Changes in serum albumin concentration and volume expanding effects following a bolus of albumin 20% in septic patients

M. P. Margarson* and N. C. Soni

Imperial College School of Science, Technology and Medicine, Magill Department of Anaesthesia, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, UK

*Corresponding author. E-mail: m.margarson@ic.ac.uk

Background. Patients with systemic sepsis develop a capillary leak syndrome, and serum albumin concentration decreases. Hyperoncotic albumin infusion can be used for volume expansion in these patients, but the degree and duration of effect are not well described. We assessed volume expansion by albumin 20% infusion and compared the retention of infused albumin in septic patients and healthy controls.

Methods. We gave albumin 20%, 200 ml as a rapid infusion to 70 patients with septic shock and 26 controls. Blood samples were taken before and 1, 5, 15, 30, 60, 120 and 240 min after the infusion for measurement of serum albumin concentration and haematocrit. Haemodilution and the percentage of administered albumin remaining intravascularly at each time were calculated.

Results. The mean proportion of the increase in albumin remaining at 4 h was 68.5 (SD 10)% in septic patients and 79 (5)% in controls (P<0.001). The albumin 20%, 200 ml caused a secondary fluid resorption and volume expansion maximal at 30 min, equivalent to a 430 ml infusion in septic patients and 500 ml in controls.

Conclusions. After giving albumin, serum albumin concentrations decrease significantly faster in septic patients than in healthy controls.

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Increased permeability of small vessels to proteins and other macromolecules is a well recognized feature of critical illness. Increased permeability leads to an increased escape of serum proteins from the vessels, especially albumin, and a decrease in plasma colloid osmotic pressure (COP). This in turn allows fluid to shift from the intravascular into the interstitial compartment and the subsequent hypovolaemia contributes to the hypotension seen in septic shock.

It is not clear how sepsis alters microvascular permeability. There may be several reasons, and the relative importance of each factor will vary from case to case. Bacterial toxins alone can reduce reflection coefficients directly.1 The host response and effects of activated neutrophils and cytokines on the integrity of endothelial junctions and a reduction of the negative charge at these junctions could have a major role.2 Whatever the cause, capillary leak is generally accepted and certainly discussed in the critically ill but there are few objective data to quantify this effect. Methods such as isotope measurement of albumin flux are informative but not easily applied at the bedside.

In a larger project to develop a bedside method of assessing ‘capillary leak’, we studied the distribution of albumin after a rapid infusion, in healthy volunteers and in patients with septic shock. As serum albumin concentrations can be measured easily, changes in the serum albumin concentration following a dose can be used to derive volumes of distribution over periods of time and thereby characterize and measure ‘leakiness’. We describe the first part of this project and report the changes in serum albumin concentration following albumin 40 g given as a 200 ml rapid infusion of a hyperoncotic 20% solution.
Patients and methods

The study was approved by the local ethics committee. All patients were sedated and ventilated in the intensive care unit, and had arterial and central venous cannulae in place as part of their routine management. Septic patients who were sick enough to fulfill entry criteria were invariably sedated and ventilated, and thus unable to give consent. In each case an explanation of the procedures and risks was given, and approval and consent by proxy (assent) sought from relatives before the study started.

The studies ran over a period of 10 months and took place on the intensive care unit of the Chelsea and Westminster Hospital, London. The septic patients were investigated in the subacute phase (i.e. 1–3 days after admission) or when a second episode of sepsis occurred, primarily because of delays obtaining assent.

Patient groups

We studied 70 patients receiving mechanical ventilation and inotrope infusions and fulfilling the ACCP/SCCM criteria for septic shock.3 We excluded patients aged 18 yr or younger, those who were actively bleeding or had undergone surgery in the previous 24 h and patients who were cardiovascularly unstable (needing changes in inotrope infusion rates by more than 10% over the 6 h before the study).

The control group consisted of 18 medical volunteers and eight orthopaedic patients about to undergo joint replacement procedures for osteoarthritis. All control subjects lay supine in bed or on a couch for at least 10 min before each sample.

Study plan

In the patients with sepsis, before giving the albumin, blood samples were taken from an arterial cannula to measure baseline albumin concentration and haematocrit.

Albumin 20%, 200 ml was given over 2 min through the 16G lumen of a central venous cannula, using a three-way tap and 50 ml syringe. Arterial samples for albumin concentration and haematocrit measurement were collected at 1, 5, 15, 30 and 60 min and 2 and 4 h. In the first 44 patients a further sample was taken at 24 h.

In the control group a similar plan was followed but the albumin 20% was given through a 14G peripheral venous cannula, blood samples were collected from a venous cannula in the contralateral arm, and the 24 h blood sample was omitted.

The serum albumin concentrations were measured in the hospital clinical chemistry department, using a bromocresol purple (BCP) dye-binding technique on a Hitachi 911 multichannel analyser (Boehringer-Mannheim, Germany). The albumin assays were quality controlled, to confirm linearity across the range of measurements performed and to confirm the albumin content of the batch of albumin 20%. All Albumin used (supplied by Bio Products Laboratories, BPL, Elstree, Herts, UK) came from the same batch to eliminate variation in the quantity of albumin in each 200 ml bolus.

Haematocrit was measured on a standard clinical laboratory coulter counter (STAKS), and specific quality control studies were not performed. The limits on the STAKS counter are described in the company literature as accurate to ±2%.

Arterial pressure of septic patients was monitored with arterial and central venous catheters, displayed together with continuous ECG and pulse oximetry, and also recorded for off-line analysis. Because of the possible risk of volume overload and acute ventricular dysfunction, central venous pressure (CVP) was observed continuously when giving the albumin. If the pressure increased by 8 mm Hg or more during the infusion of albumin, the infusion and the study would be stopped, but in no patient was this necessary.

Data analysis

Haematocrit values were plotted at each time point over the 4 h study period. From the initial haematocrit and the volume of the bolus administered (200 ml), one can calculate the expected haematocrit that would result from dilution alone (without secondary fluid shifts), if the initial plasma volume is known. It is possible to make a reasonable estimate of plasma volume from the absolute change in plasma albumin concentration at 1 min, knowing that 40 g bolus has been given. For both the patients and controls, these values and the expected dilutions from the 200 ml bolus alone are included on Figures 2 and 4. The equation used to calculate the expected dilution is:

$$Hct(\text{expected}) = 1 - \frac{Pvol_0 + 0.2}{Pvol_0(1 - Hct_0) + 0.2}$$ (1)

where $Pvol_0$ is the plasma volume before infusion and $Hct_0$ is the baseline haematocrit. The derivation of this equation is given in the Appendix.

Actual albumin concentrations, and values corrected for the subsequent change in haematocrit, were plotted against time for both septic and control groups. To compensate for haemodilution, serum albumin values were corrected using the following formula:

$$Alb_{t(\text{corr})} = Alb_t \cdot \frac{1 - 100/Hct_t}{1 - 100/Hct_0}$$ (2)

where $Alb_{t(\text{corr})}$ is the albumin concentration at time $t$ corrected for haemodilution, $Alb_t$ is the albumin concentration at time $t$ and $Hct_0$ is the haematocrit at time $t$.

To compare the profiles of serum albumin concentration, and hence to interpret the differences in intravascular retention characteristics of albumin between septic patients and controls, the percentage of the administered albumin
remaining was calculated. Because of the slightly different profiles of haematocrit change between controls and septic patients, the corrected albumin concentrations were used to calculate the maximum increase in albumin concentration and the albumin concentration calculated at each time point. Thus, it was possible to calculate and plot the percentage of albumin rise persisting at each sampling point for each group. Comparison between controls and septic patients was made at each time point using repeated-measures analysis of variance (ANOVA) with Student–Newman–Keuls correction. Unless otherwise stated values are mean (SD).

Results

Patient characteristics

Complete profiles were obtained from 66 patients with septic shock (four patients were excluded because of incomplete data collection). Their mean age was 54 yr (range 22–89), weight 75 (18) kg, with a median APACHE II score on the day of study of 17 (range 6–41).

The control group consisted of 26 volunteers and preoperative orthopaedic patients, age 44 yr (25–76), weight 74 (12) kg.

Serum albumin and haematocrit changes

Giving albumin to these patients caused a near doubling of the serum albumin concentration: concentrations increased from 12.2 (0.7) g litre\(^{-1}\) to 23.0 (0.8) g litre\(^{-1}\) at 1 min after infusion. The serum albumin concentration then decreased to 20.7 (0.7) g litre\(^{-1}\) at 30 min. Figure 1 shows the changes in serum albumin over a 24 h period in the first 44 patients studied. The detailed profiles of haematocrit and absolute albumin values over a 4 h period are shown in Figures 2 and 3 for the control group and Figures 4 and 5 for the septic patients.

Maximal haematocrit changes occurred between 15 and 30 min after giving the albumin. Comparison of the expected haematocrit change with the maximal haematocrit change demonstrated a maximal volume expanding effect of the albumin bolus to be 430 ml in septic patients and 500 ml in controls (not significantly different).

The decrease in albumin concentration is partly caused by haemodilution as the intravascular compartment expands secondary to the hyperoncotic effect of the albumin 20%, and partly by transcapillary albumin escape. The degree of haemodilution was reflected by changes to the haematocrit following the albumin infusion. The profile of albumin concentration, adjusted for the haemodilution according to equation 2, is shown in Figures 3 and 5. This profile better demonstrates the transcapillary albumin escape rate without the confounding dilutional component.

The increase in albumin concentration immediately after giving albumin was not significantly different between the
septic and control groups, implying that plasma volume in the two groups was similar. The percentage of the initial increase in albumin remaining at each sampling time point showed that beyond 15 min there was greater loss of albumin from the intravascular compartment of septic patients. After 4 h, 21% of the increase in albumin in the control group has been lost, compared with 32% in the septic group (P<0.001). These values are shown in Figure 6.

Cardiovascular changes
In each patient, systemic arterial pressure and CVP increased promptly following the albumin bolus, and returned toward the pre-infusion value over the next 30 min. After 30 min the CVP was an average of 2 mm Hg greater than baseline level (range 0–5 mm Hg).

In no patient did the percutaneous oxygen saturation decrease following the albumin, and there was no clinical evidence of pulmonary oedema in any patient.

Discussion
Albumin retention
We found that the retention of intravascular albumin in both normal volunteers and preoperative orthopaedic patients is greater than in septic patients. I.V. albumin immediately distributes throughout the plasma volume, and this immediate volume of distribution can be calculated simply from the dose given divided by the change in serum concentration. It can be recalculated at any subsequent time point, and the rate of expansion of this volume of distribution can be used as an index of leak (discussed further below). The effective volume of distribution increases steadily over 24 h, reflecting escape from the intravascular compartment into the interstitium. Clearly, over this longer time in the septic patient group, the potential effects of increased catabolism and reduced metabolism, plus urinary and gastrointestinal losses, may accentuate the acute fall in plasma concentration seen, the result of redistribution.

The albumin redistributes much more quickly in patients with sepsis than in the control subjects and this is consistent with the general concept of ‘leaky capillaries’. This has been demonstrated in much smaller isotope studies but isotope techniques are not readily applicable at the bedside.

In this study, the difference in the percentage of albumin retained only became statistically significant after 30 min,
with the initial disappearance curves in septic patients and controls appearing identical over the first 15 min. This possibly reflects a 'signal to noise' ratio (i.e. that a small genuine change at the early stage is not identifiable because of the background variation) and errors intrinsic to the measurement techniques. However, there appears to be a bi-exponential pattern of redistribution even in the corrected albumin values and this would be in keeping with the work of Bent-Hansen. He suggested that rather than a single endothelial barrier to the escape of albumin from the intravascular compartment, there might be a second barrier at a subendothelial level that also limits the rate of escape into the interstitium. This would equate to a three-compartment model of albumin distribution, with the subendothelial compartment having an effective volume of only about 500 ml. Whether this second barrier really exists is contentious, and it may be that this intermediate compartment represents slow mixing through liver sinusoids or into some other physical space. However, a bi-exponential decay can be found and has been demonstrated subsequently in more recent studies.

Albumin synthesis may be reduced during the acute septic response and catabolism may increase but these effects probably had no significant effect on the measurements made over this 4 h study. The normal metabolic half-life of albumin is 16–20 days and the normal production and catabolism is 9–12 g day\(^{-1}\) (i.e. \(<2\) g during the 4 h study). Albumin is a poor substrate and is well maintained in the malnourished (as opposed to chronically sick) state: even if there were a several-fold increase in catabolism it would be very unlikely to have any measurable effect on the albumin concentrations over this time period. However, it is important to emphasize that this study does not provide insight into the mechanism of redistribution but only quantifies the observed effect.

**Haematocrit changes**

The haematocrit was used to correct for changes in albumin concentration caused by dilution. The influence of the albumin dose on haematocrit is important, as correction for this haemodilution needs to be taken into account if a realistic estimation of the changes of albumin concentration is to be made in pathophysiologically disparate groups.

Of interest is that calculation of the expected decrease in haematocrit caused by dilution with the 200 ml fluid bolus alone accounted for almost half the total haemodilution in both groups. It is generally considered that by administering albumin 20%, a considerable volume of fluid is drawn from the interstitium into the bloodstream by osmotic forces, providing considerable volume expansion. In effect albumin 20%, 100 ml containing 20 g of albumin is thought by many to have much the same volume expanding effects as the 22.5 g of albumin found in 500 ml of the 4.5% solution. This was not supported by these studies, which suggest that the 20% solution draws in a volume of fluid little more than that equivalent to the administered volume, and certainly does not provide the two- or threefold volume expansion that some predict. The limited degree of volume expansion must in part reflect the increase in hydrostatic pressure gradient that occurs as interstitial fluid is drawn into the plasma, tending to counter the hyperoncotic effect. The observed trend toward less volume expansion in the septic patients than in controls did not reach statistical significance.

The other unexpected finding was the length of time over which haemodilution occurred, taking more than 30 min to reach equilibrium, and the relatively small degree of haemoconcentration occurring over the subsequent 3 h of the study. These findings both appeared to be consistent and genuine, but are difficult to explain.

One technical aspect of the haematocrit change that was of concern was a potential osmotic shift of fluid from the intracellular compartment of the red cells causing a reduction in red cell volume. Alterations in mean corpuscular volume that may alter the haematocrit have been addressed in a separate study and found not to be relevant, as the mean shrinkage over the total 4 h period was less than 1% and was not statistically significant.

For ease of sampling, specimens were collected from arterial cannulae in the septic patients but this was clearly not practical in healthy volunteers. The albumin concentration in arterial and venous blood is identical, but the haematocrit is marginally greater in arterial blood. However, as we were specifically interested in changes to haematocrit rather than absolute values, this difference was felt to be unimportant.

**Groups**

The volunteers were healthy and relatively young while the orthopaedic patients were healthy but older. Whilst these two control groups are not strictly comparable, they did give a population spectrum of individuals without sepsis.

 Controls lay supine for 10–15 min before each sampling. In earlier studies we found a small but statistically significant change in plasma COP with changes in posture from lying to standing for 45 min then returning to a lying position for 45 min. More than three-quarters of the total COP change of 3–4 mm Hg had occurred by 10 min in every case.

**Clinical significance**

We set out to assess changes in serum albumin concentration in septic patients compared with control groups, and found a difference that could be easily measured at the bedside over a 4 h period. This difference reflects increased vascular leak, and the technique described could form the basis of a simple test of this leak.

One suggestion is to use the initial value for the volume of distribution of albumin at 5 min as the denominator for the values for the volume of distribution at either 2 h or 4 h. This
ratio could be called the albumin distribution index. We intend to use the findings of this study to develop this concept. An easy bedside method to evaluate ‘leakiness’ could be used to assess treatments.

In conclusion, we found a more rapid reduction in serum albumin after giving albumin 20%, 200 ml to intensive care patients with septic shock than in volunteers and preoperative orthopaedic patients. In the septic patients, we found a trend toward lesser volume expansion with hypertonic albumin than in the control groups; this potentially clinically significant finding requires further investigation.

Appendix: calculation of expected change in haematocrit

Figure A1 shows equations that calculate the haematocrit expected at 1 min following a 200 ml bolus of fluid. They do not take into account any additional volume expansion resulting from the use of the hyperoncotic albumin solution. They require knowledge of the initial plasma volume.

\[
\begin{align*}
\text{Hct}_0 &= 0.40 \\
pV0 &= 3 \text{ litre} \\
RVC &= 2 \text{ litre} \\
\text{Hct}_1 &= 0.385 \\
pV0_1 &= 3.2 \text{ litre} \\
RVC &= 2 \text{ litre}
\end{align*}
\]

Initial volume + 0.2 litre bolus = one minute volumes

1. Total blood volume \( t = \text{total blood volume}_0 + 0.2 \)  
2. Plasma volume \( _t = \text{plasma volume}_0 + 0.2 \)  
3. Hct = red cell volume/total blood volume  
4. \( (1 - \text{Hct}) = \text{plasma volume}/\text{total blood volume} \)  
5. Re-arranging Equation (4) and inserting into Equation (1):

\[
\begin{align*}
\text{Total blood volume}_t &= \frac{\text{pV0}}{(1-\text{Hct})} = \frac{\text{pV0} (1-\text{Hct})}{(1-\text{Hct})} + 0.2 \\
\text{Re-arranging Equation (5)}:
\end{align*}
\]

\[
1 - \text{Hct}_t = \frac{(\text{pV0}_1 + 0.2)}{(\text{pV0} (1-\text{Hct}) + 0.2)}
\]

Therefore:

\[
\text{Hct}_t = 1 - \left[ \frac{(\text{pV0}_1 + 0.2)}{(\text{pV0} (1-\text{Hct}) + 0.2)} \right]
\]

\[
= 1 - \left[ \frac{(\text{pV0}) + 0.2}{(\text{pV0} (1-\text{Hct}) + 0.2)} \right]
\]

\( \text{pV0} \) is the immediate volume of distribution and is calculated by dividing the 40g albumin bolus by the change in plasma albumin concentration between baseline and 1 minute.

Fig A1 Equations calculating the haematocrit expected at 1 min following a 200 ml bolus of fluid.

References