# A Prospective Randomized Trial Using Blood Volume Analysis vs. Pulmonary Artery Catheter Measurements to Guide Fluid and Red Cell Management

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## Introduction

Achieving euvolemia is a desired goal in shock resuscitation. Interchangeable terms used to describe blood volume (BV) are "effective circulating blood volume", or "intravascular volume" to differentiate this important component from interstitial and intracellular space. Blood volume (BV) = Plasma Volume (PV) + Red Blood Cell Volume (RBCV). A direct measurement of BV would allow treatment to "euvolemia" and optimize red cell transfusion (trx) as well. Current practice of transfusing based on Hematocrit (Hct) may be flawed since Hct = RBCV/BV and may not reflect RBCV if plasma volume is high or low. This study was done to determine efficacy of adding the BV information to the current use of pulmonary artery catheter (PAC) directed resuscitation of critically ill surgical patients. (1)

## Methods

After informed consent, patients were randomized to the Control group vs. BV group. All patients had PAC's. Inclusion criteria were:
1) Septic shock: Any two or more of the following signs in a patient with known source of infection: a) temperature of >39 °C or <35 °C; b) a white cell count of >12,000 or <4000 cells/uL or 20% immature cells; c) a heart rate of >90 beats/min; d) a spontaneous respiratory rate of >20 breaths/minute, plus a systolic blood pressure of <90 mm Hg despite fluid resuscitation or >40 mm from baseline in absence of other causes of hypotension. Fluid resuscitation is defined as 30 ml/kg given as one liter boluses.
2) Severe sepsis: sepsis associated with signs of perfusion abnormality after 30 ml/kg bolus in increments of 1 liter, such as lactic acidosis, oliguria <0.5 mL/kg/hour, mental status alteration (or other signs of perfusion abnormality), Oxygen Challenge test <25 mm Hg using PtcO2 monitor (1), or Base deficit of ≥-6 meq/L.
3) Hypotension (SBP <90 mm Hg, or >40 mm Hg decrease from known baseline) after 30 ml/kg fluid bolus and with a history of cardiac disease or concurrent myocardial dysfunction as defined below, and requiring vasopressors. Definition of History of heart disease - prior myocardial infarction, echocardiogram showing wall abnormality or low ejection fraction (defined as <52%), abnormal treadmill report, abnormal nuclear medicine studies or coronary angiogram, history of congestive heart failure and/or arrhythmia requiring treatment. Patients with only a history of cardiac surgery, but with a normal ejection fraction or CI >3.0 L/min/m2 will not be included in this category. Concurrent myocardial dysfunction: current echocardiogram showing wall motion defect or EF <52 with an elevated troponin I.
4) Severe Oxygenation failure: PaO2/FiO2 <150, or intrapulmonary shunt ≥20% requiring PEEP ≥12 cm H20, with CXR findings of infiltrates.

**Blood Volume Measurements:**
Recent advancements in FDA approved technology (BVA-100, Daxor, New York) allow easier measurement of blood volume analysis (BVA). The principle is that a known amount of tracer with a known concentration is injected into an unknown space (blood volume). With sampling of the new concentration, the unknown volume is calculated.
After obtaining a baseline sample of 5 mL of blood, a known amount of albumin tagged with I-131 is injected intravenously and allowed for complete mixing in 12 minutes. To correct for albumin transudation, serial measurements (5 samples every 6 minutes) are drawn and extrapolated to time zero to calculate the plasma volume.
The hematocrit is measured simultaneously to obtain the red blood cell volume (RBCV) to total blood volume ratio. Blood volume is calculated as Plasma Volume + Red blood cell volume.
These ideal blood volume values were derived using a patented formula based on gender, height, weight, and optimum (ideal) weight as determined by the Metropolitan Life tables, and as previously validated by blood volume studies (2). This mathematical model of using %deviation from ideal weight to calculate the normal predicted BV for that person was more accurate than utilizing either the body surface area or a subject's weight, particularly at the extremes of weight.
Results are given as absolute numbers (mL) and as a percent deviation of ideal volume. (Table 1)

| | Whole Blood Volume | Red Cell Volume | 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% |

A "normalized hematocrit" measurement is also provided. The normalized hematocrit is an adjusted hematocrit equal to the ratio of the patient's measured red cell volume to the predicted normal whole blood volume, i.e. if the patient's plasma volume adjusted to maintain a normal whole blood volume.

BV was obtained on days 1, 2, 3, 5-7 after resuscitation in both groups, but patients in the BV group were allowed additional BVA as needed during the ICU stay. The team was blinded to the BV results in the Control group. The rounding team would guess the patients PV, RBCV and BV at times when BVA was performed and the treatment that should be administered. For the BV group, treatment would then be based on BV results, and the difference and outcome of treatment would be recorded. The Control group was treated as per protocol (see Figures below) and the outcome to treatment would be recorded.
Treatment Goal to be reached in 24 hours of study entry:
Goals of treatment for both groups (Control and BV) were:
BP >100 mm Hg or within 40 mm Hg from known baseline.
Heart rate <100 beats/minute
Urine output >0.5 ml/kg/hour
Lactate to normal values within 24 hours of resuscitation
Oxygen delivery (DO2) to achieve SvO2 ≥70% and Oxygen Challenge test (OCT) ≥25 mm Hg. (1). OCT uses the skin partial pressure of oxygen (PtcO2) and is a marker of tissue perfusion while SvO2 is a global measure of balance between DO2 and oxygen consumption .

Although data to support the optimum BV value associated with survival in critically ill patients is sparse, the patients are intravascularly expanded, and we chose to resuscitate up to 16% of normal (3). Since the optimum Hct varies with cardiac ability, the Control group had goals of Hct >25% but <35%, and for the BV group, patients were transfused to Red Cell Volume of 0-20% (3)

Protocol (see Figures 1-3).

FIGURE 1: Resuscitation protocol for PAC group

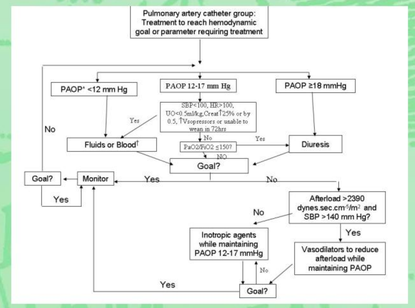



Figure 2. Resuscitation protocol for patients with pulmonary artery catheter utilizing BV information.

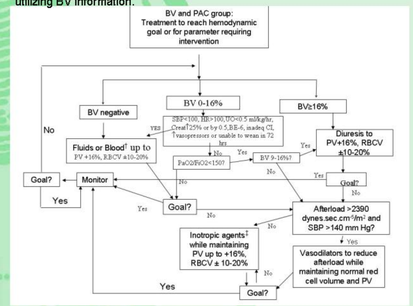
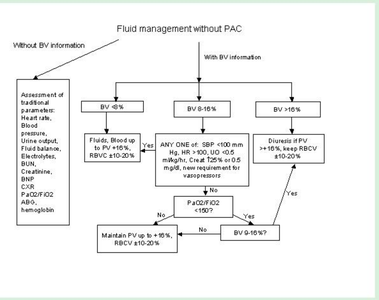



Figure 3. Fluid management in patients after removal of Pulmonary artery catheter.




*PAOP: pulmonary artery occlusion pressure. Measured with PEEP turned to zero if PEEP is ≥15 cm H20.
†Crystalloid/colloid infusion of 250-500 mL titrated to PAOP or BVA
Control group: blood infusion if Hct was <35 (keep Hct between 25-35). BV group: red cell volume (RBCV) 0 – minus 20% deviation from ideal.
‡dobutamine starting at 2 - 5 μg/kg/min, or milrinone at 0.375 ug/kg/min, with titration to desired cardiac index to achieve the perfusion goal. Norepinephrine or epinephrine starting at 1 μg/min minute titrated to desired blood pressure if hypotensive despite adequate preload.

**RESULTS: 100 patients completed the study.**
**See Tables 2-4**

Table 2. Demographics

| | Control | BV |
|---|---|---|
| Age | 63 ± 15 | 61 ± 17 |
| Male:Female | 32:18 | 27:23 |
| Septic Shock | 28 | 30 |
| Severe sepsis | 6 | 5 |
| Cardiogenic shock | 9 | 6 |
| ARDS | 14 | 21 |
| Lactic acid (mean) | 4.1 ± 3.1 | 4.0 ± 2.8 |
| APACHE II | 26 ± 2 | 27 ± 2 |

(These values were not statistically significantly different).

Table 3. How BV Analysis would change/changed treatment (values from first 7 days).

| | Control Group | BV Group | p-value |
|---|---|---|---|
| No. of BVA's | 198 | 225 | |
| More fluids | 21 (11%) | 45 (20%) | 0.01 |
| Less fluid/diuresis | 62 (31%) | 51 (23%) | <.05 |
| More Blood* | 48 (24%) | 25 (11%) | <.01 |
| No/less blood | 25 (13%) | 13 (6%) | 0.02 |

*There was an average delay of 1.5 days in the Control group before blood was given if the BV results had been available.

Table 4. Outcomes and Resource consumption.

| | Control | BV | p-value |
|---|---|---|---|
| PAC days | 9 ± 5 | 8 ± 5 | 0.33 |
| Ventilator days | 29 ± 34 | 24 ± 24 | 0.89 |
| ICU days | 28 ± 24 | 29 ± 27 | 0.35 |
| Hospital days | 55 ±41 | 44 ± 31 | 0.14 |
| Mortality | 12 (24%) | 4 (8%) | 0.02 |

**DISCUSSION**
The Control group demonstrated more times when lesser amount of fluids and more diuresis would be given. The Control group had more times when blood would be transfused. This is due to the 1.5 day delay before Hct would reflect low red blood cell volume, so several BV analysis were done without treatment (red cell transfusion). The BV group demonstrated less number of change in treatment since the team had the advantage of prior BV results and treatment to.

**CONCLUSION**
Use of BV in addition to PAC monitoring allowed more specific allocation of fluid and red cell infusion and more expeditious treatment before clinical manifestations in severely ill surgical patients and improved outcome.

1) Yu M,et al: Shock 2007;27:615
2) Feldschuh et al, Circulation 1977;56:605
3) Shoemaker et al. Arch Surg 1973;106:630

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