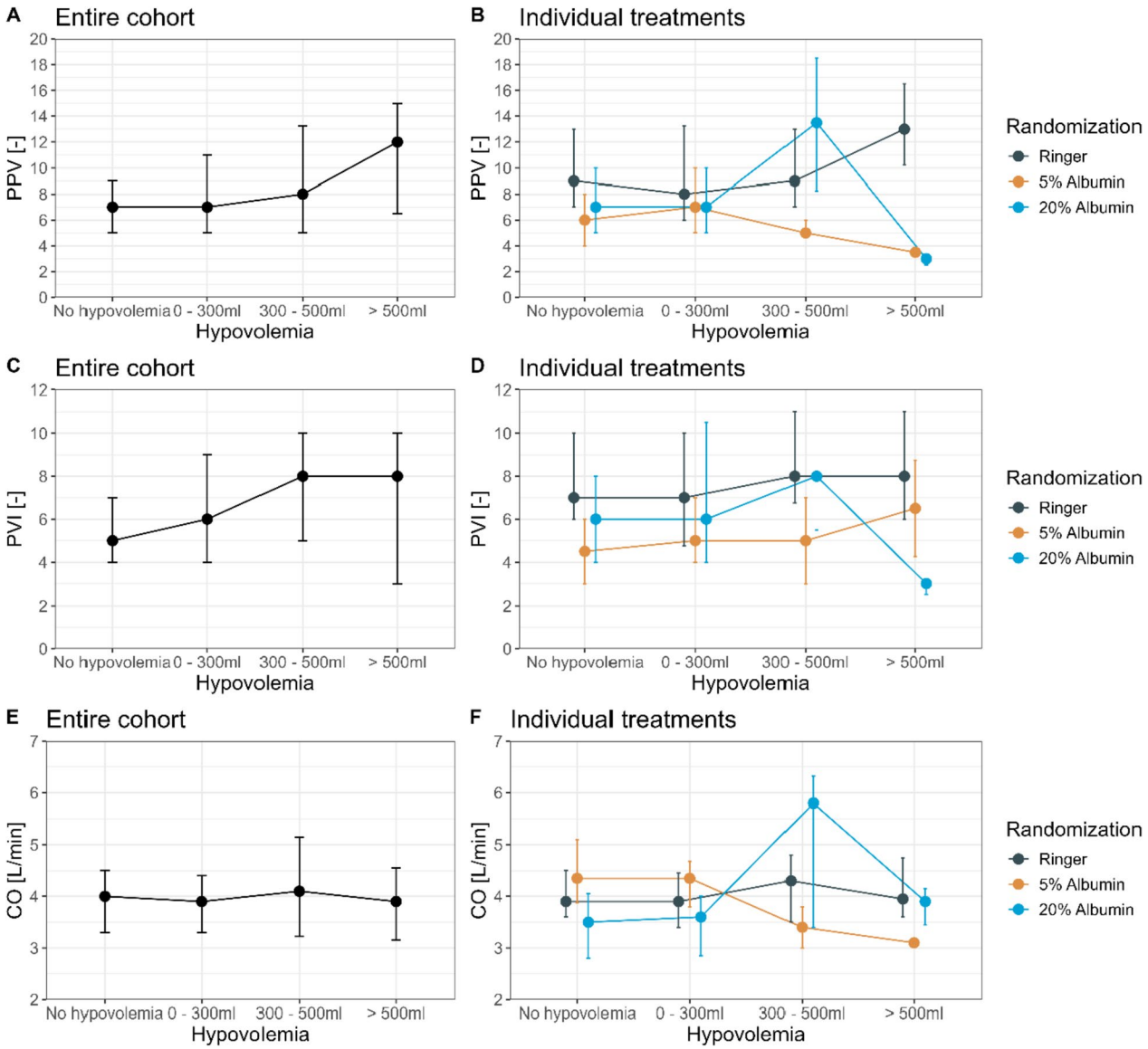

Fig. 4 Pooled PPV (pulse pressure variation) PVI (plethysmographic variation index), CO (cardiac output) values are presentedaccording to normovolemia or to the degrees of hypovolemia in the entire cohort **A**, **C**, **E** or according to the randomized groups **B**, **D**, **F**. Note that there were only a few numbers of hemorrhage > 500 ml in the 20% albumin group

thus requiring a group-specific analysis of the predictive capacities of PPV and PVI with respect to hypovolemia.

Discussion

Detecting hypovolemia by using non-invasive monitoring methods has always been a challenge. As actual tools, there are many parameters that are not considered robust enough to correctly identify a hypovolemic state. For example, CO largely depends ontoo many other factors (including timing of the assessment, amount of fluid for fluid challenges) to be taken alone as an indicator of hypovolemia [17, 18]. Heart frequency, MAP, and diuresis have also been found to be inconclusive as perioperative predictors. PPV and PVI as indicators of hypovolemia have a low predictive value of around 50–60% [19].

This paper is taking advantages of different hemodynamic parameters measured during a study initially designed to compare three different fluid therapy programs during expected major surgical hemorrhage of > 500 mL. The analyzes allowed to consider MAP, CO, PPV and PVI easy obtainable and non-invasive parameters to help detect hypovolemia when surgical hemorrhage occurs.

Main findings

Overall, the hemodynamic profile and the BV calculations showed that the RL-alone treatment was associated with a modest hypovolemia. This finding was further supported a transient hypotension at 60 to 90 min requiring more vasopressor after beginning of the bleeding phase, lower MAP, higher HR and by higher PPV and lower P_{msa} than for the albumin programs. PVI increased by 60% in response to hypovolemia amounting to 300–500 mL while PPV required hypovolemia of > 500 mL to increase by the same magnitude. The albumin solutions better filled the vascular system, which is consistent with PPV results.

In contrast, CO did not appear to be a reliable indicator of hypovolemia, which is probably due to hypovolemic stress and a blunting effect of the NE that was given to most patients, which modified the interaction between intravascular volume and venous capacitance [20].

The issue was further explored by ROC curves which, over time, showed that hypovolemia > 500 mL could only be safely detected by PPV when 5% albumin was used, PVI could only indicate the hypovolemia when RL was infused, and by CO when 20% albumin is used. When the result was split between treatments, PPV during RL administration appeared to be the only useful indicator of hypovolemia exceeding 500 mL.

The issue was further explored by ROC curves which, over time, showed that hypovolemia > 500 mL could only be safely detected by PPV when 5% albumin was used, PVI could only indicate hypovolemia when Ringer was infused, and by CO when 20% albumin was used. Thus, taken together, these hemodynamic parameters were not reliable enough to safely detect a hypovolemia of > 500 mL.

Hemodynamic profiles

In general, hypovolemia was associated with reduced CO and MAP while PPV and PVI increased. This was pronounced in the Ringer group, but not in both albumin groups: here, PPV, PVI and CO remained nearly constant.

The PPV measurements support that replacing 1 mL of blood loss with 3 mL of RL (3:1 rule) is insufficient during major surgery. After the hemorrhagic phase, approximately 50% of the patients in the RL group had a PPV value higher than 10%, which is generally considered to indicate hypovolemia. At this time point, 5% and 20% albumin performed better. The PPV show that patients were not fluid responsive when 5% and 20% albumin were given, i.e., the circulation did not signal the need for more intravascular volume. Moreover, the PPV was modestly effective in detecting hypovolemia as AUC of the ROC curves were all around 0.71.

CO is shifted upwards in the albumin groups while the BV remained unchanged, which might be due to dissociation between these parameters due to hypovolemic stress and the NE infusions [20]. Hence, CO depends on many hemodynamic factors and its value above baseline is no guarantee that the patient is euvolemic.

P_{msa} is reduced by approximately 25% when anesthesia is induced and CVP increases due to the mechanical ventilation [21]. These changes make patients sensitive to small further reductions of P_{msa} as venous return is given by $dVR = P_{msa} - CVP$. Overall, P_{msa} was higher for the albumin solutions than for RL, meaning that the stressed blood volume was better maintained by albumin. An evaluation of the changes in P_{msa} from baseline showed a decrease for RL and an increase for the albumin solutions. In addition, in our euvolemic situations: 20% albumin increased SVR whereas 5% albumin decreased SVR. Moreover, the vasoconstrictive response to hypovolemia is blunted during anesthesia. All these three changes make the anesthetized patient more susceptible to disturbances of venous return due to hypovolemia. Here, all patients received a preemptive concomitant continuous low-dose administration of NE, aiming to maintain MAP > 65 mmHg, and thus counteract the anesthesia-induced vasodilation [10]. This could explain the counter-intuitive and previously described decrease in SVR after administration of hyper-oncotic fluids in severe hypovolemic patients [22].

Finally, the different responses in SVR might be attributed to whether the patient is fluid responsive or not. In our experiment, patients in the 20% albumin groups were not fluid responsive, as PPV was low when they were fluid loaded. If they had been fluid responsive, CO would increase, MAP would be unchanged, and SVR would decrease. On the other hand, patients in the Ringer group were fluid responsive as their PPV were higher than 10. Due to the three treatment groups, we have a Simpson's paradox here: in the entire cohort we have a negative association of PPV and BV change, which however disappears within the individual groups.

The 20% albumin preparation also elevated the SVR, which might be due to the increased blood viscosity that result from infusion of hyperoncotic solutions. The clinical efficacy of 5% albumin was slightly better than of 20% albumin due to the greater BVE, higher CO and unchanged SVR. However, the 5% albumin infusions contained of much more fluid volume than 20% albumin did (884 *versus* 239 mL). This effect has been shown to be long-lasting for all the albumin solutions [23].

Treatment of hemorrhage-induced hypovolemia:

The adult human body responds to hemorrhage up to 1 L by increasing SVR, which is mainly due to

secretion of NE. This reaction maintains MAP while CO decreases as there is less blood to pump [4, 20, 24]. Recruitment of interstitial fluid to the plasma by "capillary refill" is initiated but operates too slowly to compensate for major hemorrhage [25, 26]. Experiments in sheep show that capillary refill is seriously blunted by volatile anesthetics, which is probably due to the inhibitory effects on lymphatic pumping by all anesthetic agents [27, 28].

Volume treatment by infusing fluid that matches the blood loss restores all physiological responses to hypovolemia provided that irreversible shock has not yet developed. Crystalloids are the standard care for the treatment of more-than-minimal hypovolemia. Support for this practice are from animal studies [1, 5, 29], volunteer experiments, and trauma studies [30]. In addition, a large body of literature has accumulated over the past decades that evaluates the usefulness of hypertonic or hyper-oncotic solutions to combat hypovolemic states, but these approaches are not currently favored [22, 24, 31]. However, the nature of the optimal fluid solution, amount, and timing of administration are still matter of debate [4, 20, 24]. Target endpoints for fluid resuscitation are also still debated and undefined. A too aggressive fluid replacement could result in hypervolemia and re-bleeding due to dilution of coagulation factors, [1, 5, 29] and necessitate a de-escalation therapy thereafter due to fluid accumulation syndrome.

The rationale behind the use of solutions with oncotic strength is a reduced positive fluid balance, increased CO, and decreased SVR if administered in hypovolemic state. Here, this could be demonstrated only in part as SVR increased during the administration of 20% albumin, albeit in non-fluid responding patients.

The concomitant administration of albumin solution in a 5% or 20% concentration and a restricted amount of RL suggests a formulation with potentially high usefulness as conventional resuscitation therapy in hemorrhage and continuous bleeding for a period of around 1 h. Administration of additional fluids is unlikely to be needed, which reduces the positive fluid balance. This is of importance as excessive postoperative fluid balance has been related to poorer outcome including anastomotic leakage in major surgery involving intestines or colon [32, 33]. In addition, our study shows that a replacement in a 3:1 ratio with RL alone resulted in a modest reduced blood volume and elevated PPV value. Reasons to the inability to RL to fully maintain the BV might involve transudation into the operating field or else to accumulation of fluid in the "third fluid space", which is an issue when > 1.5 L of RL has been infused [34].

Limitations:

The amount of infused fluid in the RL alone group was titrated to match the bled volume in the proportion 3:1. By contrast, albumin was administered as bolus infusions over 30 min when a known phase of hemorrhage started. The strategies to administer fluid study arms were not fully congruent, but we believe that our protocol well reflects how the two types of fluid would be provided in the clinical situation. Moreover, there is no widely accepted rule for how much of albumin should be infused to combat major blood loss during surgery.

Overall, given the limited sample size in each treatment group, the AUROC display large variability and uncertainty with respect to the reference value and these results should be considered exploratory.

Also, this study was adapted to evaluate the BVE comparing 3 fluid therapies. We are limited in the evaluation of the hemodynamics parameters (SVR) due to the small sample sizes. Thus, the predictive capacities of the hemodynamic variables considered here with respect to hypovolemia feature inherent uncertainties and should be interpreted with caution.

The NE therapy was adapted to the discretion of the anesthesiologist during the intervention and the minimal targeted MAP was 65 mmHg. The hemodynamics can be disturbed by this important setting.

P_{msa} is most adequately measured by stopping the circulation and allowing the pressures in the arterial and venous blood equilibrate. This can be done by inflating a blood pressure cuff in the arm. Other approaches are based on ventilatory maneuvers during invasive hemodynamic monitoring (Wijnberge et al.) [35]. We used the empirical equations suggested in the literature for calculation of P_{msa} and the other variables in Guyton´s hemodynamic theory and, therefore, cannot be the true values.

Conclusions

The BVE obtained with RL according to the 3:1 rule was insufficient, which received support from the PPV measurements as approximately 50% of the patients had a PPV value higher than 10%. Hypovolemia of 500 mL was best indicated by PPV when 5% albumin was infused, by PVI when Ringer was used, and by CO when 20% albumin was infused. Both 5% and 20% albumin were potent plasma volume expanders with higher mean systemic filling pressures.

Abbreviations

GFR	Glomerular filtration rate
BVE	Blood volume expansion
MAP	Mean arterial pressure
PPV	Pulse pressure variation
PVI	Plethysmography variability index
CO	Cardiac output

NE	Norepinephrine
POD	Postoperative day
i.v.	Intravenous
BV	Blood volume
Hb	Hemoglobin
SD	Standard deviation
BMI	Body mass index
FFP	Fresh frozen plasma
PRBC	Packed red blood cells
P_{msa}	Mean systemic filling pressure
Eh	Global pumping efficiency
SVR	Systemic vascular resistance
dVR	Pressure gradient promoting venous return
RVR	Resistance to venous return
ROC	Receiver operating characteristics
AUC	Area under the curve
AUROC	Area under the curve receiver operating characteristic curves
RL	Ringer's lactate

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05357-z.

Supplementary file 1.

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None

Author contributions
F. J., MD: This author helped plan the study, write applications, organize and collect the patient data and co-write the paper, and submitted the manuscript. R.G. H., MD, PhD: This author helped plan the study, analyse the data, design graphs and tables, and co-write the manuscript. M. H., Dr. sc. ETH: This author helped calculate and analyse the data, design graphs and tables, and co-write the manuscript P.Y. W., MD: This author helped plan the study, write applications, collect the patient data, analyze the data, co-write the paper.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Swiss government's local ethics committee (cantonal ethics committee KEK Bern, Switzerland, KEKBE ID 2022–00209, chairperson Prof C. Seiler, May 11 2022); All patients gave preoperative written informed consent to participate Consent for publication.

Competing interest
The authors declare no competing interests.

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