

**Would hypovolemia be an advantage or disadvantage in
the management of critically ill patients with septic
shock?**

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ABSTRACT

Background: Septic shock continues to be a difficult entity to treat. Multiple factors play a vital role in the ultimate outcome of a patient in septic shock. Volume resuscitation has been one of the most important factors in the resuscitation of a patient in septic shock. Over the decades volume has been assessed as an inferred value from multiple invasive and non-invasive monitoring parameters. With the advent of the new BVA100 machine, accurate blood volume measurements are no longer an inferred value.

Aim: Compare outcome in patients in septic shock, between patients who remained hypovolemic and those who were normovolemic or hypervolemic toward the end of resuscitation as determined by the intensivist, using the BVA100 machine.

Materials and Methods: Serial blood volume measurements were done in 40 patients admitted to the Surgical and Medical ICU's using the BVA100 machine, after IRB approval and patient consent was obtained. The instrument was used in conjunction with a special patented syringe, which delivers a precise, quantitative injection of Albumin tagged I-131 isotope to the patient. Blood samples were taken at regular intervals and Total blood volume (TBV), Plasma Volume and red cell volumes were calculated. All patients were classified according to the APACHE II severity of disease classification. Height, weight, age, sex, Blood pressure, hematocrit, fluid and electrolyte balance, BUN, Creatinine, duration of stay in ICU and use of vassopressors were considered in our study. 20 patients with septic shock were selected randomly as a control group. In the study group blood volumes were measured an average of 3(2-5) times in each patient using the BVA100. Volume status manipulation was left to the discretion of the Intensivist.

Results: Patient age (27-93 year.) with a median of 75.5 years, 28 males and 12 females, APACHE II scores ranged from 8-30 with a mean of 17.875. Of the forty patients 25 remained hypovolemic, seven were hypervolemic and eight patients were normovolemic towards the end of resuscitation. Four patients died in the ICU and all four patients were from the hypovolemic group. Average ICU stay for the hypovolemic group was 12.3 days, Normovolemic group was 12.8 days and hypervolemic group was 13.2 days.

Conclusion: Our study showed that there was a significant difference in the mortality between patients' who fell in the hypovolemic group towards the end of resuscitation and the normovolemic group and hypervolemic group. However the study did not show any significant difference in the length of ICU stay for the three groups of patients. Early resuscitation with serial blood volume monitoring can help the intensivist optimize treatment for individual patients based on their respective co-morbid conditions

INTRODUCTION

The septic shock syndrome and its sequelae continue to be a significant health care challenge for the next millennium. There are 300,000 to 500,000 episodes of sepsis each year in the USA (1) and the incidence seems to be on the rise (2), despite our current knowledge and recent advances in the pathophysiology of this complex medical problem. The reasons for this rise are multifactorial and septic shock as a result of sepsis is the 13th most common cause of death in the USA. It is also one of the most common causes of death in the non-coronary ICU's (2). The estimated crude mortality rate is around 50%, but it ranges widely between 8-90% (3, 5). The cause of septic shock is not clear. Extensive research has been focused on finding a specific toxin as prime cause for septic shock. The role of blood volume in septic shock has not been clear and it has been very difficult to assess the volume status of individual septic shock patients. The degree to which hypovolemia is the primary factor can be very confusing. A major problem has been the difficulty of accurately and rapidly assessing the Blood Volume status of septic patients. Patients with septic shock are occasionally treated with large quantities of crystalloid in the first 24 hours (4, 6). Currently there are a number of tools in use that help the intensivist deal with this complex problem, including invasive and non-invasive forms of monitoring which are used indirectly to evaluate the Blood volume status. (7, 8). A rapid and an accurate method of blood volume measurement has recently become available that recently has been compared with invasive and non-invasive methods of monitoring. (9).

Our aim with this study was to compare the outcome of septic shock patients in relation to the volume status toward the end point of the resuscitation. Outcomes were compared using two parameters: mortality rate and length of stay in the ICU.

PATIENTS AND METHODS

The study was performed at Lutheran Medical Center in Brooklyn, New York. After approval of the experimental protocol by the Institutional Review Board, written informed consent was obtained from the study patients.

Inclusion criteria were: Septic shock patients with classical features such as fever, hypotension, positive blood cultures and patients older than 18 year admitted to the Medical or Surgical Intensive Care Units, PAC insertion and an APACHE II (Acute Physiology and Chronic Health Evaluation) score of 8-30, mean of 17.3. Exclusion criteria were: pediatric patients, hemodynamically normal patients, pregnant, and critically ill patients that were managed in an ICU setting without the use of a PAC catheter.

The weight (in pounds) and height (in inches) of each of the individuals from the study group was obtained for further calculation of the individual's normal predicted blood volume as a function of the patient's body weight deviation from ideal weight (16, 17).

Blood volume measurement:

In 1998, the Federal Drug Administration (FDA) from United States cleared for marketing the Daxor Blood Volume Analyzer (BVA-100), the first of its type, which utilizes a pre-calibrated set of standards and injectate in conjunction with a counting instrument that significantly simplifies the performance of a blood volume measurement using dilution and distribution principal. **Picture 1**

Blood volume measurements were done on all patients. The process starts with the placement of a saline lock into one of the peripheral veins, and subsequent collection of an initial blood sample (5 cc). Separate venous access must be obtained to inject a precise amount of radioactive material using a pre calibrated patented syringe (Max100) that delivers 1 cc of I^{125} tagged albumin (15-25 microcuries). The time of the injection of the radioactive albumin was recorded. Venous samples were collected at approximately 12, 18, 24, 30, and 36 minutes after the injection. The actual collection times were entered into the BVA-100. **Picture 2**

Hematocrit measurements were performed in duplicate using a HematoStat microhematocrit centrifuge from STI Technology, and these values were also entered into the BVA-100. After obtaining the microhematocrit, blood samples were centrifuged at 7000 rpm x 2 minutes using a Baxter Star 60 Centrifuge. After separation, 1ml from the plasma of each sample was pipetted into the sample tube then placed into the BVA-100. All samples were pipetted in duplicate and counted in duplicate. The use of multiple-point sampling permits the calculation of the mixing time and the rate of tracer transudation. The BVA-100 calculates the normal blood volume from the ideal height weight system (13). This system eliminates the systemic errors which occurs when utilizing norms based on fixed BV/ body wt ratio or BV/ surface ratios. The BVA-100 computes the mean body hematocrit (20), plasma packing factors (21), and anticoagulant dilution factor as part of the final results. By extrapolating to zero time, a true instantaneous or zero time blood volume can be calculated as well as plasma and red cell volume components. Individual's standard deviations were computed for each blood volume measurement and averaged less than 3%. The degree of hypervolemia or

hypovolemia was ranked according to the percentage of deviation from the ideal blood volume calculated for that specific patient.

The following scale was used: $\pm 8\%$ is considered *normal*, $\pm 9-16\%$ *mild*, $\pm 17-24\%$ *moderate*, $\pm 25-32\%$ *severe*, and $< > 32\%$ *extreme* hypo or hypervolemia. **Table 1**

Preliminary results were available within twenty minutes and the final results within 35-45 minutes. The blood volume measurements are accurate to approximately $\pm 2.5\%$. The system permits easy recognition of individual sampling error or technical error in preparing the samples. The system is unique for blood volume measurement because it produces more rapid results with a higher degree of accuracy for both plasma and red cell volume than previously available.

RESULTS

Forty ICU patients, 28 males and 12 females aged 27-93 years (median age = 77.5 years)(**Graph 1**) were included in the study done between June 1998 and April 2000.

Aggressive therapy with fluids was initiated in these patients as soon as the bedside diagnosis was established (2). Toward the end point of resuscitation the patient found with variable volume status inspite of aggressive therapy and fluid and blood product manipulation, guided by the intensivist in the ICU. **Table 2**

The mortality rate in the hypovolemic group was 16% (4 patients) as compared to mortality in the hyper and normovolemic group, which was 0%. **Table 3**

The average hospital stay for patients who were hypovolemic was 12.6 days (*SD*=6.6) vs. 12.8 days for patients were hypervolemic and (13.2) who were normovolemic.

DISCUSSION

Fluid administration to maintain blood pressure and to prevent hypotension and hypoperfusion has been a significant part of therapy in septic shock patients (6) but not necessarily a primary focus. In this series correction of documented hypovolemia was a primary goal. Adequate volume replacement is extremely difficult to evaluate in patients with septic shock (10). The availability of a rapid and accurate method for assessing blood volume made it possible to more accurately evaluate volume status at the beginning of fluid therapy and the result of aggressive fluid therapy on volume status. The hemodynamic status of these critically ill patients was monitored by the ICU teams using common variables such as vital signs and standard laboratory values, as well as invasive and noninvasive forms of monitoring such as pulmonary artery catheter. However, these common parameters are indirect reflections of the fluid volume status because of the multiple secondary compensatory mechanisms that maintain homeostasis (3, 10). Blood volume measurement with the BVA-100 method is a rapid and reliable indicator of the volume status (9, 11).

In our study group of 40 patients there was a 16% mortality rate among the patients who remained hypovolemic despite aggressive therapy. We believe this to be one of the lowest reported mortality death rates in a series on septic shock. The most significant finding was a mortality rate of 0% in the other subgroups who were treated to the point of normo or mild hypervolemia. Therapy aimed at restoring normal blood volume was strongly correlated with survival. This study suggests that collapse of the blood volume is a major factor associated with mortality in septic shock. Unidentified toxins may play a

significant role in altering capillary permeability leading to a collapse of vascular volume. Despite aggressive fluid therapy some patients remained hypovolemic. These patients may have altered capillary permeability which may cause extra vascular fluid shift and edema formation. The BVA-100 computes the transudation time of albuminated I^{131} within the vascular system. This may be a useful measure of altered permeability, however further evaluation of this measurement is needed.

With regard to the duration of stay in the ICU, we found that there was no statistically significant difference between the patients who remained hypovolemic and those who remained normovolemic or hypervolemic toward the end point of resuscitation. No follow up was done post ICU stay. The length of stay in the ICU for our study group (hypovolemic patients 12.6 days, 12.8 days for hypervolemic patients, and 13.2 days for normovolemic patients) is not significantly different from the values published in the literature (average of 16.5 days) (12).

The significance of mortality found in the hypovolemic group in this study need to be verified by further studies with a larger study group and stratifying the various coexistent morbid conditions in the study population. No follow up was done post ICU stay in this study and so mortality outside the ICU setting has not been taken into account.

CONCLUSIONS

Survival in septic shock strongly correlates with successful restoration of blood volume. Many patients with septic shock remain hypovolemic despite aggressive volume replacement. The amount of fluid infused does not necessarily correlate with the subsequent volume status of the patient. Repeat BV measurement was important in evaluating the effectiveness of the replacement therapy. Correction of blood volume deficit to normovolemic or mild hypervolemic levels in septic shock resulted in zero deaths in this study. The group that had partially corrected Blood Volume also had a significantly lower death rate than usually reported for septic shock. Fluid or blood administration with the aim of achieving normovolemia is strongly correlated with survival of patients in septic shock.

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LEGEND

Volume status	Normal	Mild	Moderate	Severe	Extreme
% Deviation	±0 to 8	±8 to 16	±16 to 24	±24 to 32	</> 32

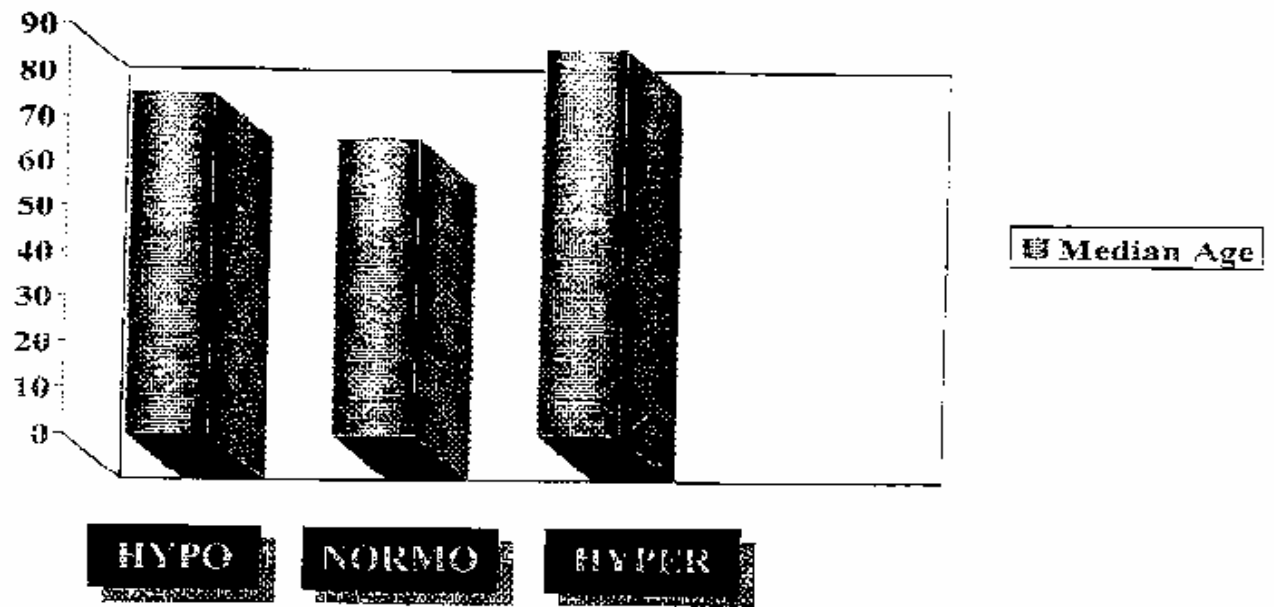
Table 1: Criteria used for definition of volume status

Volume Status	No of Patients	Percentage
Hypovolemia	25	62.50%
Normovolemia	8	20%
Hypervolemia	7	17.50%

Table 2:- Volume status at the end of resuscitation

Volume Status	No of Patients	Survival %
Hypovolemia	21	84%
Normovolemia	8	100%
Hypervolemia	7	100%

Table 3:-Percentage of survival in different Blood volume groups.



Graph 1: The distribution of age in different volume groups