

Blood Volume Analysis Can Distinguish True Anemia From Hemodilution in Critically Ill Patients

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Background: Peripheral hematocrit (pHct) is traditionally used as a marker for blood loss. In critically ill patients who are fluid resuscitated, pHct may not adequately represent red blood cell volume (RBCV). We hypothesize that the use of pHct alone may overestimate anemia, potentially leading to unnecessary interventions.

Methods: Patients admitted to the intensive care unit underwent blood volume analysis. Serial blood samples were collected after injection of ¹³¹I-albumin. Samples were then processed by the Blood Volume Analyzer-100. RBCV and total blood volume (TBV) were calculated using the directly measured plasma volume (PV) and pHct. A computed normalized hematocrit (nHct) adjusts pHct to the patient's ideal blood volume.

Results: Thirty-six patients (21 men), aged 49.8 years \pm 18.4 years, Acute Physiology And Chronic Health Evaluation II score 14.9 \pm 8.1, and injury severity score 29.4 \pm 12.4 had 84 blood volume analyses performed on 3 consecutive days. Using ratios of TBV compared with ideal TBV, patients were stratified into three separate groups: hypovolemic (16 of 84), normovolemic (23 of 84), and hypervolemic (45 of 84). Mean differences between pHct and nHct in each group were 4.5% \pm 3.1% ($p \leq 0.01$), 0.0% \pm 1.2% ($p = 0.85$), and -6.5% \pm 4.1% ($p \leq 0.01$), respectively. pHct, when compared with nHct, diagnosed anemia (Hct <30) nearly equal within the hypovolemic and normovolemic groups. However, pHct overdiagnosed anemia in 46.7% of hypervolemic patients.

Conclusion: Use of blood volume analysis in critically ill patients may help to distinguish true anemia from hemodilution, potentially preventing unnecessary interventions.

Key Words: Blood volume analysis; Hemodilution; Normalized hematocrit.

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Critically injured and postoperative surgical patients often undergo massive resuscitations during their postinjury and postoperative course. Hypovolemic shock, multiple injury, the postoperative state, and sepsis are some of the factors that can contribute to both significant fluid requirements and significant fluid shifts. The hematocrit level is used as a surrogate measure for the blood volume and is used in

conjunction with blood pressure, heart rate, central venous pressure (CVP), and pulmonary artery (PA) catheter values to analyze the overall fluid status of the patient. In the first few days postinjury or postoperatively, a decrease in the hematocrit level is commonly observed, which is often attributed to hemodilution rather than a loss of red cell mass. However, this is neither routinely quantified nor is there a rapid, convenient, and accurate test to measure this phenomenon. The hematocrit has also been shown to correlate poorly with the degree of blood loss.¹ Furthermore, the clinical measures previously mentioned cannot be used to measure the blood volume.

There is a lack of ability, then, to accurately measure not only the blood volume but also the plasma volume (PV) and third-space volume. The attendant reliance on surrogate measures such as the hematocrit, heart rate, blood pressure, and invasively monitored hemodynamic parameters may poorly reflect the patients' true fluid status. As an example, since its introduction in 1970, the PA catheter has been widely used in critical care settings because of its ability to measure a wide range of hemodynamic parameters.² However, several recent randomized controlled trials have shown no benefit in survival or decrease in complications for patients managed with a PA catheter compared with less-invasive methods in a variety of populations including high-risk surgical patients,³ patients with acute lung injury,⁴ general medical intensive care unit (ICU) patients,⁵ or patients with sepsis and acute respiratory distress syndrome.⁶

It is possible that a safe, accurate, rapid, and convenient measure of the blood volume could significantly decrease the number of unnecessary measures such as blood draws, blood transfusions, radiographs, computed tomography (CT) scans, CVP measurements, and PA catheter placements. Accurate assessment of patients' fluid status could also decrease complications resulting from undiagnosed hypovolemia or volume overload including organ failure, atrial fibrillation, myocardial injury, transfusion reactions, skin necrosis and pressure sores, acute lung injury, acute respiratory distress syndrome, and death. Furthermore, better characterization of the blood volume could decrease usage and even placement of central lines in many instances for the purpose of hemodynamic monitoring, decreasing the risks associated with central venous catheters. To date, there is no published data regarding the measurement of the blood volume in critically ill trauma and postoperative surgical patients or the potential effect this technique may have in comparison with traditional

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parameters in reducing the number of tests and complications in this population.

Blood Volume Analysis

Measurement of the blood volume in humans was first described in 1915⁷ and used indicator dye dilution. Since then, the development of radiolabeled biological tracers has further refined these techniques. Currently, ¹³¹I-labeled albumin and ⁵¹Cr- or ⁹⁹Tc-labeled red blood cells are used to measure blood volume and are considered the gold standards.⁷ Although accurate, these tests are uniformly expensive, time consuming, and difficult to obtain, making them less clinically applicable in a critical care setting. To label red blood cells, they must be harvested from the patient, labeled with ⁵¹Cr or ⁹⁹Tc and then infused. Other techniques such as pulse-dye techniques and exhaled carboxyhemoglobin dilution have also been described, with variable success and generalizability.^{8,9}

The Blood Volume Analyzer (BVA)-100 (Daxor Corporation, New York, NY) uses ¹³¹I-labeled albumin (Volumex; Daxor Corporation) in a refinement of the indicator dilution principle. This is based on the fact that a known concentration of injectate will equilibrate in the circulation, thus the subsequent degree of dilution is directly proportional to the volume of the diluent. A known concentration of the tracer is infused, and after allowing for mixing time, five consecutive blood draws are performed at fixed time intervals. This built-in redundancy compensates for possible mixing error as well as allowing a linear extrapolation of the concentrations to time zero resulting in more accurate volume determinations. Measurements at serial time points also allows for the calculation of the third-space volume by giving an estimation of the rate and quantity of tracer transudation out of the vascular space.¹⁰ The use of albumin ensures that the tracer readily equilibrates between the intra- and extravascular compartments. This device is Food and Drug Administration approved and is in use in >50 hospitals across the United States. It is currently being used to guide decisions in the management of congestive heart failure, hypertension, cardiac surgery, and critical care. Its use is well represented in the literature in these fields.^{7,11–13}

In our study, we aim to measure the PV and calculate total blood volume (TBV), red blood cell volume (RBCV), and normalized hematocrit (nHct). We hypothesize that the use of peripheral hematocrit (pHct) alone in critically ill trauma patients will result in overdiagnosis of anemia, potentially leading to unnecessary interventions.

PATIENT AND METHODS

This study was reviewed and approved by the Institutional Review Board at Oregon Health and Science University.

Patient Selection

A member of the study team screened patients for eligibility on Mondays to Wednesdays as the goal was to perform blood volume evaluations on 3 consecutive days and nuclear medicine capability was not available on weekends. Adult patients requiring admission to the ICU at Oregon Health & Science University after trauma or major surgery

were eligible for study inclusion. To be enrolled, the presence of a central line or arterial line was required because of the need for frequent blood draws. Patients were not enrolled until they were hemodynamically stable and no longer required active resuscitation or pressor therapy. Patients were also not enrolled until their blood could be drawn on 3 consecutive weekdays. Therefore, patients were enrolled a minimum of 24 hours after ICU admission and up to 14 days after admission.

Additional exclusion criteria included renal failure requiring hemodialysis or renal replacement therapy and pregnancy, because of known changes in blood volume in this population.

Study Protocol

After informed consent was obtained from the patient or a legal surrogate, Volumex tracer (¹³¹I-labeled serum albumin with 25 μ Ci of radioactivity) was infused as a single bolus during a time period of 60 seconds via a preexisting peripheral or central venous line. Collection of 6 mL of blood was performed from a separate site at –1 minute, 12 minutes, 18 minutes, 24 minutes, 30 minutes, and 36 minutes relative to the Volumex infusion for each respective single blood volume analysis event. The blood was then centrifuged and the plasma was processed on the BVA-100 by a certified nuclear medicine technician. The generated data were then electronically tabulated automatically and a report was printed. The blood volume was measured up to 3 consecutive days, and thus, each subject would have a maximum of one blood volume analysis per day for 3 days. If the patient was discharged or had their central line or arterial line removed before the end of the study, they underwent less than three analyses. Study variables such as age, gender, height, weight, Injury Severity Score (ISS), Acute Physiology and Chronic Health Evaluation II score, and mean CVP before each analysis were recorded. Intake and output volume data were collected from ICU flow sheets and entered into the database.

BVA-100

Using the indicator dilution principle, PV was analyzed by the BVA-100 at five separate time points after Volumex injection. A best fit line was then generated to extrapolate back to time zero to analyze the PV at the initiation of the study. The slope of the line represents the rate of albumin transudation. Given both PV and pHct, RBCV and TBV were calculated algebraically. $\text{Peripheral Hct} = \text{RBCV}/(\text{RBCV} + \text{PV})$ and $\text{TBV} = \text{RBCV} + \text{PV}$. A validated formula is then applied to the subject characteristics (height, weight, gender, and ideal weight) to determine ideal TBV, RBCV, and PV. The proprietary formula used to calculate the ideal values was derived from >100,000 measurements of height and weight from the metropolitan life tables,¹⁰ which has previously been validated in critically ill surgical patients.¹⁴ These data were then used to determine ideal weights at which people of different heights have the same body composition. Fat tissue has less blood volume per unit mass when compared with lean tissue. Therefore, if a subject is below ideal weight, there is a higher proportion of lean tissue and more blood volume per unit mass. If a subject is above ideal weight, there is a

higher proportion of fat tissue and therefore a lower blood volume per unit mass. This method of ideal blood volume calculation avoids systematic errors from norms based on weight or body surface area alone. SD data from this method were used to establish severity of blood volume abnormalities and to define the cutoffs of normal blood volumes at >8% deviation, as previously determined by Feldschuh and Enson.¹⁵ For example, if blood volume was >8% in excess relative to ideal, then the subject was considered to be hypervolemic. If the blood volume was >8% in deficit relative to ideal, then the subject was considered hypovolemic. Subjects were categorized as normovolemic if the deviation from ideal was <8%. By applying a previously validated correction factor to the pHct for the volume derangement,¹⁶ an nHct was computed by the BVA-100.

TABLE 1. Patient Characteristics

	n = 36
Male/female	21/15
Age (yr)	49.8 ± 18.4
Body mass index	29.4 ± 6.2
ISS	29.4 ± 12.4
APACHE-II score	14.9 ± 8.1
Median (IQR) days from admit to enrollment	4.0 (2.0–5.0)
Mean fluid balance (mL) 24 h before initiation	1,255 ± 2,337

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation. Values shown are means ± SD if not specific otherwise.

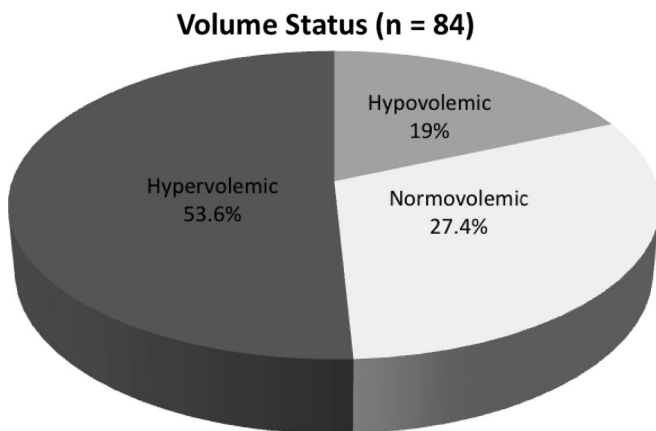


Figure 1. Proportions of volume status determined by blood volume analysis.

Statistical Analysis

Statistical analyses were performed using PASW Statistics 17.0.3 (SPSS, Inc., Chicago, IL). The Shapiro–Wilk test was used to determine normal distribution of data points. Continuous data were analyzed using Student’s *t* test or the Mann–Whitney *U* test where appropriate. The Pearson product–moment correlation coefficient was used to determine linear dependence. Categorical data were analyzed using the χ^2 or Fisher’s exact test where appropriate. Significance was defined as a *p* value <0.05.

RESULTS

Thirty-six patients admitted to the ICU were enrolled and had a total of 84 blood volume analyses performed on up to 3 consecutive days (Table 1). On average, subjects had a positive fluid balance of 1,255 mL, for the 24 hours before study initiation. Of the 84 blood volume analyses performed (Fig. 1), 16 were hypovolemic (19.0%), 23 were normovolemic (27.4%), and 45 were hypervolemic (53.6%).

When comparing the median total input volumes across the three volume status groups (hypovolemic, normovolemic, and hypervolemic), there were no significant differences between the groups. In addition, there were no significant differences across the volume status groups in median net fluid balance or mean CVP before blood volume analysis (Table 2).

Using the Pearson correlation coefficient, no consistent or significant linear relationships were observed between net fluid balance and changes in blood volumes (PV, RBCV, and TBV) and pHct between each analysis (i.e., day 1–2, day 2–3, and day 1–3). There was also a lack of linear relationship between changes in blood volume and changes in the rate of albumin transudation between each analysis. No significant correlation was observed between ISS and the rate of albumin transudation. In addition, there were no significant differences in ISS when the scores were compared across the three volume status groups. There was a moderate linear correlation between pHct and RBCV (Fig. 2, A) with a Pearson correlation coefficient of 0.47 and *p* < 0.01. A strong linear correlation was observed between nHct and RBCV (Fig. 2, B) with a Pearson correlation coefficient of 0.87 and *p* < 0.01.

The difference between the measured pHct, the calculated nHct, and the sensitivity of each test for diagnosing anemia was compared (Table 3). Those in the normovolemic group showed no difference (*p* = 0.85) between pHct and nHct measurements. In this volume status group, both pHct and nHct tests were adequately sensitive to detect a he-

TABLE 2. Volume Status and Fluids Administered/Net Fluid Balance/Mean CVP Before Each Blood Volume Analysis

	Hypovolemic (n = 16)	Normovolemic (n = 23)	Hypervolemic (n = 45)
Fluid in (mL)	21,647 (3,136–37,715)	24,194 (18,210–42,221)	21,769 (16,367–34,610)
Net fluid balance (mL)	13,579 (4,702–18,969)	6,330 (1,969–13,520)	9,535 (4,373–17,373)
Mean CVP (mm Hg)	(n = 11) 9 (8–12)	(n = 12) 11 (6–14)	(n = 27) 11 (9–14)

Within the mean CVP data row, n represents the number of CVP measurements for the respective volume status category. All values are reported as medians (interquartile range). All comparisons *p* = NS, Mann–Whitney *U* test.

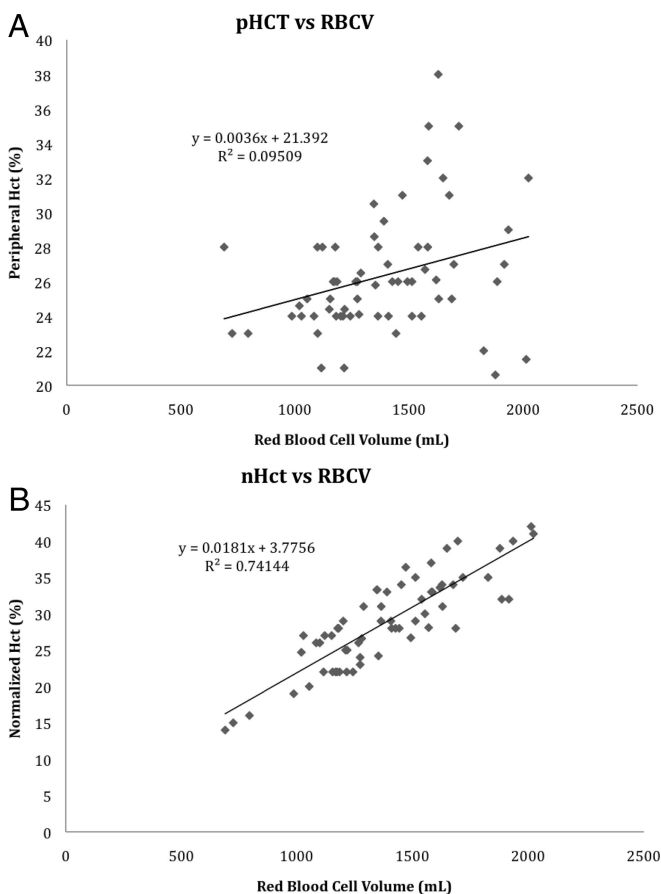


Figure 2. (A) Scatter plot of peripheral hematocrit (pHct) versus red blood cell volume (RBCV). (B) Scatter plot of normalized hematocrit (nHct) versus red blood cell volume.

matocrit <30% in 78.3% (18 of 23) of the cases. In the hypovolemic group, both pHct and nHct were nearly equally sensitive (87.5% vs. 93.8%, $p = 0.76$) in diagnosing anemia. However, there was a mean difference of $4.5\% \pm 3.1\%$ between pHct and nHct in the hypovolemic group (25.9% vs. 21.4%, $p \leq 0.01$). Analysis of the hypervolemic group showed a significant difference of $6.5\% \pm 4.1\%$ between the pHct and nHct (26.8% vs. 33.3%, $p \leq 0.01$). The pHct method diagnosed anemia 46.7% more often when compared with nHct in the hypervolemic group. When comparing pHct and nHct in all patients and all blood volume analyses, the mean difference was significantly different

(26.7% vs. 29.4%, $p \leq 0.01$). pHct diagnosed anemia 23.8% more often than nHct in the overall group.

DISCUSSION

Hemorrhage remains the leading cause of preventable death in trauma patients. Physicians often use a decreasing hematocrit as a marker for ongoing blood loss. Other physiologic measures, such as heart rate, blood pressure, CVP, pulmonary capillary wedge pressure, and physical examination findings, such as peripheral edema and jugular vein distention, are all used in combination with hematocrit to estimate a patient's overall fluid status. However, data have shown that these surrogate measures have a concordance rate of 50% at best¹⁷ in determining the true volume status of the patient and hematocrit may not represent true RBCV.¹⁴

Blood volume measurement and analysis is not a new technique. It was first described in the early 20th century and has become more refined during time and evolved to use radiolabeled tracers. Although the use of dual radiolabeled tracers is considered to be the gold standard, it requires removing, labeling, and reinfusion of red blood cells, making this process time consuming and expensive. The development of the single radiolabeled tracer technique without the necessity of labeling red blood cells makes the BVA-100 more convenient and practical. Dworkin et al.¹⁶ have shown that use of the single radiolabeled tracer is equivalent to the dual radiolabeled tracer method.

Measurement of blood volumes in ICU patients has lead to several interesting findings. In this population of severely injured patients, the total volume of fluid received and the net fluid balance was not significantly different across hypovolemic, normovolemic, or hypervolemic patients. Based on these results, the volume status of the patient cannot be predicted by the volume of fluid administered. In addition, the mean CVP measured before blood volume analysis in each of the three volume categories was not significantly different. Prior studies have revealed a poor correlation between CVP and intravascular volume status,^{18,19} and this study supports these findings.

Comparisons of changes in net fluid volume balance with changes in blood volumes and pHct showed no significant correlations at any time point. It would be expected that an increase in net fluid balance would be reflected by a concomitant increase in TBV, or a decrease in pHct would have a negative correlation with net fluid balance. With an increasing rate of transudation, a corresponding decrease in TBV, PV, and increase in pHct should be observed. These

TABLE 3. Comparison of Peripheral to Normalized Hematocrit

	pHct	nHct	Difference	pHct <30	nHct <30	Overdiagnosis of Anemia
Hypovolemic (n = 16)	25.9	21.4*	4.5 ± 3.1	87.5% (14)	93.8% (15)	—
Normovolemic (n = 23)	27.2	27.2	0.0 ± 1.2	78.3% (18)	78.3% (18)	—
Hypervolemic (n = 45)	26.8	33.3*	-6.5 ± 4.1	77.8% (35)	31.1% (14)†	46.7% (21)
All (n = 84)	26.7	29.4*	-2.7 ± 5.5	79.8% (67)	56.0% (47)†	23.8% (20)

* $p \leq 0.01$ (paired *t* test).

† $p < 0.05$ (χ^2 test).

correlations with the rate of transudation and change in net fluid volume balance were weak. With more data points, a stronger correlation may emerge. Also interesting was the lack of correlation between ISS and rate of transudation and the absence of differences in ISS between different volume status groups. Previous studies have shown a positive correlation between the degree of injury and glomerular permeability/microalbuminuria.²⁰

Applying the Pearson correlation coefficient to the relationship between pHct and RBCV showed only a moderate correlation in the scatter plot. In contrast, the nHct, which is adjusted for volume status derangement, had a strongly positive correlation with RBCV (also shown in the scatter plot), suggesting that nHct is superior to pHct as a surrogate measure of RBCV.

Given the differences between pHct and nHct, and the relative sensitivity of each test to diagnose anemia (Hct <30), nHct seems to be a better test to diagnose anemia. In this study, reliance on pHct resulted in overdiagnosis of anemia in 23.8% of all blood volume analyses and in 46.7% of the hypovolemic group. This is significant as more than half of the study population is in the hypovolemic group. Because the nHct is adjusted to account for deviation in TBV, the resulting value is not influenced by hemodilution.

There were several limitations to this study. First, hematocrit, a calculated value, was used for this study instead of hemoglobin (Hgb), a measured value. This selection was applied based on the fact that all past literature involving blood volume analysis and measurements involved the utilization of Hct and not Hgb.^{14,16} For the sake of continuity, to avoid any confusion between this study and prior studies and to assure that comparisons between this and prior studies could be performed, hematocrit was therefore used. An additional limitation is that a selection bias may exist, as those patients enrolled in our study were admitted to the ICU for at least 24 hours and as long as 14 days before the first blood volume analysis. After this time period, the majority of patients have been adequately fluid resuscitated or may have received too much fluid resuscitation. In addition, this was a preliminary study including only a small number of patients. The sample size may have been too small to provide adequate power to show correlations in volume of fluid administered to changes in blood volume or significant differences between the volume status groups. Recruitment is ongoing and we hope to enroll 100 subjects in this study. Many potential subjects have been reluctant to participate in a study, which involves the use of radiolabeled tracer. The blood volume analysis is not a dynamic test. The results are a “snapshot in time” giving information about blood volume for that specific time point. Fluid status is constantly in flux, dependent on many variables. The test assumes that the RBCV is constant during the testing period (36 minutes). Results of the test may be skewed if the patient is bleeding >100 mL/h.

In the future, we hope to perform blood volume analysis on patients at ICU admission. This would allow health-care providers to determine the patient’s baseline blood volume status and initiate therapies based on these data. Those patients deemed to be hypovolemic with a low pHct

due to hemodilution would avoid unnecessary CT scans looking for a bleeding source and unnecessary blood product transfusions. Hypovolemic patients may then receive crystalloid or blood products dependent on whether blood volume analysis shows a deficiency in PV or RBCV. We would also further characterize and quantitatively measure the effects of fluid and blood product administration on volume status and specific blood volume measurements.

Assessment of volume status in critically ill patients is challenging. Analysis of our data showed no differences in the amount of fluid given to a patient determined to be hypovolemic, normovolemic, or hypervolemic by blood volume analysis. When comparing pHct with nHct, pHct tends to overestimate anemia in hypervolemic patients and underestimates anemia in hypovolemic patients. Having the ability to determine the overall volume status of a critically ill patient can accurately help physicians to tailor their fluid management plan and eliminate unnecessary interventions.

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