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A PROSPECTIVE RANDOMIZED TRIAL USING BLOOD VOLUME ANALYSIS IN ADDITION TO PULMONARY ARTERY CATHETER, COMPARED WITH PULMONARY ARTERY CATHETER ALONE, TO GUIDE SHOCK RESUSCITATION IN CRITICALLY ILL SURGICAL PATIENTS

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ABSTRACT—Measurement of blood volume (BV) may guide fluid and red blood cell management in critically ill patients when capillary leak from shock and fluid resuscitation makes assessment of intravascular volume difficult. This is a prospective randomized trial of critically ill surgical patients with septic shock, severe sepsis, severe respiratory failure, and/or cardiovascular collapse. The control group received fluid management based on pulmonary artery catheter parameters and red blood cell transfusions based on hematocrit values. The BV group received fluid and red blood cell transfusions based on BV analyses in addition to pulmonary artery catheter parameters. Blood volume was measured using the radioisotope tracer technique with iodine 131–labeled albumin. This allowed direct measurement of plasma volume and calculation of the red blood cell volume. The control group was blinded to the BV results. There were statistically significantly more times when the control group (compared with the BV group) demonstrated hypervolemia (48% vs. 37%) and red blood cell deficiency (33% vs. 16%). There was a delay in red blood cell transfusions administered to the control group by 1.5 ± 2 days at which time the abnormality became clinically evident. Blood volume analyses provided additional information to the clinicians resulting in a change in treatment in 44% of the time to patients randomized to the BV group. The mortality rates were significantly different between the two groups (8% for the BV group and 24% in the control group; $P = 0.03$). Blood volume measurements allowed the physicians to promptly treat physiologic disturbances in both red blood cell volume and plasma volume, resulting in improved survival.

KEYWORDS—Intravascular volume, fluid resuscitation, red blood cell transfusion, septic shock

INTRODUCTION

Achieving euvolemia or normovolemia is the first principle of shock resuscitation irrespective of etiology. Although there is agreement that survival is dependent on the timing of resuscitation (1–4), the optimum end point of fluid titration remains in question. One major problem is that surrogate markers, rather than direct measurement of blood volume (BV), is used to guide fluid and red blood cell therapy. Clinical examination has limitations in predicting BV. Blood pressure (BP) deterioration may be a late sign due to hormonal response and compensation. Chest roentgenograph discrimination for cardiac filling pressures may be poor. An "adequate" urine output (UO) depends on the concentrating ability of the kidneys and the amount of nitrogenous waste products, with oliguria being a late sign of renal failure. Previous studies have shown that experienced cardiologists were unable to predict volume status in 49% of their congestive heart failure (CHF) patients including evaluation of S3 (5), and brain natriuretic peptide levels (6). Resuscitation to treat shock states leads to third spacing of fluid, edema, weight gain, and a positive fluid balance, and it becomes difficult to estimate a patient's intravascular volume. Agreement among physicians regarding estimation of BV in patients may also be poor (7).

Central hemodynamic pressures such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) are commonly used to guide fluid therapy. However, they may not reflect intravascular volume status because CVP and PAOP depend on the relationship between the volumes presented to the heart, cardiac function, and compliance of the ventricles. Previous studies have demonstrated little correlation between CVP and circulating BV (8–12). One study demonstrated a weak relationship between PAOP and BV (12), but this was not a consistent finding (8, 10, 13). A better correlation between BV and either cardiac output (CO) or stroke volume has been observed, when compared with CVP or PAOP values (11, 13).

Despite the inconsistencies in the literature, CVP of 8 mmHg or greater (1, 2, 4) and up to 15 mmHg (14) has been advocated as end points of fluid resuscitation with some success, but these treatments are part of "bundled care" (i.e., standardized protocols), which makes the contribution from individual components difficult to assess (15). There may be better end points to guide fluid resuscitation such as actual measurements of intravascular volume.

Although clinicians inherently embrace the concept of direct measurement of intravascular volume, the technology used to conduct the testing was cumbersome and limited its use. With the introduction of a semiautomated technique for measuring

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BV (BVA-100; Daxor Corporation, New York, NY), there has been renewed interest in using this tool to guide fluid and blood management. Using the BV analyzer (BVA), we demonstrated that clinical parameters including information derived from pulmonary artery catheters (PACs) were not reliable in predicting BV in the surgical intensive care unit (SICU) patients (16). Treatment changed 36% of the time based on BV values, with 39% of the treatments resulting in improvement, and no episode resulting in worsening of the parameters treated (16). In patients in whom BV results were not used, an element of delay was recognized where, 1 to 2 days later, the volume status of the patient became clinically manifest leading to the same treatment had BV information been available. This delay in treatment was recognized as a potential area for improvement. Other researchers have reported similar findings in the intensive care unit (ICU) patients: use of BV information may lead to different fluid management 30% to 50% of the time (17).

In the last decade, the goals of resuscitation have evolved from treatment to a single value of cardiac index (CI), oxygen delivery (D_{O_2}), and mixed venous oxygen saturation (S_{VO_2}) (18), to individual titration of D_{O_2} to ensure adequate tissue oxygenation (19) with improved mortality rates. Although the merits of PACs have been questioned, the PAC provides a reliable continuous method of monitoring CI, S_{VO_2}, PAOP, and CVP, and its value is supported by prospective randomized trials (18, 19) if interpreted and utilized properly (20). Our group has been evaluating the utility of BVA in guiding fluid and red blood cell management in the ICU since 2004 (12, 16, 21). This report describes a prospective randomized trial using the BVA in addition to PAC parameters and hematocrit (Hct) in critically ill SICU patients. The aims of the study was to assess (*a*) the number of times the BV data resulted in changed treatment, (*b*) whether treatment resulted in favorable or unfavorable response, (*c*) whether there were differences in resource consumption (ventilator, SICU, hospital days), and (*d*) whether there were differences in mortality rates.

MATERIALS AND METHODS

The institutional review board approved the study. All subjects (or surrogate decision makers) gave informed consent before study enrollment. The patients were randomized to the control group (fluid management guided by PAC parameters) or the BV group (fluid management guided by BV results in addition to PAC parameters).

Patient selection

Patients with the following diagnoses were enrolled:

(1) Septic shock: Any two or more of the following signs in a patient with known source of infection: (*a*) temperature of greater than 39°C or less than 35°C; (*b*) a white cell count of greater than 12,000 or less than 4,000 cells/μL or 20% immature cells; (*c*) a heart rate of greater than 90 beats/min; (*d*) a spontaneous respiratory rate of greater than 20 breaths/min: plus a systolic BP (SBP) of less than 90 mmHg despite fluid resuscitation or greater than 40 mm from baseline in absence of other causes of hypotension.

(2) Severe sepsis: Sepsis associated with signs of perfusion abnormality after a bolus of 30 mL/kg in increments of 1 L, such as lactic acidosis, oliguria of less than 0.5 mL/kg per h, mental status alteration (or other signs of perfusion abnormality), or oxygen challenge test (OCT) of less than 25 mmHg (see below) (19).

(3) Cardiovascular collapse: any surgical patient in the ICU with hypotension (SBP <90 mmHg, or >40-mmHg decrease from known baseline) after a fluid bolus of 30 mL/kg and requiring vasopressors, with a history of cardiac disease or concurrent myocardial dysfunction, and elevated troponin I levels. History of cardiac disease is defined as prior myocardial infarction, echocardiogram showing wall abnormality or low ejection fraction (<52%), abnormal treadmill report, abnormal nuclear medicine studies or coronary angiogram, and history of CHF and/or arrhythmia requiring treatment.

(4) Severe oxygenation failure: P_{aO_2}/F_{IO_2} of less than 150 mmHg or intrapulmonary shunt 20% or greater while on positive end-expiratory pressure (PEEP) of 12 cm H_2O or greater, with PAOP of less than 18 mmHg, and chest roentgenograph with infiltrates.

Exclusion criteria were having surrogates who were unable or unwilling to give consent, being younger than 18 years, being pregnant, having brain injury documented on computed tomography with a Glasgow Coma Scale of 12 or less, quadriplegia, do-not-resuscitate status, height less than 122 cm or greater than 218 cm, and weight less than 21.3 kg or greater than 379 kg in men and greater than 351 kg in women.

Treatment protocol

The start time for resuscitation was defined as the time of PAC insertion or the time of SICU arrival if the patients came with a PAC inserted in the operating room. Goals of resuscitation for both groups were the same (Table 1) and were the standard of care in our SICU and were intended to be achieved within 24 h of PAC insertion (2, 3, 19) using hemodynamic guidelines as presented in Figure 1. All PAOPs were measured off PEEP if the PEEP settings were 15 cm H_2O or greater.

Two measurements of tissue ischemia were used: lactic acid level and the OCT. The OCT is based on the principle that skin is the first tissue bed to vasoconstrict in shock and the last to reperfuse. A well-perfused skin implies adequate blood flow to vital organs. A noninvasive probe measuring transcutaneous pressure of oxygen (P_{tcO_2}) is placed on the skin of the upper chest wall. Studies have shown that P_{tcO_2} correlates with P_{aO_2} (and therefore F_{IO_2}) during normal perfusion. In shock states, P_{tcO_2} changes with CO but fails to increase in response to F_{IO_2} of 1.0 because of vasoconstriction of the skin. The P_{tcO_2} response to F_{IO_2} of 1.0, called the OCT, is a marker of tissue perfusion, and a rise of 25 mmHg or greater in P_{tcO_2} (the dividing value between survivors and nonsurvivors) has been used as an end point of resuscitation (19).

Blood volume analysis

After obtaining a baseline sample of 5 mL of blood and a simultaneous blood Hct, a tracer consisting of human serum albumin tagged with iodine 131 (^{131}I) (5–30 microcuries) is injected intravenously over 1 min and allowed to mix completely throughout the circulation for 12 min. To correct for albumin transudation, serial blood measurements of 5 mL were collected at 12, 18, 24, 30, and 36 min after albumin ^{131}I injection and extrapolated to time zero to calculate the plasma volume (PV). Radioactivity was measured in duplicate in a semiautomated counter, and a minimum of three samples with an SD of less than 3.9% were used to calculate PV. The red blood cell volume (RBCV) was then derived based on the calculation: Hct = (RBCV)/(RBCV + PV). Whole (total) BV = PV + RBCV.

To interpret the volume results, the RBCV, PV, and BV were compared with the patient's ideal or normal volumes to account for size differences. Blood volume abnormalities were categorized and presented as percent deviation from the individual's normal/ideal BV (Table 2).

Treatment goals for BV values and the rationale for determination of the BV goals

The optimum PV and RBCV associated with survival in critically ill patients may differ from the optimum BV in a normal population. Shoemaker and colleagues (22) suggested that the optimum blood and PV in the critically ill patient should contain approximately 500 mL PV in excess of predicted norms and a normal red blood cell mass. Because of expanded vasculature in shock states (23), our study design aimed for a total BV that was 0% to 16% in excess of the predicted normal/ideal BV for a healthy individual (Figs. 2 and 3).

One area of controversy is the appropriate end point for red blood cell transfusion. Two problems currently exist in transfusion medicine: (*a*) using surrogate markers such as hemoglobin (Hb) or Hct to estimate RBCV and to serve as transfusion triggers and (*b*) absence of tissue oxygenation monitoring to determine the end point and benefit of red blood cell transfusion. A 30% to

TABLE 1. **Goals of resuscitation for both control and BV groups**

SBP >100 mmHg or within 40 mmHg from known baseline
Heart rate <100 beats/min
Urine output >0.5 mL/kg per h
Lactate to normal values within 24 h of resuscitation
Oxygen delivery adequate to achieve S_{VO_2} ≥70% and OCT ≥25 mmHg

For definition of OCT, refer to Materials and Methods (19).

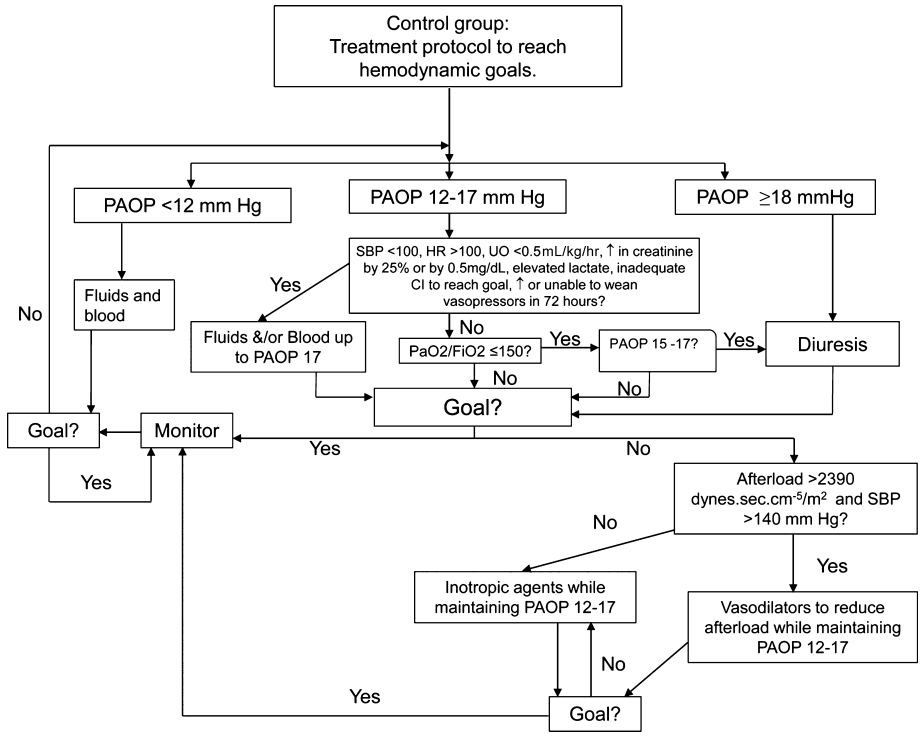

FIG. 1. **Treatment protocol for patients randomized to the control group**. The goals are presented in Table 1. Treatment was administered in the following sequence as necessary to reach the goals: (1) crystalloid/colloid infusion of 250 to 500 mL or blood infusion if Hct was less than 35% (Hct goal was 25%–35%). (2) Inotropes initiated with milrinone at 0.375 μg/kg per min or dobutamine at 2 to 5 μg/kg per min, titrated to desired CI to achieve the perfusion goal. (3) Norepinephrine or epinephrine initiated at 1 μg/min titrated to desired BP if hypotensive despite adequate preload. All PAOPs (in mmHg) are measured off-PEEP if on PEEP ≥15 cm H_2O. SBP values are in mmHg; heart rate (HR) values are in beats/min.

40% deficit in RBCV is possible with an Hct of greater than 30% if low RBCV and low PV coexist in the classically "hemoconcentrated" patients (21, 24–26), and this study was designed to keep the RBCV between 0% to −20% to avoid the consequences of anemic hypoxia. For the control group in which BV measurements were not used, an Hct between 25% and 35% (22) was used as the RBCV target to allow for wide variation in Hct goals, depending on whether the therapeutic end points as outlined in Table 1 had been reached.

Timing of BV measurements

The BV measurements were obtained after the initial resuscitation had been completed because large amounts of fluid and blood infusion would not allow steady state to occur during the BV measurements. The following four time points were selected based on our previous experience (16):

- BV 1: Performed 12 to 36 h after resuscitation. This allowed time for resuscitation to be "complete" and to reach a steady state in which large amounts of fluid or blood were not being infused.
- BV 2: Performed 24 to 36 h after BV 1. This represented the period when further fluid equilibration between body compartments may be occurring with possible early fluid mobilization.
- BV 3: Performed 24 to 36 h after BV 2. This represented the period when fluid mobilization should be occurring.
- BV 4: Between days 5 and 7 after study enrollment. This represented the period when secondary events may occur for patients remaining in the SICU.

All patients who remained in the SICU for 5 or more days received four BV tests regardless of their treatment group. The rounding team recorded parameters requiring treatment and estimated the patients' BV, RBCV, and PV as high, low, or normal and then developed a treatment plan. This allowed the team to assess whether its estimate of the patient's BV was accurate and whether the treatment changed significantly based on the BV results. For the control group, the results of BV analyses were blinded, and treatment was carried out using the available clinical parameters as outlined in Figure 1.

TABLE 2. **A method of categorizing deviations from the ideal or normal BV**

	Whole BV	RBCV	Plasma volume
Normal	±8%	±10%	±8%
Mild deviation	±9%–16%	±11%–20%	±9%–16%
Moderate deviation	±17%–24%	±21%–30%	±17%–24%
Severe deviation	±25%–32%	±31%–40%	±25%–32%
Extreme deviation	>32%	>41%	>32%

For the BV group, results of the BV measurements were used to guide fluid treatment as outlined in Figure 2. All hemodynamic data were collected simultaneously while the BV analyses were being done. Net fluid balance was calculated daily.

The rounding team documented response to treatment in both groups. The definition of a significant response consisted of (*a*) achieving the goals as presented in Table 1 if those were the parameters that needed treatment and/or a change of greater than (*b*) 10 mmHg in BP, (*c*) 10 beats/min in heart rate, (*d*) 15% in CI or stroke volume index, (*e*) 25% in dosage of vasoactive agents, (*f*) 20 points in Pao_2/Fio_2 ratio, and (*g*) 25% in blood urea nitrogen or creatinine levels. There was no attempt to categorize a response as being attributed to the treatment or to the natural progression of the illness. Response was categorized as favorable or unfavorable, depending on how the parameters changed as defined above. If the parameter did not change significantly as defined above, the response was determined to be neutral.

To simulate the anticipated normal utilization of BV measurements, patients randomized to the BV group were permitted to have additional BV analyses during the SICU course whenever the rounding team deemed it necessary (16). Removal of PACs occurred when the patient was off vasoactive agents for more than 24 h and if the PAC values such as PAOP, CI, and Svo_2 did not change management in the preceding 24 h. Fluid management protocol for both groups without PAC is presented in Figure 3.

SICU bundle for shock resuscitation

In addition to the hemodynamic goals, all SICU patients received the following care as part of our routine (27): (*a*) early enteral feedings (within 24 h of shock resuscitation) to promote mesenteric flow and decrease enteric source of cytokine release; (*b*) glutamine 10 mg three times a day for enterocyte fuel source and immune-enhancing activity; (*c*) antioxidants vitamin A 10,000 U, vitamin E 800 U, or selenium 200 μg + ascorbic acid 3 g in 0.9% NaCl at 20 mL/h; (*d*) steroids for septic shock based on adrenal function; (*e*) activated protein C for those with tissue hypoxia based on OCT value of less than 25 mmHg and with the diagnosis of septic shock or severe sepsis (28); and (*f*) glycemic control with blood sugar 80 to 110 mg/dL.

Statistical analyses and data studied

To address the goals of the study, which were (*a*) to assess the number of times the BV data resulted in changed treatment, (*b*) whether treatment resulted in favorable or unfavorable response, (*c*) whether there were differences in resource consumption (ventilator, SICU, hospital days), and (*d*) whether there were differences in mortality rates, the following parameters were analyzed: BP; HR; UO; lactic acid; CVP; PAOP; CI; stroke volume; Do_2; Svo_2; Pao_2; Sao_2; Fio_2; requirement and dosages of vasoactive agents; fluid balance; the SICU team's estimate of RBCV, PV, total BV, and treatment plan before obtaining BV; types of treatment (including red blood cells)

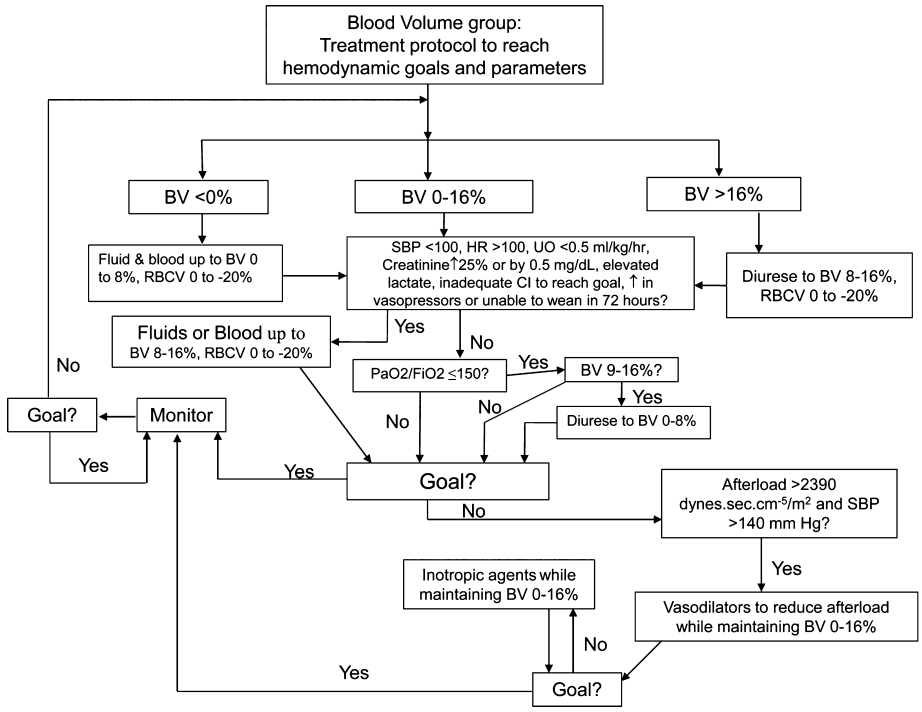

FIG. 2. **Treatment protocol for patients randomized to the BV group**. The goals are presented in Table 1. Treatment was administered in the following sequence as necessary to reach the goals: (1) crystalloid/colloid infusion of 250 to 500 mL and blood transfusion to reach RBCV of 0 to −20% of ideal/norm, and BV goal of 0% to 16% of ideal/norm. (2) Inotropes initiated with milrinone at 0.375 μg/kg per min or dobutamine at 2 to 5 μg/kg per min, titrated to desired CI to achieve the perfusion goal. (3) Norepinephrine or epinephrine initiated at 1 μg/min titrated to desired BP if hypotensive despite adequate preload. BVs are presented as % deviation from the patient's normal/ideal BV; RBCVs are presented as % deviation from the patient's normal/ideal RBCV. SBP values are in mmHg; heart rate (HR) values are in beats/min.

administered; response to treatment; ventilator, ICU, and hospital days; and hospital mortality.

Independent-samples *t* tests and chi-square or Fisher exact test were used to analyze continuous and nominal data, respectively. For all analyses, the level of significance was set to 0.05. Analyzed were patient demographics, hemodynamic parameters, whether and how the BV measurements changed treatment in the BV group or would have changed treatment in the control group, the response to treatment, blood transfusions, fluid balance, and outcome.

RESULTS

Patient demographics and comorbidities are presented in Table 3. There were no significant differences between the two groups in their baseline characteristics. The average age was 60 years, with 40% having elevated troponin I levels at the time of study entry. Approximately 70% of patients had septic shock/severe sepsis. There were no differences in the number of patients who received vasoactive agents (37/50 control group vs. 36/50 BV groups; $P = 0.82$), steroids (40/50 control group vs. 38/50 BV group; $P = 0.81$), and activated protein C (11/50 control group vs. 16/50 BV group; $P = 0.37$).

Table 4 displays the hemodynamic data, Hct, fluid balance, and BV results after the initial resuscitation and at the time of BV 1. This first data set represents values before using the BV information for treatment, and no differences existed between the control and BV groups.

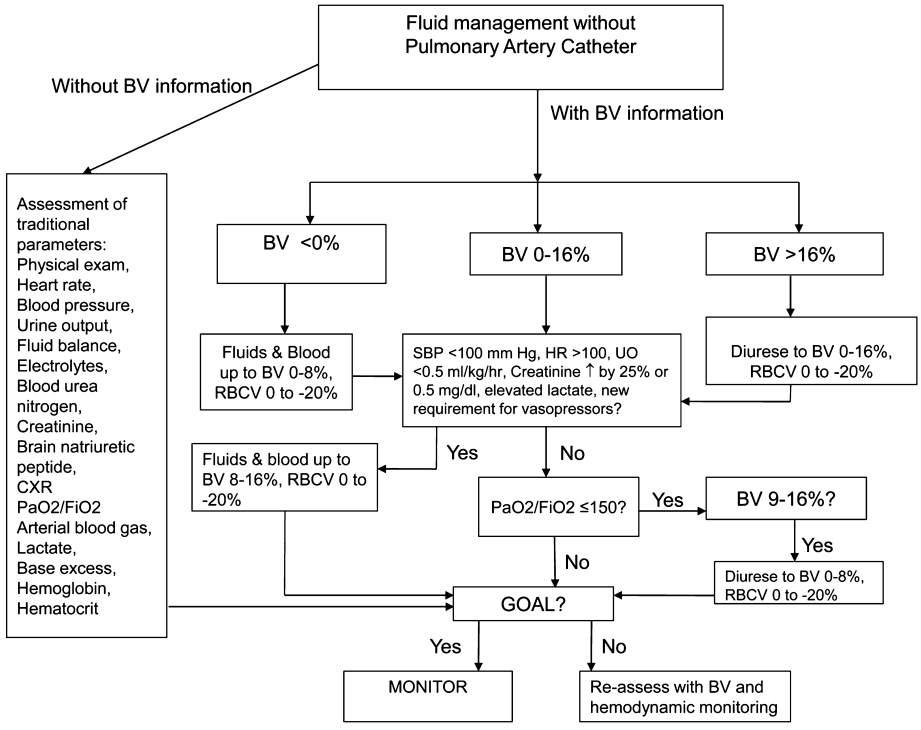

FIG. 3. **Fluid management without PAC**. The standard clinical parameters and laboratory values were used to guide fluid and red blood cell management in instances when BV analysis was not available, or if the patients were in the control group. BV presented as % deviation from the patient's normal/ideal BV; RBCVs are presented as % deviation from the patient's normal/ideal RBCV. SBP values are in mmHg; heart rate (HR) values are in beats/min.

Table 5 presents the average values of hemodynamic variables, Hct, fluid balance, and the BV results at BV 2, BV 3, and BV 4, which occurred from days 2 to 7 after the initial resuscitation. The control group demonstrated significantly lower Hct and higher deviation from the ideal PV and ideal BV values compared with the BV group.

During the first 7 days, the control group underwent 198 BV analyses, whereas the BV group received 254 BV analyses. The numbers of BV tests that resulted in management change in the BV group, or that would have changed treatment in the control group if the results had been available, are presented in Table 6. The control group demonstrated significantly more times when treatment would have changed with BV information and more times when patients would have been diuresed and given red blood cell transfusions compared with the BV group.

Table 7 compares the frequency of significant deviations in BV measurements in the control vs. BV groups, the number of red blood cell transfusions administered, and the response to treatment throughout the first 7 days. There were significantly more times when the control group exhibited significant red blood cell deficit, PV excess, and BV excess relative to the BV group (Table 7). Patients in the BV group were transfused with a greater amount of red blood cells than patients in the control group, and there was an average delay of 1.5 ± 2 days in administering red blood cell transfusions to patients in the control group had the BV results been available. The BV group demonstrated a significantly higher rate of favorable response to treatment compared with the control group (Table 7).

TABLE 3. **Patient demographics at time of study entry**

	Control group (n = 50)	BV group (n = 50)	*P*
Age, mean (SD), y	63 (16)	60 (17)	0.56
No. female: no. male	18:32	23:27	0.42
APACHE II, mean (SD),	24 (3)	25 (4)	0.16
Septic shock, no. patients	28/50	30/50	0.83
Severe sepsis, no. patients	6/50	5/50	0.75
Cardiovascular collapse, no. patients	9/50	6/50	0.57
Severe ARDS, no. patients	14/50	21/50	0.21
Cardiac history, no. patients	19/50	20/50	0.84
COPD, no. patients	5/50	9/50	0.39
Cirrhosis, no. patients	3/50	4/50	0.70
Diabetes mellitus, no. patients	18/50	16/50	0.83
Lactic acid, mean (SD), mEq/L	4.1 (3.1)	4.0 (2.8)	0.86
Creatinine, mean (SD), mg/dL	1.7 (1.0)	1.9 (1.7)	0.83
Creatinine clearance, mean (SD), mL/min	48 (25)	52 (30)	0.93
↑ Troponin, no. patients	19/50	21/50	0.84
Platelet count, mean (SD), $\times 10^3$	149 (190)	191 (190)	0.27
Bilirubin, mean (SD), mg/dL	2.6 (2.0)	4.0 (4.8)	0.06
OCT <25 mmHg,* no. patients	19/50	21/50	0.83

*Refer to Materials and Methods for definition. OCT <25 mmHg implies tissue hypoperfusion (19).
APACHE II indicates Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease.

TABLE 4. **Hemodynamic data and BV results at time of first BV analysis after the acute resuscitation**

	Control	BV	*P*
CVP, mmHg	13.5 (4.8)	13.8 (4.7)	0.75
PAOP, mmHg	16.0 (4.8)	16.6 (4.8)	0.48
Cardiac index, L/min/ per m^2	3.6 (0.9)	3.5 (0.9)	0.41
Do_2I, mL/min per m^2	552 (143)	549 (149)	0.91
Svo_2, %	76 (5)	74 (7)	0.10
Qs/Qt, %	25 (12)	22 (10)	0.18
Hematocrit, %	33 (4)	33 (6)	1.0
BV 1, % deviation	15 (26)	13 (15)	0.54
RBCV 1, % deviation	−10 (24)	−11 (17)	0.77
PV 1, % deviation	32 (32)	28 (20)	0.46
Fluid balance, mL, last 24 h	5,068 (3,744)	5,397 (4,855)	0.85

Values are presented as mean (SD).
Do_2I indicates Do_2 (indexed); Qs/Qt, intrapulmonary shunt; BV 1, the first BV analysis done after the initial resuscitation (presented as % deviation from the patient's ideal/normal volume); RBCV 1, first RBCV after the initial resuscitation (presented as % deviation from the patient's ideal/normal volume); PV 1, first PV after the initial resuscitation (presented as % deviation from the patient's ideal/normal volume).

After day 7, 282 additional BV analyses were performed in the 31 patients who remained in the SICU in the BV group. There was a treatment change based on 150 (53%) of 282 BV results relative to the treatment chosen based on clinical data alone. Red blood cell transfusions changed based on RBCV results in 87 incidences, in which 65 cases received more and 22 received fewer red blood cells. Fluid management changed based on PV results in 129 incidences, in which 37 cases received more fluids and 92 received less fluids or were diuresed. Of the total of 150 treatment changes resulting from BV analyses, 83 (55%) resulted in favorable responses, 24 (16%) led to

TABLE 5. **Averaged values of hemodynamic parameters, fluid balance, and BV results (days 2–7 after initial resuscitation)**

	Control	BV	*P*
Heart rate, beats/min	82 (17)	87 (17)	0.14
SBP, mmHg	134 (22)	139 (23)	0.28
CVP, mmHg	14 (4)	13 (5)	0.27
PAOP, mmHg	17 (5)	16 (4)	0.31
CI, L/min per m^2	3.5 (0.8)	3.6 (0.8)	0.53
Do_2, mL/min per m^2	529 (133)	567 (137)	0.16
Svo_2	77 (6)	76 (6)	0.40
Qs/Qt, %	29 (12)	22 (9)	0.35
Hematocrit, %	33 (4)	35 (5)	0.03
BV, % deviation	29 (21)	13 (17)	0.04
RBCV, % deviation	−8 (21)	−6 (14)	0.57
PV, % deviation	37 (25)	26 (23)	0.014
Fluid balance, mL	583 (2,739)	−20 (2,356)	0.24

Values are presented as mean (SD).
Do_2 indicates Do_2 indexed; Qs/Qt, intrapulmonary shunt; BV, BV presented as % deviation from the patient's normal/ideal BV; RBCV, red blood cell volume presented as % deviation from the patient's normal/ideal BV; PV, PV presented as % deviation from the patient's normal/ideal PV.

TABLE 6. **Number of BV analyses that would have changed treatment in the control group or resulted in changed treatment in the BV group (first 7 days)**

	Control group	BV group	*P*
No. of BVs performed	198	254	
No. of BVs with Rx change	121/198 (61%)	112/254 (44%)	0.004
More fluid	21/198 (11%)	34/254 (13%)	0.39
Less fluid/diuresis	62/198 (31%)	56/254 (22%)	0.03
More red blood cell	53/198 (27%)	32/254 (13%)	0.0002
Less or no red blood cell	21/198 (11%)	16/254 (6%)	0.12

Control group was blinded to the BV results.
BVs indicates BV analyses; Rx, treatment.

unfavorable responses, and 43 (29%) resulted in neutral responses.

Outcome data for the study group are presented in Table 8. Although the BV group had 5.4 less ventilator days and 11 less hospital days than the control group, these values did not reach statistical significance. There was a significant survival advantage in the BV group.

DISCUSSION

Assessment of intravascular circulating BV is useful, but the clinical utilization of BV information requires knowledge on how to use the individual values. To interpret the volume results, the RBCV, PV, and BV have to be compared with the patient's ideal or normal volumes to account for size differences. The limitations of using the standard calculation of 60 to 70 mL/kg have long been recognized, especially in the extremes of weight. The BVA-100 automatically estimates the patient's ideal or normal BV using an established formula based on sex, height, baseline weight, and deviation from optimum longevity-related weight as determined by the Metropolitan Life Table and previously validated by BV studies (29). Blood volume abnormalities are then categorized and presented as percent deviation from the individual's normal/ideal BV (Table 2).

TABLE 7. **Number of times when major deviations in BV analysis were present, transfusions administered, and response to treatment (first 7 days)**

	Control group	BV group	*P*
No. BVs performed	198	254	
No. BVs with >−20% deficit RBCV	66/198 (33%)	40/254 (16%)	<0.001
No. BVs with BV <0%	39/198 (18%)	49/254 (19%)	0.86
No. BVs with BV >16%	96/198 (48%)	94/254 (37%)	0.02
No. BVs with PV <0%	12/198 (6%)	24/254 (9%)	0.25
No. BVs with PV >16%	152/198 (76%)	165/254 (65%)	<0.001
Units of red blood cells given	137	177	
Units of red blood cells/ patient, mean (SD)	2.74 (2.19)	3.85 (3.18)	0.049
Favorable response to Rx	87/198 (44%)	150/254 (59%)	0.002
Unfavorable response to Rx	49/198 (25%)	46/254 (18%)	0.10
Neutral response to Rx	62/198 (31%)	58/254 (23%)	<0.05

Refer to Materials and Methods for definition of favorable, unfavorable, and neutral response. Control group was blinded to BV results and was treated as outlined in Figures 1 and 3.
BV indicates BV presented as % deviation from the patient's ideal/normal BV; RBCV, red blood cell volume presented as % deviation from the patient's ideal/normal BV; PV, PV presented as % deviation from the patient's ideal/normal BV; Rx, treatment.

TABLE 8. **Outcomes and resource utilization**

	Control group (n = 50)	BV group (n = 50)	*P*
PAC days, mean (SD)	9.3 (5.2)	8.3 (5.1)	0.57
Ventilator days, mean (SD)	29.2 (33.5)	23.8 (23.9)	0.38
Ventilator-free days (at 28 d), mean (SD)	9 (9)	12 (11)	0.13
Ventilator-free days (at 45 d), mean (SD)	18 (17)	23 (17)	0.15
ICU days, mean (SD)	28.0 (24.6)	28.7 (27.0)	0.90
Hospital days, mean (SD)	54.7 (41.0)	43.7 (31.3)	0.14
Mortality rate	13/50 (26%)	4/50 (8%)	0.02
Mortality from MSOF	12/50 (24%)	4/50 (8%)	0.03

Ventilator days may be longer than ICU days because of being in intermediate care unit stay. Ventilator-free days are calculated at both 28 and 45 days. Mortality rate is for the entire hospital stay. One patient in the control group died of massive stroke and was not considered to have died of multisystem organ failure (MSOF).

Interpretations of BV results were performed as follows: whole BV value was noted first, then RBCV followed by PV. Plasma volume should change to compensate for any changes in RBCV as a normal homeostatic response to preserve a normal BV. Both the absolute values of volumes in milliliters as well as the percent deviation from the patient's normal/ideal values were noted. As an example, if the patient's normal/ideal RBCV is calculated at 1,945 mL, and the BVA reports the patient's RBCV of 1,309 mL, then the deficit is 636 mL of red blood cells (−32.7% deficit), and the patient may receive 1 to 2 U of blood (300 mL/U). If the patient's normal/ideal PV is 2,853 mL and BVA reports a PV of 3,649 mL, which represents an excess of 796 mL (27.9% excess), the patient will be diuresed.

The optimum PV and RBCV associated with survival in critically ill patients may differ from the optimum BV in a normal population. There is poor tolerance (a decrease in cardiac function) when BV is reduced by as little as 8% (30). Although a prospective randomized trial has not been performed, previous studies have associated BV values to outcome (5, 24, 25, 31, 32), or with the need for red blood cell transfusions (26, 33). Because of the type of patients we chose to study and our awareness that intravascular volume may be expanded in shock states (23), we aimed for a slightly elevated BV goal (0%–16%) based on previous recommendations (22) rather than aiming for an ideal BV of 0% deviation from the norm (Table 2). Also factored in the algorithm was the allowance to keep the BV goal at a more normal level (0%–8% of normal) or PAOP (12–14 mmHg) if a patient had severe oxygenation deficit and did not have signs of hemodynamic instability (Figs. 1 and 2). This approach provides a guideline for using BV data to guide fluid management in the critically ill surgical patients.

The benefit of BV analyses occurs after the initial resuscitation when the patients have total body fluid elevated with

edema and weight gain. Determining the intravascular volume state in these patients can be particularly difficult in the presence of mixed signals from the classic combination of vital signs, UO, and laboratory values (16, 17, 22), resulting in disputes among experienced clinicians (7). Our study demonstrated that the addition of BV analysis to hemodynamic monitoring allowed us to treat patients so that they achieved a more physiologically normal range of RBCV and PV. Hemodynamic data, Hct, and fluid balance were similar between the two groups immediately after the initial resuscitation (Table 4) because similar resuscitation goals and treatment were used for both groups. Accurate BV testing requires circulatory stability so that the patient is not losing or receiving blood and fluids rapidly for the tracer (albumin ^{131}I) to mix completely throughout the circulation and reach steady state. Therefore, we did not attempt to perform BV measurements when large amounts of fluid and blood were being infused as typically occurs in the initial 24 h of resuscitation.

The average values for Hct, PV, and BV were significantly different between the two groups for days 2 to 7 after resuscitation, but the fluid balance did not reach significance because of a large SD (Table 5). A more meaningful way of assessing the functional utility of BV analyses was to determine the number of times the use of BV analysis would have changed treatment (Table 6). In that case, the control group demonstrated more instances when the BV results would have altered management, most likely due to ongoing blinding of BV results throughout the treatment of the control group. Any BV abnormality that was not clinically detected and treated would persist at the next BV analysis. The control group would have been either diuresed more frequently or given more blood transfusions compared with the BV group if the BV information had been available to physicians (Table 6).

This resulted in more times when the control group exhibited significant abnormalities in BV, RBCV, and PV compared with the BV group (Table 7). The results shown in Tables 6 and 7 demonstrate the limitations of relying on surrogate markers (including central hemodynamic pressures) to predict BV. Despite guidance in fluid management from BV data and knowledge of the results of the any preceding BV tests, the BV group still required treatment alteration in 44% of the time (Table 6). This may reflect the fact that this patient population is experiencing rapid and continuous changes in its intravascular volume status. Other studies have similarly reported 30% to 50% rates of change in treatment based on BV data relative to clinical assessment alone (16, 17, 22).

Patients who were treated based on BV findings showed a higher rate of favorable response relative to the control group (Table 7), demonstrating that the BV measurements show a better relationship to clinical parameters and outcome. Based on BV results, patients in the BV group were diuresed and given red blood cells more frequently and in a timelier fashion (by 1.5–2 days) as reported previously (16). The timeliness of treatment may be one factor that accounts for better outcome in the BV group. Although the importance of expeditious treatment in the acute resuscitation phase is well appreciated (1–4), earlier correction of PV with respect to whole BV and prompt replacement of red blood cell deficit may also prove beneficial after the initial resuscitation. The patients in this study were well hydrated, with 37% of the BV group and 48% of the control group exhibiting hypervolemia (Table 7). Although it may seem counterintuitive to diurese patients while they are on vasopressors, we did so if PV and BV were elevated as per protocol (Fig. 2). Other investigators (4) have observed that patients who achieved zero or negative fluid balance on 2 consecutive days during the first 7 days of septic shock and acute lung injury had the best mortality.

Fine tuning fluid balance based on BV measurements may be beneficial not only in the first week, but also at later times during the SICU stay. The use of BV data after 7 days in the long-term SICU patients demonstrated a similar proportion of favorable, unfavorable, or neutral responses as had been observed in the first 7 days. Secondary events are not unusual in this study population who averaged 28 SICU days and is consistent with our previous observation (16). Financial constraints did not permit the control group to have additional (blinded) BV analyses, which could have provided information on how frequently fluid management may have changed in the control group as well after day 7. The impact of BV information with resultant tailoring of fluid and red blood cell management throughout the hospital course is an area that deserves further study.

We did not attempt to determine whether a response to treatment was due to the treatment itself or the natural course of the disease. However, unlike our pilot study in which no unfavorable responses were observed to BV treatment (16), there was a 18% to 25% unfavorable response rate in the BV and control groups, respectively (Table 7), which is not unexpected in this critically ill group of patients.

Central pressures may still play an important role in the acute resuscitative phase as they provide information on cardiac reserve and help to avoid pressure related edema on the lungs and viscera. Although current guidelines recommend fluid resuscitation to a CVP of 8 (1–3) and up to 15 mmHg (14), PAOP may be a better guide to cardiac response (12, 34), and one study demonstrated a correlation of PAOP to BV (12). The PAC provides a reliable method of monitoring CO, Svo_2, and the PAOP as well as pulmonary artery pressures, and our group has a long history of titrating Do_2 to the end points of lactate, Svo_2, and OCT with good success (19). We concur with the leaders of *Critical Care Medicine* (20) that the PAC serves a valuable purpose when used appropriately. The design of our study was to use the PAC to reach similar goals (Table 1) for both the control and BV groups during the acute resuscitation because this is the standard of care in our SICU, followed by additional guide from BV analyses for patients randomized to the BV group. After the initial resuscitation, BV played an important role in guiding fluid therapy beyond the surrogate markers of intravascular volume as seen by the results presented in Tables 4 and 5. Although central pressures remain important in determining preload for optimum cardiac function, the BV analysis allows clinicians to measure intravascular volume (BV), which may be important for tissue perfusion for the rest of the body. Clinicians need to assess both volumes (preload for the heart and BV for the body) to optimize these parameters, which are important for Do_2.

The mortality rate for the control group was similar to prior published rates (19), but the mortality rate in the BV group was significantly decreased relative to the control group (Table 8). One possible explanation may be that the BV information guided our treatment earlier, and the treatment was not exclusively in one direction: diuresis was prompted in 40% of the time, more fluids in 20%, and prompt blood transfusions were administered to patients who had red blood cell deficits (Table 7). A relationship between hypervolemia (both recognized and unrecognized) with increased mortality rate in the CHF patients has been reported (5). Also contributing to the respectable mortality rate of even the control group may be the SICU bundled care (see Materials and Methods), which encompasses more than what is currently advocated (15). Our SICU protocol at the time of this project used strict glycemic control between 70 and 110 mg/dL, but we have recently elevated the upper limit to 140 mg/dL. Controversy continues on the optimum value of blood sugar control because the studies are not conclusive.

There may be criticism of the liberal red blood cell transfusions administered to the study subjects with Hct of greater than 30%, particularly in the BV group, but it was deemed appropriate for this older patient population, 40% of whom had significant cardiac history and 40% demonstrated elevated troponin I levels at time of study entry (Table 3). There is evidence that −40% deficit in RBCV may be poorly tolerated in stressed states even in the younger patient population (24, 25). Although reasonably tolerated in nonstressed states, hypovolemic anemia may have devastating consequences during physiologic stress or surgery (24, 25). These situations of falsely high Hct may exist in the current ICUs (21, 26). Although the RBCV goal of 0 to −20% may have resulted in liberal red blood cell transfusions, the mortality rate for the BV group of 8% is favorable compared with previous trial of similar patients (19). Reevaluation of the Transfusion Requirement in Critical Care trial suggests that patients with a history of cardiac problems fare more poorly with a restrictive red blood cell practice (35). A normal Hct may be the optimum Hct in situations where CO cannot increase in response to anemia (36), and a normal Hct may be the best to ensure optimum oxygen transport to all organs (37) with the best blood viscosity (38). A previous study assessing the components of bundled care in septic shock patients have also demonstrated more red blood cells given to the goal directed group, although statistical significance was not reached (15). It may be that some patients with adequate cardiac reserve will do well with RBCV deficit of −20% to −30%, but we do not advocate keeping patients at −40% deficit in the acute phase of critical illness, particularly because we do not have a good method of monitoring their cellular bioenergetic state. One limitation of this study was that we did not try to control for the age of the red blood cells being transfused.

The problem inherent with using Hct, which is a ratio of RBCV to (PV + RBCV), is well known because clinicians have long talked about "hemodilution" and "hemoconcentration" based on their estimate of whether the PV is expanded or contracted. Profound (>30%) deficits in RBCVs may occur with Hct of greater than 30% (16, 24, 25, 39). It has been difficult to arrive at optimum guidelines for transfusion (40) because one Hct cannot suit all (9, 21, 26). The problem is that we are measuring a surrogate marker of RBCV instead of measuring RBCV. Using a single value of Hb or Hct as a transfusion trigger may be inappropriate because the Hct reflects RBCV only with the assumption that the patients are euvolemic. Using Hct as a transfusion trigger may lead to overtransfusion or undertransfusion. Also, Hb levels may be a poor predictor of benefit from transfusions (39, 41). A more physiologic end point of red blood cell titration may be to measure RBCV, and the degree of red blood cell deficit that can be tolerated may vary for each individual value based on cardiac function and markers of tissue ischemia.

Some authorities have questioned the validity of a single tracer (tagged albumin) test compared with the double dye test (tagging albumin and red blood cells) to measure BV. Tagging red blood cells introduces complexity as well as the possibility of technical errors to the test, and chromated red blood cell studies require at least two measurements and preferably three to document close agreement. Tagging of albumin allows for the direct measurement of PV, which constitutes a proportionately larger percentage (60%–65%) of the total BV than does RBCV (35%–40%). Previous study has confirmed that the single isotope tagging with albumin gives equivalent results to the dual-isotope test with less time (1.5 vs. 5 h) (42). Inherent in the test are multiple blood draws, the cost of radioactive material, and the reliance on the accuracy of timed blood draws by the technician. Once-a-day test is intermittent, and although it provides guidance, an easier method that allows frequent BV assessments is needed. Despite these issues, the knowledge gained may be valuable for outcome.

Despite a decrease in mortality, the ventilator, ICU, and hospital days were not statistically significantly different between the two groups (Table 8). Because of the type of patient selection, the length of stay was long, and there were large SDs for both groups. It may be that the BV information does not help to decrease resource consumption in this group of patients or that the sample size was inadequate to detect these differences.

Caution should be used in extrapolating the results of our study to all critically ill patients because there are always the potential biases inherent in a single-center trial. We chose to study a select group of SICU patients likely to demonstrate large fluid shifts and requiring PAC monitoring. Future studies conducted in a variety of hospital and outpatient settings will be needed to confirm the benefits of using BV analyses for various disease states. The optimum BV (and RBCV) may not be the same for different patient groups and may even change for a given patient as the disease or the recovery phase progresses. Technology that makes BV analyses easier and more frequently available at the bedside, as well as a continuous monitor of tissue hypoxia, may assuage the debate on the appropriate end points of fluid and blood transfusion.

CONCLUSIONS

The incorporation of BV data that contain information on red blood cell and PV may lead to a more physiologic end point of fluid and red blood cell resuscitation. The current study showed that the use of directly measured BV data to

guide therapy in the SICU patients produced improved outcomes relative to those obtained with conventional central hemodynamic pressures and surrogate markers of intravascular volume and RBCV (Hb and Hct). This prospective randomized trial used PAC information to guide the initial stages of fluid resuscitation, followed by the use of BV data to more precisely determine patients' need for fluids and blood transfusions. An important aspect of care was the earlier treatment of intravascular volume deviations from the norm in the BV group, before the abnormality became clinically manifested. Utilization of BV analyses after the initial resuscitation and its impact on mortality and length of stay are an area that deserves further study.

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REFERENCES

1. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345:1368–1377, 2001.
2. Tisherman SA, Barie P, Bokhari F, Bonadies J, Daley B, Diebel L, Eachempati SR, Kurek S, Luchette F, Puyana J, et al.: Clinical practice guideline: endpoints of resuscitation. *J Trauma* 57:898–912, 2004.
3. Jones AE, Brown MD, Trzeciak S, Shapiro NI, Garrett JS, Heffner AC, Kline JA: The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis. *Crit Care Med* 36:2734–2739, 2008.
4. Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, Micek ST, Kollef MH: The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 136:102–109, 2009.
5. Androne AS, Hryniewicz K, Hudaihed A, Mancini D, Lamanca J, Katz SD: Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. *Am J Cardiol* 93:1254–1259, 2004.
6. Androne AS, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, Mancini DM: Hemodilution is common in patients with advanced heart failure. *Circulation* 107:226–229, 2003.
7. Junghans T, Bohm B, Haase O, Fritzmann J, Zuckermann-Becker H: Conventional monitoring and intravascular volume measurement can lead to different therapy after upper gastrointestinal tract surgery. *Intensive Care Med* 28: 1273–1275, 2002.
8. Shippy CR, Appel PL, Shoemaker WC: Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med* 12:107–112, 1984.
9. Jones JG, Wardrop CA: Measurement of blood volume in surgical and intensive care practice. *Br J Anaesth* 84:226–235, 2000.
10. Oohashi S, Endoh H: Does central venous pressure or pulmonary capillary wedge pressure reflect the status of circulating blood volume in patients after extended transthoracic esophagectomy? *J Anesth* 19:21–25, 2005.
11. Kuntscher MV, Germann G, Hartmann B: Correlations between cardiac output, stroke volume, central venous pressure, intra-abdominal pressure and total circulating blood volume in resuscitation of major burns. *Resuscitation* 70:37–43, 2006.
12. Yamauchi H, Biuk-Aghai EN, Yu M, Ho HC, Chapital AD, Koss W, Takanishi, DM Jr: Circulating blood volume measurements correlate poorly with pulmonary artery catheter measurements. *Hawaii Med J* 67:8–11, 2008.
13. Alrawi SJ, Miranda LS, Cunningham JN Jr, Acinapura AJ, Raju R: Correlation of blood volume values and pulmonary artery catheter measurements. *Saudi Med J* 23:1367–1372, 2002.
14. Moore FA, McKinley BA, Moore EE, Nathens AB, West M, Shapiro MB, Bankey P, Freeman B, Harbrecht BG, Johnson JL, et al.: Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core–standard operating procedures for clinical care. III. Guidelines for shock resuscitation. *J Trauma* 61:82–89, 2006.
15. Barochia AV, Cui X, Vitberg D, Suffredini AF, O'Grady NP, Banks SM, Minneci P, Kern SJ, Danner RL, Natanson C, et al.: Bundled care for septic shock: an analysis of clinical trials. *Crit Care Med* 38:668–678, 2010.
16. Takanishi DM Jr, Biuk-Aghai EN, Yu M, Lurie F, Yamauchi H, Ho HC, Chapital AD, Koss W: The availability of circulating blood volume values alters fluid management in critically ill surgical patients. *Am J Surg* 197:232–237, 2009.
17. Stephan F, Flahault A, Dieudonne N, Hollande J, Paillard F, Bonnet F: Clinical evaluation of circulating blood volume in critically ill patients—contribution of a clinical scoring system. *Br J Anaesth* 86:754–762, 2001.
18. Yu M, Burchell S, Hasaniya NW, Takanishi DM, Myers SA, Takiguchi SA: Relationship of mortality to increasing oxygen delivery in patients > or = 50 years of age: a prospective, randomized trial. *Crit Care Med* 26:1011–1019, 1998.
19. Yu M, Chapital A, Ho HC, Wang J, Takanishi D Jr: A prospective randomized trial comparing oxygen delivery versus transcutaneous pressure of oxygen values as resuscitative goals. *Shock* 27:615–622, 2007.
20. Vincent JL, Pinsky MR, Sprung CL, Levy M, Marini JJ, Payen D, Rhodes A, Takala J: The pulmonary artery catheter: *in medio virtus*. *Crit Care Med* 36: 3093–3096, 2008.
21. Takanishi DM, Yu M, Lurie F, Biuk-Aghai E, Yamauchi H, Ho HC, Chapital AD: Peripheral blood hematocrit in critically ill surgical patients: an imprecise surrogate of true red blood cell volume. *Anesth Analg* 106:1808–1812, 2008.
22. Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH: Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. *Arch Surg* 106:630–636, 1973.
23. Marx G, Schuerholz T, Pedder S, Simon T, Grime S, Sumpelmann R, Leuwer M: Blood volume measurements using an integrated fiberoptic monitoring system in a porcine septic shock model. *Crit Care Med* 34:1483–1488, 2006.
24. Biron PE, Howard J, Valeri CR: Chronic deficits in red-cell mass in patients with orthopaedic injuries (stress anemia). *J Bone Joint Surg Am* 54:1001–1014, 1972.
25. Valeri CR, Altschule MD: Hypovolemic anemia of trauma: the missing blood syndrome. Boca Raton, FL: CRC Press, Inc, 1981, pp 1–15; 85–104; 141–145.
26. Valeri CR, Dennis RC, Ragno G, Macgregor H, Menzoian JO, Khuri SF: Limitations of the hematocrit level to assess the need for red blood cell transfusion in hypovolemic anemic patients. *Transfusion* 46:365–371, 2006.
27. Beale RJ, Sherry T, Lei K, Campbell-Stephen L, McCook J, Smith J, Venetz W, Alteheld B, Stehle P, Schneider H: Early enteral supplementation with key pharmaconutrients improves Sequential Organ Failure Assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial. *Crit Care Med* 36:131–144, 2008.
28. Chapital AD, Yu M, Ho HC, Wang J, Koss W, Takanishi D: Using transcutaneous oxygen pressure measurements as selection criteria for activated protein C use. *J Trauma* 65:30–33, 2008.
29. Feldschuh J, Enson Y: Prediction of the normal blood volume. Relation of blood volume to body habitus. *Circulation* 56:605–612, 1977.
30. Guyton AC, Hall JE: Circulatory shock and physiology of its treatment. In: *Textbook of Medical Physiology*. Philadelphia, PA: WB Saunders, 253–254, 2000.
31. Katz SD: Blood volume assessment in the diagnosis and treatment of chronic heart failure. *Am J Med Sci* 334:47–52, 2007.
32. Wang P, Ba ZF, Lu MC, Ayala A, Harkema JM, Chaudry IH: Measurement of circulating blood volume *in vivo* after trauma-hemorrhage and hemodilution. *Am J Physiol* 266:R368–R374, 1994.
33. Shevde K, Pagala M, Tyagaraj C, Udeh C, Punjala M, Arora S, Elfaham A: Preoperative blood volume deficit influences blood transfusion requirements in females and males undergoing coronary bypass graft surgery. *J Clin Anesth* 14: 512–517, 2002.
34. Michard F, Teboul JL: Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* 121:2000–2008, 2002.
35. Deans KJ, Minneci PC, Suffredini AF, Danner RL, Hoffman WD, Ciu X, Klein HG, Schechter AN, Banks SM, Eichacker PQ, et al.: Randomization in clinical trials of titrated therapies: unintended consequences of using fixed treatment protocols. *Crit Care Med* 35:1509–1516, 2007.
36. Case RB, Berglund E, Sarnoff SJ: Ventricular function. VII. Changes in coronary resistance and ventricular function resulting from acutely induced anemia and the effect thereon of coronary stenosis. *Am J Med* 18:397–405, 1955.
37. Fan FC, Chen RY, Schuessler GB, Chien S: Effects of hematocrit variations on regional hemodynamics and oxygen transport in the dog. *Am J Physiol* 238: H545–H522, 1980.
38. Crowell JW, Smith EE: Determinant of the optimal hematocrit. *J Appl Physiol* 22:501–504, 1967.
39. Slight RD, Bappu NJ, Nzewi OC, McClelland DB, Mankad PS: Perioperative red cell, plasma, and blood volume change in patients undergoing cardiac surgery. *Transfusion* 46:392–397, 2006.
40. Napolitano LM, Kurek S, Luchette FA, Corwin HL, Barie PS, Tisherman SA, Hebert PC, Anderson GL, Bard MR, Bromberg W, et al.: Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *Crit Care Med* 37:3124–3157, 2009.
41. Hudson I, Cooke A, Holland B, Houston A, Jones JG, Turner T, Wardrop CAJ: Red cell volume and cardiac output in anaemic preterm infants. *Arch Dis Child* 65:672–675, 1990.
42. Dworkin HJ, Premo M, Dees S: Comparison of red cell and whole blood volume as performed using both chromium-51–tagged red cells and iodine-125–tagged albumin and using I-131–tagged albumin and extrapolated red cell volume. *Am J Med Sci* 334:37–40, 2007.