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# Circulating Blood Volume Measurements Correlate Poorly with Pulmonary Artery Catheter Measurements

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## Abstract

**Background:** Determination of the intravascular volume status of a critically ill surgical patient is paramount for appropriate fluid and cardiovascular management. Many clinical parameters have been utilized to estimate intravascular volume but none are precise indicators of circulating blood volume. The purpose of this observational pilot study was to compare measured blood volume with hemodynamic parameters obtained from the pulmonary artery catheter and to determine if incorporation of these measurements altered treatment decisions in critically ill surgical patients.

**Methods:** Blood volume measurements were prospectively obtained in twenty surgical intensive care unit patients with a pulmonary artery catheter when intravascular volume status was deemed uncertain by traditional clinical parameters.

**Results:** There was a statistically significant, but weak, correlation between blood volume results and pulmonary artery occlusion pressure, but no correlation with central venous pressure, cardiac index, and stroke volume index. Blood volume information altered treatment in 21% of instances, and 5 of these 6 patients demonstrated a favorable clinical response.

**Conclusions:** Circulating blood volume measurements may be useful in critically ill surgical patients when clinical appraisal of intravascular volume is uncertain. This remains to be validated in a larger, prospective randomized trial.

## Introduction

The ability to directly measure circulating blood volume (BV) has been available for more than 60 years but has not been widely utilized in daily clinical practice due to cumbersome methodology.<sup>1</sup> Historically, many techniques have been employed to measure BV using indicator dilution techniques with radio-labeled substances (albumin, autologous red blood cells), or fluorescent-labeled colloids (hetastarch, dextran, indocyanine green).<sup>1-9</sup> With technological improvements, a semi-automated analyzer (BVA-100, Daxor Corporation, Inc., New York, NY) became available and was approved in 1998 by the Food and Drug Administration. The <sup>131</sup>I radio-labeled albumin technique used by this apparatus is the recommended assay for quantitative assessment of plasma volume (PV) by the International

Committee for Standardization in Haematology due to its accuracy and reproducibility.<sup>9</sup> This technology has been validated and has made measurement of BV feasible at the bedside due to more rapid turnaround time for results. In parallel, there has been renewed interest in the utility of BV measurements in many clinical settings, such as in the treatment of hypertension, congestive heart failure and renal failure.<sup>10-14</sup>

Determination of the intravascular volume status of a critically ill patient is important for prudent fluid and cardiovascular management. After initial resuscitation, microvascular permeability and capillary leakage initiated by the inflammatory mediator cascade can result in interstitial fluid accumulation and tissue edema. Uncertainty regarding intravascular volume status occurs when patients are edematous and total body fluid overloaded while exhibiting clinical parameters that require treatment, such as tachycardia, hypotension, low cardiac output associated with low mixed venous oxygen saturation or hypoxia, low urinary output, and deteriorating renal function. In these settings, patients may be hypovolemic, hypervolemic, or euvolemic (normovolemic) intravascularly, and it is imperative to distinguish between these various volume categories. This determination is crucial to assure that appropriate therapy is rendered, which bridges the spectrum from fluid boluses; to diuresis and fluid restriction; to the administration of maintenance intravenous fluids, respectively. Conventional surrogate parameters such as vital signs, fluid balance (intake and output), urinary output, peripheral edema, weight gain, jugular venous distention, chest radiographs and laboratory data (hematocrit, lactic acid, base excess, blood urea nitrogen to creatinine ratio, brain natriuretic peptide) have been used collectively to estimate intravascular volume but are not reliably accurate indicators of BV.<sup>15-18</sup> Transesophageal echocardiography and pulmonary artery catheters are common adjuncts used to guide fluid management. However, pressure measurements of central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) reflect volume in relationship to myocardial compliance, cardiac function, and vascular capacitance

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and may not accurately characterize intravascular volume. In practice, assessment of volume status often includes a combination of clinical evaluation, laboratory measurements, and when available, pulmonary artery catheter measurements. The prevailing hypothesis, albeit not unequivocally substantiated, is that measurement of circulating BV will more precisely guide therapeutic interventions.

The purpose of this observational pilot study was to compare measured BV with hemodynamic parameters obtained from the pulmonary artery catheter and to determine if incorporation of BV measurements altered treatment decisions in critically ill surgical patients.

## Methods

This study was performed at a University affiliated, tertiary care medical center. The Institutional Review Board approved this study. Consecutive surgical intensive care unit (SICU) patients with a pulmonary artery catheter were identified and BV measurements were obtained if intravascular volume status was indeterminate.

Conventional parameters utilized by the SICU team in evaluating volume status included vital signs, urinary output, fluid balance, peripheral edema, weight gain, chest radiographs, and laboratory data (electrolytes, blood urea nitrogen, creatinine, hematocrit, lactic acid). Clinical parameters requiring treatment included persistent tachycardia (heart rate  $>100$  beats/minute), hypotension (systolic blood pressure  $<100$  mm Hg despite adequate fluid resuscitation to a PAOP of 15 to 18 mm Hg), urinary output of  $<0.5$  mL/kg/hour after fluid replacement, low cardiac output with mixed venous oxygen saturation  $<70\%$ , poor or worsening oxygenation ( $\text{PaO}_2/\text{FiO}_2$  ratio  $<200$ ; or intrapulmonary shunt  $>20\%$ ), deteriorating renal function (serum creatinine level increase by  $>20\%$  from baseline), or a combination of these. Patients were excluded during the first 24 hours of active fluid resuscitation to minimize any impact that rapidly shifting intravascular volume, or vasoactive drug use may potentially exert on blood volume analysis. At the time of blood volume measurement all patients were receiving maintenance intravenous fluids and were not receiving fluid boluses or blood transfusions. Those patients requiring ongoing, active fluid resuscitation beyond 24 hours were not included in the present study, again to ensure that the comparison of pulmonary artery catheter values and blood volume measurements were not confounded by rapidly shifting intravascular volumes seen during the active fluid resuscitation phase. Patients were also excluded if they were pregnant, there was a known iodine or shellfish allergy, or if younger than 18 years of age.

Pulmonary artery catheter measurements were performed according to manufacturer's instructions (Edwards CCOMBO Pulmonary Artery Catheter, Edward LifeSciences, Irvine, CA). Hemodynamic values obtained included blood pressure, heart rate, CVP, PAOP, cardiac index (CI), and stroke volume index (SVI), in addition to simultaneous BV measurements. Laboratory data obtained (at the discretion of the clinical team) included hemoglobin, hematocrit, lactic acid, electrolytes, blood urea nitrogen, creatinine, arterial blood gases, and chest radiographs. Each patient enrolled in this study received at least one BV measurement simultaneously with pulmonary artery catheter measurements.

Blood volume was measured by using a commercially available kit (BVA-100, Daxor Corporation, Inc., New York, NY). After

obtaining a baseline sample of 5 ml of blood, I131-labeled albumin was injected intravenously over 1 minute. Serial blood samples were drawn at 12, 18, 24, 30, and 36 minutes from the time of isotope injection. Sample radioactivity was measured in duplicate and a minimum of three samples with a standard deviation of less than 3.9% were used to calculate plasma volume (PV) by extrapolating to time zero. The use of multiple timed samples and extrapolation to zero time is of particular importance in critically ill patients, since many may have capillary leak syndrome attributable to sepsis and other inflammatory conditions. This method can identify and correct for transudation of albumin into the interstitial space.<sup>4,9</sup>

The red blood cell volume (RBCV) was calculated from the PV and the peripheral blood hematocrit, after correcting for plasma packing and mean body hematocrit. Blood volume was then equal to  $\text{PV} + \text{RBCV}$ . This method has been found to be comparable to simultaneous, combined radioisotopic measurement of PV and RBCV.<sup>7,19-21</sup>

The predicted normal BV level was determined from the patient's height and ideal body weight based on the ideal weight method as described by Feldschuh and Enson.<sup>22</sup> This method has been shown to eliminate systematic errors found in norms based on fixed ratios of BV to body weight. Euvolemia was defined as within 8% of the normalized BV. The definitions of mild, moderate, and severe deviations were  $\pm 8\%$ ,  $\pm 16\%$ , and  $\pm 32\%$ , respectively, from the predicted normal volumes for that patient.<sup>22</sup> A "normalized" hematocrit measurement is also provided by this method. The normalized hematocrit is an adjusted hematocrit measurement equal to the ratio of the patient's measured RBCV to the predicted normal total BV. Unlike the peripheral blood hematocrit, this measurement provides an accurate indication of the degree of anemia or polycythemia, without being distorted by variations in plasma volume.<sup>18</sup> Blood volume results became available to the treating team one hour after measurement. Once the decision was made to obtain BV analysis, patient therapy was based on the blood volume results. The protocol followed for hemodynamic management was based on prior randomized trials conducted in our Institution and published elsewhere.<sup>23</sup> In brief, patients were treated to a mean arterial pressure of  $> 65$  mm Hg, systolic blood pressure (SBP) of  $> 100$  mm Hg or within 40 mm Hg from known baseline, heart rate (HR)  $< 100$  beats/minute, urine output  $> 1$  mL/kg/hr, lactate level decreasing if elevated,  $\text{PaO}_2/\text{FiO}_2 > 200$ , mixed venous oxygen saturation ( $\text{SvO}_2$ )  $> 70\%$ , and oxygen delivery ( $\text{DO}_2$ )  $> 600$  mL/min/m<sup>2</sup>, or  $> 450$  mL/min/m<sup>2</sup> if  $\geq 75$  years of age, by infusing crystalloid or colloid at 250 to 500 ml increments, or blood infusion if the hemoglobin was  $< 10$  gm/dl and if the  $\text{SvO}_2$  was  $< 70\%$  or if the  $\text{DO}_2$  was  $< 600$  mL/min/m<sup>2</sup> (or  $< 450$  mL/min/m<sup>2</sup> if  $\geq 75$  years of age), to achieve a PAOP of 15 - 18 mm Hg. Once this PAOP was achieved, or urinary output was  $> 1$  mL/kg/hr, lactate level was decreasing if elevated, or HR  $< 100$  beats/minute, fluid resuscitation was deemed adequate. If the  $\text{SvO}_2$  was  $< 70\%$ ,  $\text{DO}_2$  was  $< 600$  mL/min/m<sup>2</sup> (or  $< 450$  mL/min/m<sup>2</sup> if  $\geq 75$  years of age), and SBP was  $> 100$  mm Hg, dobutamine at doses of 2 to 5 mcg/kg/min was started, titrated to achieve the noted predetermined treatment goals up to 20 mcg/min/m<sup>2</sup> or until patients became tachycardic (defined for this study as HR  $> 100$  beats/minute). All patients received either norepinephrine or epinephrine starting at 1 mcg/minute titrated to predetermined SBP  $> 100$  mm Hg, if patients were hypotensive despite adequate urinary output, lactate

level decreasing if elevated, HR < 100 beats/minute, and if the PAOP was between 15 - 18 mm Hg.

If a measured BV showed normovolemia, no volume-related treatment change was initiated despite what the pulmonary artery catheter results and clinical parameters showed; if the BV was consistent with hypovolemia, crystalloids or blood (if hemoglobin < 10 gm/dl, SvO<sub>2</sub> < 70% or DO<sub>2</sub> < 600 mL/min/m<sup>2</sup>, or if age ≥ 75 years DO<sub>2</sub> < 450 mL/min/m<sup>2</sup>) was infused; and if BV was consistent with hypervolemia, diuresis was implemented. In this structure, volume infusion would be carried out if a BV measurement showed hypovolemia, regardless of the status of the pulmonary system (i.e., respiratory insufficiency), for example. Moreover, once an intervention was made a subsequent, follow-up BV was obtained, and additional treatment provided until the BV showed normovolemia.

Three of the investigators blinded to each other, independently reviewed patient charts retrospectively after discharge from the SICU. Clinical data evaluated included cardiac (blood pressure, heart rate, CVP, PAOP, CI, SVI, mixed venous oxygen saturation, and requirement for vasopressors or inotropic agents), pulmonary (PF ratio, intrapulmonary shunt fraction, ventilator dependency, and chest radiographs) and renal function (urinary output, blood urea nitrogen, and creatinine level). We operationally defined a positive clinical response as one where there were at least two clinical parameters that demonstrated improvement six to twelve hours after therapy based on BV results, and a negative clinical response if there was no change, improvement in only one clinical parameter, or if there was clinical deterioration. For measured laboratory variables, to be considered a change (either positive or negative) there needed to be a difference greater than the standard error of the test. For example, difference in creatinine levels greater than ± 0.5 mg/dl was considered to be a change; measured values within that range were not considered to be a significant change. This was based on the laboratory's established quality control ranges for the respective assays.

Measured variables were compared using scatter plotting and Pearson correlation. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using OpenStat 3 software.

## Results

Twenty SICU patients contributed twenty-nine simultaneous BV and pulmonary artery catheter values. Sixteen males and four females, mean age (± S.D.) 62.5 ± 20.7 years, with mean (± S.D.) APACHE II scores of 21.1 ± 4.8 comprised the study group. Six patients were admitted for severe sepsis/septic shock, nine for hemorrhagic shock, and five for respiratory failure. Mortality rate was 1/20 (5%).

There was no significant correlation between BV and CVP (r=0.27, p=0.13), BV and CI (r=0.24, p=0.21), and BV and SVI (r=-0.29, p=0.45). Blood volume was significantly but weakly correlated with PAOP (r=0.44, p=0.02). For PAOP values ≤12 mm Hg (n=6), BV results showed 2 hypervolemic and 4 euvoletic states. For PAOP values between 13-18 mm Hg (n=14), BV revealed 9 hypervolemic, 4 euvoletic and 1 hypovolemic state. For PAOP values >18 mm Hg (n=9), BV demonstrated 6 hypervolemic and 3 euvoletic states.

In 6 of 29 instances (21%), treatment was changed based on BV information (despite discordant pulmonary artery catheter measurements) with 5 of 6 patients experiencing improvement

in cardiac, pulmonary and or/renal function following the change in treatment. Results of BV measurements for all 5 instances demonstrated hypervolemia. All patients received less fluid or diuresis, and three patients also received blood transfusion for correction of anemia, based on low RBCV results, if these results were also associated with decreased oxygen delivery or low mixed venous oxygen saturation, based on our Institutional protocol.<sup>23</sup>

## Discussion

Several reports have been published to assess the feasibility and the utility BV measurements. This study was performed to evaluate the degree to which blood volume measurement affects treatment decisions, prior to the design and implementation of a larger prospective controlled study.

The pulmonary artery catheter is not an unequivocally accepted gold standard for evaluating intravascular volume status, particularly based on data from randomized trials demonstrating no significant impact on patient outcome and that pulmonary artery catheter measurements poorly reflects response to fluids.<sup>24</sup> Traditionally, however, pulmonary artery catheter parameters have been used as a guide for fluid management. Our current study showed that there was a statistically significant, but weak, correlation between PAOP and BV. Despite this finding, the utilization of pulmonary artery catheter readings as a surrogate for BV measurement would have resulted in an incorrect treatment approach in six of twenty-nine instances. Five of these patients demonstrated hypervolemia based on blood volume measurements. It is difficult to speculate if our treatment protocols promote hypervolemia and if this represents a selection bias, given the small sample size, although there is a clear trend towards hypervolemia. Notably, our protocols were established based on a prior randomized trial conducted in our Institution that demonstrated that our current protocol was the treatment arm associated with significantly higher survival.<sup>23</sup>

Previous investigators have shown that BV measurements did not correlate with PAOP in 24 hemodynamically unstable ICU patients<sup>25</sup> and in patients during the acute and post-resuscitation phase.<sup>16</sup> This may be related to differences in the study populations and the timing of measurements. Alwari et al reported on a comparative study of BV values and pulmonary artery catheter measurements in 24 intensive care unit patients. Their exclusion criteria included hemodynamically normal or stable patients, and critically ill patients who were managed in an intensive care unit setting without the use of a pulmonary artery catheter.<sup>25</sup> Shippy and colleagues included patients during the acute resuscitation phase.<sup>16</sup> Our study was conducted in patients after the acute resuscitation phase was completed. Similar to our results, Androne et al. showed significant correlation between BV results and PAOP in 17 patients with chronic congestive heart failure.<sup>11</sup> Many clinical situations may alter the pressure-volume relationship of the myocardium resulting in these differences. Measuring pressure to infer volume continues to be problematic.

Furthermore, circulating BV analysis provides distinct measurement of disturbances in the RBCV and in the PV (since BV = RBCV + PV). This precise information, resulting in treatment targeted at improving each individual component of total BV, is not obtainable from pressure measurements provided by the pulmonary artery catheter. Most of the patients in this study were hypervolemic. Notably, in the presence of PV expansion, BV measurement can

quantify the degree of RBCV depletion in relation to the degree of dilutional anemia. Anemia has been associated with poorer outcomes in a variety of conditions,<sup>18</sup> so accurately diagnosing and correcting anemia may be a defining factor in whether or not a patient improves. In those patients with altered treatment based on BV analysis, three patients (10% of the entire cohort) received blood transfusion to correct anemia. Two of those patients showed improvement in two or more clinical parameters, while the other showed improvement in only one parameter but none demonstrated any immediate adverse clinical response. Blood volume measurement is promising and may also be valuable in precisely defining the presence and degree of anemia, and in ultimately determining optimal protocols to treat true and dilutional anemia.

This investigation has a number of limitations. A small number of patients with heterogeneous diagnoses for admission to the SICU were evaluated, limiting the statistical power of this analysis and increasing the risk of a type II error. Treatment responses were evaluated, but in the absence of a control group cause and effect cannot be clearly established; neither, therefore, could outcomes be determined, and our conclusions are limited by the observational design of the present study. Incorporation of BV results into treatment decisions was left to the discretion of the treating team. Despite this uncertainty, none of the patients studied demonstrated an unfavorable or adverse clinical response following treatment changes based on BV results. In addition, three independent reviewers blinded to each other had to agree before categorizing the clinical response as favorable, so this tended to underestimate any immediate benefit. This may have resulted in a study bias, even if the investigators were blinded to patient names and to each other, given that these investigators were part of the study. To minimize bias, any improvement in at least two measured parameters (beyond the standard error of the test parameter being measured if it was a laboratory assay) was defined at study inception as a favorable clinical response.

At this time, there is a paucity of data in the peer-reviewed literature defining optimum intravascular volume associated with survival. Shippy et al recommended, in the critical care setting, resuscitation to greater than normal volumes based on survival characteristics.<sup>16</sup> Other investigators found, in ambulatory heart failure patients, improved outcomes for normovolemic patients compared to hypervolemic patients.<sup>11</sup> The optimal BV in different conditions remains to be determined.<sup>17</sup>

## Conclusions

There may be a role for BV measurement in a cohort of critically ill surgical patients after the acute resuscitation phase, when presented with the dilemma of determining intravascular volume status based on conventional clinical parameters. Blood volume measurement may be particularly beneficial to establish fluid management goals and endpoints of treatment in sepsis and septic shock patients. Despite advances in formalized critical care research, sepsis and septic shock are still the most significant cause of mortality in the intensive care unit. Increased microvascular permeability and capillary leak initiated by the inflammatory cascade results in interstitial fluid accumulation and tissue edema, which may also effect changes in venous compliance. Achieving euvolemia is a fundamental principle in fluid management. Clinical surrogates of intravascular volume status and information obtained from pulmonary artery catheters

may be deceptive in this group of patients. Early, and clinically appropriate, achievement of fluid resuscitation endpoints to avoid multiorgan system failure may be assisted by BV analysis, which provides an attractive noninvasive alternative for volume assessment. Additional studies, including prospective controlled studies, should be performed to evaluate the effects of utilizing BV measurement on patient outcomes, as well as to determine optimal treatment protocols and to quantify the optimal intravascular volume status for patients in the critical care setting.

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