ELEVATED TRANSCAPILLARY ALBUMIN ESCAPE: A MARKER OF INCREASED MORTALITY

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Introduction

"Third-spacing" of intravascular fluids is a well-observed clinical phenomenon in critically ill patients. In normal physiologic states small amount of fluid shifts occur into and out from the intravascular compartment to maintain euvolemia. However, in patients with systemic inflammatory response syndrome (SIRS) or sepsis, the loss of endothelial integrity results in a loss of fluid and proteins from the intravascular space. Without intervention, hypovolemia ensues. Inversely, clinical recovery from SIRS or sepsis with the repair of the endothelial injury is heralded by the cessation of intravascular fluid losses and the return or "mobilization" of this fluid into the vascular compartment. While the multifactorial nature of endothelial injury and increased capillary permeability in critical illness continues to be discovered and described, the simple observation of third-spacing and its reversal have served generations of physicians as a qualitative marker that the systemic inflammatory response has subsided in critically-ill patients. Inversely, prolonged third-spacing of fluids, a marker of a continuing inflammatory process, is a harbinger of prolonged or poor recovery.

Normal endothelial function provides an excellent barrier against the loss of plasma proteins such as albumin. In its normal state, the endothelial barrier of most organs allows only a small amount of transcapillary escape of proteins into the interstitial space [1]. However in inflammatory states increased vascular permeability results in increased losses of intravascular fluid as well as plasma proteins, one of which is plasma albumin. In SIRS and sepsis, the increased vascular permeability is believed to occur in all organ beds, including that of the renal capillaries.

Introduction continued

Likewise, in ARDS, the increased permeability is believed to occur within the pulmonary capillaries [2]. Transcapillary escape of plasma proteins in the renal vasculature can be measured as proteinuria or specifically with serum albumin leak, albuminuria. Many studies have demonstrated the utility of microalbuminuria (μAU) as marker of injury severity, mortality risk, and the degree of surgical physiologic stress [3,4,5]. However, μAU may occur in chronic renal disease not associated with SIRS or sepsis and in such cases, does not reflect an acute increase in systemic capillary leak [6]. Alternatively, several methods capable of measuring vascular permeability and leakage of plasma proteins exist, one of which is the albumin leak rate obtained through the Blood Volume Analyzer (BVA-100, Daxor, NY)

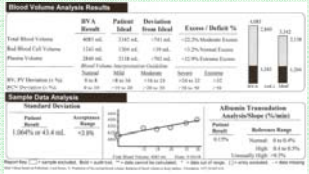
In this study, we investigate the relationship between the systemic transvascular escape rate of albumin to mortality in critically ill patients.

Methods

The study was approved by the Institutional Research and Review Committee of The Queen's Medical Center and informed consent was obtained from all patients or next of kin. Patients requiring a radial artery catheter or pulmonary artery catheter for acute resuscitation of severe sepsis, septic shock, cardiogenic shock, and/or ARDS were enrolled. One-hundred study patients were enrolled and scheduled for blood volume analysis (BVA) on day 1 and day 5-7 after resuscitation if still present in the ICU. Plasma volume was measured with the BVA-100.

Methods

This method uses 0.6μ*Cu* of I-131 labeled albumin injected intravenously with 5 sequential blood draws at timed intervals to measure tracer levels. Plasma volume is calculated via the dye-dilution method. A natural product of this method is the escape rate of I-131 albumin from the intravascular space. An elevated albumin leak rate (ALR) was defined as a value greater than 0.25% (0.25 of 1% per minute exiting the circulation). ALR and additional data were then retrospectively reviewed for this current investigation. Patients without BVA data were excluded from this retrospective investigation.



Statistical analysis

ALR between survivors and non-survivors was performed using the Chi-square test. To account for potential influence of variables known to influence mortality, a stepwise backward logistic regression analysis between mortality and the independent variables of gender, APACHE II score (which includes age), lactate level on admission, albumin level, and albumin leak rate at day 1 and albumin leak rate at day 5-7 was performed. In this analysis, an abnormally elevated ALR (>0.25%) was represented as a binary variable of "1." A normal ALR (<0.25%) was assigned a value of "0." In all methods, $p < 0.05$ was considered statistically significant.

Results

Ninety-four of the 100 patients had ALR at day 5-7. Of the 94 patients, there were 78 survivors and 16 non-survivors for an overall mortality of 17%. Age, gender, APACHE II, lactate, and albumin were equivalent between groups. The enrollment diagnoses were as follows: 69 patients with septic shock/severe sepsis, 15 patients with cardiogenic shock, and 35 patients with ARDS. Some patients had > 1 diagnosis. At day 5-7, 51 patients had normal ALR while 43 patients had elevated ALR. Mortality was only 7.8% in patients with normal ALR. However, patients with elevated ALR had a mortality of 27.9%. On day 5-7, the mean albumin leak rate was higher in non-survivors (0.35 ± 0.18) from survivors (0.23 ± 0.13 survivors), p<0.05.

	Survivors	Non-survivors	Total
Normal ALR	47 (47/51 = 92.2%)	4 (4/51 = 7.8%)	51
Elevated ALR	31 (31/43 = 72.1%)	12 (12/43 = 27.9%)	43
	78 (83%)	16 (17%)	94 (100%)

Gender, ALR at day 1, and lactate were not significant and eliminated from the stepwise logistic regression model. The best model fit of 85.5% occurred with APACHE II, Albumin, and ALR at day 5-7. In all of the stepwise iterations, ALR consistently yielded $p < 0.05$. The risk ratio obtained for elevated ALR was 5.54.

	β	*p*	Exp(β) (95% CI)
APACHE II	.125	.312	1.13 (.89 - 1.44)
Albumin	1.129	.133	3.09 (.71 - 13.51)
Elevated ALR	1.711	**.034**	5.54 (1.14 - 26.83)
Constant	-8.371	.025	.000

Conclusions

A persistently elevated ALR is a risk factor for increased mortality in patients with severe sepsis, septic shock, cardiogenic shock, and/or ARDS. Logistic regression revealed a 5-fold increased risk of mortality in patients with elevated ALR at days 5-7. In this study, initial lactate, APACHE II score, gender, and albumin level did not reach statistical significance. Timely measurements of blood volume and the ALR using the Blood Volume Analyzer can provide useful prognostic information in the management of the critically-ill patient. Additionally, if the leak rate of I-131 albumin reflects the integrity of the endothelium barrier to plasma proteins, it may also serve as a tool that measures the response of the endothelium to novel therapies in critically ill patients.

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