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The availability of circulating blood volume values alters fluid management in critically ill surgical patients

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Abstract

BACKGROUND: This study evaluated whether commercially available blood volume measurements in critically ill surgical patients altered fluid management.

METHODS: Patients admitted to the surgical intensive care unit of a tertiary care teaching hospital were prospectively evaluated. The frequency of changes in fluid management when results of blood volume measurements were available was determined.

RESULTS: In a pilot study, the frequency of instances when measurement of blood volume would have altered fluid management was statistically significant ($P = .0003$). In 40 subsequent patients, treatment change occurred in 36% of instances when blood volume results were obtained ($P < .001$). In the majority, no immediate qualitative change in clinical status occurred, with a desirable clinical response in 39% and no negative treatment responses ($P < .001$).

CONCLUSIONS: Blood volume measurements may assist in the management of critically ill surgical patients by providing a direct measure of intravascular volume. Further studies are warranted to determine its effect on outcome.

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Maintaining euvolemia is essential in the management of critically ill patients.¹ Until recently, direct measurements of circulating plasma volume and total blood volume were not suitable for use in clinical practice, and surrogate markers have been used to estimate blood volume. Hemodynamic parameters (such as heart rate and blood pressure) in combination with chest radiographs, hematocrit, blood urea nitrogen, creatinine, base excess, lactic acid, urinary output,

daily weight, and fluid balance usually serve as such markers. Substantial evidence supporting this approach is lacking, however, and calculation of an absolute value of circulating blood volume is impossible with use of these surrogates.^{2–12}

Data obtained from pulmonary artery catheters may add information but reflect volume in relationship to cardiac function, myocardial compliance, and venous capacitance.⁸ Furthermore, the use of pulmonary artery catheters in the management of patients with hemodynamic and/or respiratory compromise has been called into question, based on randomized trials showing no significant impact on mortality and other outcome measures.⁹ Newer, evolving technology, such as pulse-contour continuous cardiac output monitoring systems,

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have been increasingly used for the purpose of providing continuous hemodynamic monitoring, but this methodology does have its limitations in the critical care setting.^{10–12}

The complexity of physiologic changes in critically ill patients, especially fluid shifts between intravascular and extravascular spaces, further complicates the relationship between changes in surrogate markers and changes in circulating blood volume. In addition, the validity and practicality of direct plasma volume and blood volume measurements in critically ill patients may also be questioned, given that measurements have been time-consuming and cumbersome in the past.^{13,14}

Recent advances in technology make direct plasma volume and blood volume measurements more feasible for use in clinical settings.^{15–17} One example is a semiautomated, commercially available blood volume analyzer (BVA-100; Daxor Corporation, Inc, New York, NY), which has been approved by the Food and Drug Administration. Using this device makes results of circulating blood volume available within 45 minutes, with preliminary results available within 20 minutes. The gold standard for direct measurement of circulating blood volume (and its component plasma volume and red blood cell volume) has been the combined radioisotope dilution technique using radiolabeled albumin and chromium 51–tagged red blood cells.¹⁴ Dworkin et al¹⁸ compared the International Council for Standardization in Haematology–recommended combined radioisotope dilution method with this semiautomated commercial device and found that measuring plasma volume alone using this device provided comparable results to those achieved from simultaneous measurement of both plasma volume and red blood cell volume. It is likely that as this technology becomes even easier to use, the possibly point-of-care devices for blood volume measurements will become more readily available in the near future.

At least 2 potential barriers for wider clinical use of direct blood volume measurements can be identified. First, the benefits of using absolute values of circulating blood volume instead of a combination of readily available, surrogate, clinical and physiological values in the management of critically ill patients remain primarily theoretical and need to be tested in clinical settings. Second, the proportion of critically ill patients in which a physician will be willing to significantly alter the treatment plan based on the circulating blood volume values may be too small to justify the routine use of this technology.

In this study, we aimed to address the latter issue, specifically to estimate how often physicians will alter fluid and transfusion management of surgical intensive care unit patients if circulating blood volume values are available and, second, how often these changes in management resulted in achieving a desirable clinical response.

Methods

After approval by the Institutional Review Board, this prospective study was implemented in 2 stages. Written

informed consent for participation in this investigation was obtained from all subjects or, when unable to sign, by a legal surrogate. Patients admitted to the surgical intensive care unit of a 500-bed, tertiary care teaching hospital had blood volume measurements if there was difficulty in determining their intravascular volume status clinically. Patients were considered eligible both on admission to the unit and during their surgical intensive care unit stay. These patients had either persistent tachycardia (defined as heart rate >100 beats per minute [bpm]), hypotension (systolic blood pressure <90 mm Hg despite adequate fluid resuscitation to a pulmonary artery occlusion pressure of 15 to 18 mm Hg, if a pulmonary artery catheter was present), poor oxygenation (P_{aO_2} /fraction of inspired oxygen ratio <200 or Q_s/Q_t ratio of >20%, if a pulmonary artery catheter was present), low cardiac index with mixed venous oxygen saturation <70%, low urinary output (<0.5 mL/kg/h) and/or worsening renal function (serum creatinine increase of >20% of baseline), or a combination of these. Patients were excluded during the first 24 hours of resuscitation if they were pregnant, if there was a known iodine or shellfish allergy, or if younger than 18 years of age. Exclusion during the first 24 hours of resuscitation was to minimize any impact that rapidly shifting intravascular volumes, vasopressor, or inotrope use may exert on blood volume analysis.

All surgical and trauma patients admitted to the surgical intensive care unit are admitted specifically to this team care service for management. The investigators for this study rotate as surgical critical care fellows or American Board of Surgery–qualified surgical intensivists on this service, and the surgical intensivists are responsible for direct oversight and management of these patients. All clinical decision making, including selection of patients for blood volume measurements, was made by the surgical intensivists assigned to the surgical intensive care unit while the patient was hospitalized. All were inserviced on use of the blood volume methodology, interpretation of results, and our standardized treatment algorithm (which has been reported elsewhere) before implementation of the pilot study of the first 8 patients.^{19,20}

During the first stage (pilot), the investigators were blinded to the plasma volume and blood volume values and were asked to re-evaluate their management retrospectively after measured values became available 2 to 3 days later. The results of blood volume measurements were not available because the samples were processed in New York City by the Daxor Corporation, Inc. After the enrollment of 8 consecutive patients, it became obvious that the availability of the blood volume values may significantly alter fluid management in up to 50% of instances. At this point, the pilot phase was terminated, and 40 consecutive subjects were enrolled to the main group prospectively.

This phase had an experimental interventional design with pre- and postintervention comparison. Participating surgical intensivists made initial circulating blood volume assessment and management recommendations based on

routinely used, surrogate clinical criteria at the time when direct plasma volume and blood volume measurements were initiated. Thirty to forty-five minutes later, the informational intervention was implemented in the form of presenting the intensivists with results of direct plasma volume measurement and calculated total blood volume and red blood cell volume. Changes in management caused by this informational intervention were recorded in the charts.

In brief, based on previous randomized trials conducted in our institution, 1,920 patients were treated to a mean arterial pressure of ≥ 65 mm Hg, systolic blood pressure ≥ 100 mm Hg or within 40 mm Hg from known baseline, heart rate < 100 bpm, urine output ≥ 1 mL/kg/h, lactate level decreasing if elevated, P_{aO_2} /fraction of inspired oxygen ≥ 200 , mixed venous oxygen saturation $\geq 70\%$, and oxygen delivery ≥ 600 mL/min/m² if 75 years of age or younger and > 450 mL/min/m² for age older than 75 years by infusing crystalloid or colloid to achieve a pulmonary artery occlusion pressure of 15 to 18 mm Hg (if the patient had a pulmonary catheter). Once this pulmonary arterial occlusion pressure was achieved or urinary output was ≥ 1 mL/kg/h, lactate level was decreasing if elevated, or heart rate < 100 bpm, fluid resuscitation was deemed adequate. If the mixed venous oxygen saturation was $< 70\%$, oxygen delivery was < 600 mL/min/m² if 75 years of age or younger or < 450 mL/min/m² for age older than 75 years, and systolic blood pressure was ≥ 100 mm Hg, dobutamine at doses of 2 to 5 μ g/kg/min was started, titrated to achieve predetermined treatment goals up to 20 μ g/min/m² or until patients became tachycardic (defined for this study as heart rate > 100 bpm). All patients received norepinephrine or epinephrine starting at 1 μ g/min titrated to a predetermined systolic blood pressure ≥ 100 mm Hg if patients were hypotensive despite adequate urinary output, lactate level decreasing if elevated, heart rate < 100 bpm, if a pulmonary artery catheter was present, and if a pulmonary arterial occlusion pressure of 15 to 18 mm Hg had been achieved.^{19,20}

If the measured blood volume results showed normovolemia, no treatment change in the form of fluid or blood was initiated; if the blood volume values were consistent with hypovolemia, crystalloids or blood (if hemoglobin ≤ 10 g/dl, red blood cell volume was correspondingly low, and oxygen delivery was < 600 mL/min/m² if 75 years of age or younger or < 450 mL/min/m² for age older than 75 years or mixed venous saturation was $< 70\%$) was infused, in accordance with our previously reported protocol^{19,20}; if blood volume values were consistent with hypervolemia, diuresis was implemented. These interventions were done regardless of pulmonary artery or central venous catheter values (such as pulmonary artery occlusion pressure or central venous pressure) if these catheters had been placed in the patient before the blood volume assessment. In this framework, volume infusion would be performed if a blood volume measurement showed hypovolemia, regardless of the status of the lungs (ie, lung compromise), for example. Additionally, once an intervention was made, a follow-up, subse-

quent, blood volume was obtained, on average 24 hours later, and additional treatment rendered, as outlined earlier until the blood volume measurements showed normovolemia.

All instances of changes in management were analyzed after patient discharge from the surgical intensive care unit by 2 independent reviewers blinded to each other. Renal function, oxygenation, and hemodynamics before and 6 to 12 hours after implementation of a treatment change because of directly measured circulating blood volume results were operationally categorized as resulting in a desirable response (positive clinical response) or not resulting in desirable response (negative clinical response or no clinical response). If there was disagreement, a third investigator reviewed the clinical response to arrive at a collective decision. Any degree of immediate improvement in at least 2 treated clinical parameters was defined qualitatively as a positive response.

Blood volume was measured by using a commercially available kit (BVA-100). After obtaining a baseline sample of 5 mL of blood as a control for background radiation, I-131-labeled albumin was injected intravenously over 1 minute. Serial arterial blood samples of 5 mL were drawn at 12, 18, 24, 30, and 36 minutes from the time of isotope injection. Sample radioactivity was measured in duplicate in a semiautomated counter, and a minimum of 3 samples with a standard deviation of less than 3.9% was used to determine plasma volume by extrapolating to time 0.

The hematocrit was measured simultaneously to calculate the red blood cell volume from the plasma volume, with calculation of total blood volume as equal to plasma volume + red blood cell volume. This approach has been found to be equivalent to concurrent radioisotopic measurement of plasma volume and red blood cell volume using chromium 51-tagged red cells and iodine 125-tagged albumin.^{13,17,18} The predicted normal ("ideal") blood volume level was determined from the patient's height and weight based on the ideal weight method as described by Feldschuh and Enson² and a proprietary algorithm established by the manufacturer of the assay.²¹ These investigators used the Metropolitan Life height and weight tables, which were developed from over 100,000 measurements, with a range of weight for each height. A mathematic model was constructed, and it was found that subjects tested validated this model. Furthermore, measured blood volume correlated well with this model. Most notably, there was no significant systematic divergence based on weight, height, or deviation from ideal weight. Systematic errors related to fixed ratios of blood volume to body weight are corrected for by this approach. Therefore, results are given both as absolute numbers (in milliliters) and as a percent deviation of ideal blood volume.

Statistical analysis was performed by using the SPSS 11.5 statistical software (Chicago, IL). Descriptive statistics were used to summarize the patient characteristics (means and percentages for categorical data and means and standard deviations for continuous data). Pearson correlations were used

to test the association between measured blood volume and surrogate parameters used for blood volume estimation. The nonparametric McNemar test comparing 2 related samples (paired observations) was used to test the significance of frequencies in management changes after informational intervention compared with management decisions prior.^{22,23} A *P* value of $<.05$ and a 95% confidence interval were considered significant.

Results

Pilot study

The demographics of patients ($n = 8$) included in the pilot study were as follows: mean age 58 ± 8 years (range 38–59 years), 6 men and 2 women, Acute Physiology and Chronic Health Evaluation II score 16 ± 4 (range 10–18). Five patients had severe sepsis/septic shock, 1 had acute respiratory distress syndrome, 1 had severe right ventricular failure from cardiac contusion, and 1 was a preoperative optimization. Of the 29 measurements, a treatment change would have occurred in 13 of 29 occasions (45%) if the blood volume information were known.

Five patients with a pulmonary artery catheter generated 20 of the 29 data points. For 10 out of these 20 measurements (50%), a different treatment would have resulted if blood volume values were available. Of those 10 instances, the following treatment differences would have resulted: less fluid infusion in 6, no blood transfusion in 2, no blood or fluid administration in 1, and more volume infusion in 1 instance. Nine data points came from patients without a pulmonary artery catheter, and in 3 of 9 cases (33%) a treatment change would have occurred. Two would have received blood transfusion, and one would have received more fluid infusion. Earlier treatment of hypovolemic and anemic patients theoretically would have avoided development of overt clinical signs that became manifest 1 to 2 days later. There was no statistically significant correlation between the percentage of plasma volume and blood volume deviation from ideal and pulmonary artery occlusion pressure, central venous pressure, and stroke volume index.

Despite the small sample size, the frequency of instances when direct measurement of blood volume would have altered fluid and transfusion management (45%) was statistically significant ($P = .0003$, McNemar test) and similar in patients with or without the presence of a pulmonary artery catheter.

Main group

Forty patients enrolled in this group included 32 men and 8 women with a mean age of 61 ± 20 years (range 13–88 years) and an Acute Physiology and Chronic Health Evaluation II score of 20 ± 6 . Fourteen patients were trauma victims, 22 were general surgical patients, and 4 were from other

surgical subspecialties. Eleven had severe sepsis or septic shock, 7 had hemorrhagic shock, 20 had acute respiratory distress syndrome, and 2 patients had cardiovascular collapse. The mortality rate was 13% (5/40). Blood volume measurements were done on the following surgical intensive care unit days: day 2 ($n = 12$), day 3 ($n = 13$), day 4 ($n = 7$), days 5 to 7 ($n = 10$), days 8 to 10 ($n = 15$), and day >10 ($n = 29$). Each patient had at least 1 blood volume measurement. The 86 blood volume measurements resulted in a treatment change in 31 cases (36%, $P < .001$, McNemar test). In the 31 instances, treatment changed in the following way: less fluid infused or diuresis instituted ($n = 13$), more fluid infused ($n = 8$), and transfusion of blood ($n = 10$). In 55 of 86 instances (64%), clinical assessment correlated with blood volume measurements and did not result in a change of treatment.

The 2 blinded investigators agreed on treatment responses in 28 of 31 instances (90%) when blood volume results altered treatment. For the remaining 3 instances, a third investigator adjudicated the treatment responses to arrive at a collective decision. No negative treatment responses occurred in instances when information on measured blood volume caused change in treatment; however, the achievement of desirable responses was significantly less frequent (39% or 12/31 instances) than no change in clinical status ($P < .001$, McNemar test).

There was no significant correlation between measured plasma volume (or calculated total blood volume) and mean arterial pressure, heart rate, urinary output, blood urea nitrogen level, creatinine, hemoglobin/hematocrit, lactic acid, and base excess.

Comments

Results of this prospective, observational study showed that in 36% of instances the management of critically ill surgical patients was altered after plasma volume and blood volume values became available to physicians. No negative treatment responses occurred in these instances, with desirable clinical responses noted in 39%. Notably, there was no statistically significant correlation between blood volume values and other clinical surrogates that estimate intravascular volume.

The achievement of hemodynamic stability and adequacy of resuscitation is traditionally inferred from clinical parameters such as systolic blood pressure or mean arterial pressure, heart rate, urinary output, and laboratory values. After the initial phase of resuscitation is completed, the assessment of intravascular blood volume remains challenging because of edema, weight gain, and positive fluid balance. Hematocrit levels vary depending on sampling time after transfusion and transcapillary migration of interstitial fluid.^{3,24,25} Information from a pulmonary artery catheter can assist in this analysis but gives only secondary information about volume through pressure measurements.

Direct measurement of blood volume may be useful after acute resuscitation when patients have increased total body volume and edema that may be attended by concomitantly low circulatory (intravascular) volume or increased vascular capacitance. Blood volume may also give valuable information during the fluid mobilization phase when intravascular volume overload may result in pulmonary and cardiac dysfunction²⁶ or congestive heart failure patients.²⁷ The difficulty of accurately determining blood volume by traditional clinical approaches is exemplified by this study and the study by Androne et al,²⁷ which included nonedematous, ambulatory heart failure patients, in which clinical assessment of volume status by an experienced cardiologist did not agree with measured volume status 49% of the time.

The ability to measure circulating blood volume has existed for many years.^{5,13,14} Radioisotope dilution methods, considered to be the gold standard, were used to generate the norms defined for plasma volume, red blood cell volume, and total blood volume in healthy persons.^{13,14} The availability of measured plasma volume values has been previously shown to improve survival in the critically ill.²⁸ Resuscitation to a goal of plasma volume levels 500 mL in excess of predicted or idealized norms used in the cited study may relate to increased vascular capacitance associated with shock conditions. This increased vascular capacitance may not be readily apparent based on traditional approaches to the estimation of intravascular blood volume. A semiautomated, radioisotope indicator dilution technique using isotope I-131 (BVA-100; Daxor Corp. Inc., New York, NY USA), which was used in our study, has been used before in polycythemic and cardiac patients but without widespread use in critically ill patients.^{15-17,26,27} To measure and correct for any transudation of albumin in critically ill patients, this semiautomated methodology uses serial measurements that are extrapolated to time 0 to calculate the contribution exclusively from the intravascular space. The use of multiple timed specimens allows for quantitative determination of the rate of albumin transudation from the vascular space. This method therefore detects and adjusts for the loss of albumin into the interstitial space that occurs with capillary leak syndrome and has been validated in this setting.^{29,30}

This study has a number of limitations. The assay itself requires injection of a small dose of a radioactive isotope, limiting the technique from being applied to pregnant patients and children. Furthermore, it does not allow for continuous readings, and there is a time lapse of approximately 45 minutes before results are available (preliminary results may be available within 20 minutes). There is a theoretical possibility that the algorithm used to calculate ideal body weight may not be applicable to the obese patient, and more studies must be done to determine what the appropriate estimation of ideal weight is in this patient population of rising incidence and how it impacts on blood volume measurements. Subjects were excluded during the first 24 hours of resuscitation to minimize any impact that rapidly shifting

intravascular volumes, vasopressor, or inotrope use may exert on blood volume analysis. However, the first 24 hours of resuscitation is also a critical period for appropriate fluid resuscitation, and the establishment of measurable end-points of resuscitation that correlate with outcome is also an important consideration for future studies. Furthermore, once the decision was made to obtain blood volume measurements, management decisions were based on these results, despite what other surrogates of intravascular volume status indicated. The validity of direct circulating blood volume measurements in different pathophysiologic conditions, particularly in critically ill subjects, needs to be established. The prospective, observational design of this study with the lack of a control group limits our interpretation of the effect of blood volume measurements on patient outcome. Accordingly, it is not possible to quantitatively state whether the integration of measured blood volume information in treatment and fluid management translated into improved overall patient outcome, measured by such traditional benchmarks of surgical intensive care unit and total hospital length of stay, ventilator days, morbidity and complication rates, or mortality. Conversely, the present study was not designed to determine if management of patients using conventional, surrogate, clinical parameters of intravascular volume despite blood volume values indicating a contradictory volume status will result in an adverse, or negative, clinical response. Notwithstanding, although our study was not designed to address the clinical benefits of direct blood volume measurements, management changes caused by information on plasma volume, red blood cell volume, and total circulating blood volume values never resulted in a negative or adverse clinical change.

Clinical benefits of using measured plasma volume and blood volume values should be compared with current standards of care in a prospective randomized trial. However, regardless of validity and efficacy, it is also important to determine how frequently this type of information alters the management of critically ill patients. This information is directly related to the feasibility and cost-effectiveness of new technologies and therefore is complimentary in the consideration of future clinical trial design. Similar, even easier to use, and more rapid technology may appear in the near future. Therefore, further studies are warranted to define the precise role of this promising technology in the management of critically ill surgical patients.

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