Effects of albumin supplementation on microvascular permeability in septic patients

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Margarson, Michael P., and Neil C. Soni. Effects of albumin supplementation on microvascular permeability in septic patients. J Appl Physiol 92: 2139–2145, 2002; 10.1152/japplphysiol.00201.2001.—Albumin has a stabilizing effect on endothelium and helps maintain capillary permeability to macromolecules. Critically ill patients with sepsis may have profound hypoalbuminemia, but the effect of this hypoalbuminemia on microvascular permeability is unknown. To determine the degree and potential importance of this effect, we measured the transcapillary escape rate (TER) of 125I-labeled albumin in 12 adult patients fulfilling American College of Chest Physicians/Society of Critical Care Medicine criteria for septic shock. We measured TER over a 90-min baseline period and then repeated these measurements immediately after the rapid infusion of 200 ml of 20% albumin. At baseline, patients had a mean serum albumin concentration of 10.3 ± 3.8 g/l, which, at 30 min after the albumin infusion, was 18.5 ± 3.7 g/l. The baseline TER was 6.7 ± 1.5%/h, with a postinfusion TER of 6.4 ± 2.1%/h (P = 0.550). Albumin supplementation sufficient to nearly double serum concentrations in profoundly hypoalbuminemic septic patients had no clinically significant effect in reducing microvascular permeability.

INCREASED MICROVASCULAR PERMEABILITY to proteins and other macromolecules is a well-recognized feature of critical illness. Increased permeability leads to an increased transcapillary escape of serum proteins, especially albumin, and thus to a fall in plasma colloid osmotic pressure. This in turn allows fluid to shift from the intravascular into the interstitial compartment, and the subsequent hypovolemia is a major component of the hypotension seen in septic shock.

There is evidence to suggest that hypoalbuminemia may accentuate increased microvascular permeability. Since the initial observation by Drinker in 1927 (5) that protein levels in serum affect the permeability of capillaries, there have been dozens of studies confirming this effect. These have demonstrated that, when compared with a perfusate containing no albumin, the presence of albumin in perfusing fluids decreases the rate of solute and fluid flux across the endothelial monolayer (6, 12, 13) or microvasculature (17) being studied. It is thus possible that the very low concentrations of serum albumin that develop in septic patients may not only be a reflection of the increased vascular permeability but also contribute further toward escape of proteins from the intravascular to the interstitial space.

If it were shown that acutely raising the plasma albumin level significantly reduced microvascular permeability to albumin in septic patients, and it was believed that reducing permeability was beneficial, then this would support the use of albumin solutions as a first-choice fluid replacement therapy in this group of patients. The corollary is that an inability to demonstrate an effect on vascular permeability in the clinical setting after markedly altering the plasma albumin level would suggest that albumin supplementation in septic patients is not of value in attempting to reduce capillary permeability. The following study was performed to address this issue.

METHODS

Inclusion Criteria

Twelve patients admitted to the intensive care unit, ventilated and receiving inotrope infusions and fulfilling the American College of Chest Physicians/Society of Critical Care Medicine criteria for septic shock (3), were studied. Patients aged 18 yr or younger and women of childbearing age were excluded. Patients who were actively bleeding or had undergone surgery in the previous 24 h were also excluded, as were patients who were cardiovasculary unstable as defined by a requirement to vary inotrope infusion rates by >10% over the 6 h before the study.

We were only able to investigate patients in the subacute phase, i.e., ~1–3 days after admission, or when a second episode of sepsis occurred, because of delays obtaining assent and the time required to prepare the radiolabeled doses.

Study Protocol

The thyroid uptake of iodine was blocked before the study by the administration of potassium iodide. This is a standard technique used to prevent concentration of radioactive iodine in the thyroid tissues, and it has no clinical impact on the patient. We gave 2.5 mmol of potassium iodide as a slow intravenous injection over 10 min with electrocardiograph (ECG) monitoring.

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Each subject was administered an injection of $^{125}$I-labeled 20% albumin, given over a period of 90 s via a central venous catheter, and the syringe was then flushed twice with 5 ml of saline to ensure the complete dose was given. The volume of this radiolabel injection was $\sim 1-2.5$ ml, determined by the activity (i.e., freshness) of the label. The half-life of $^{125}$I is 60 days, which meant that, over the 6-h period of each study and the subsequent period of scintillation counting, there was negligible reduction in activity. Because of longer term decreasing activity within each batch, we did find that, over a 3-mo period, we had to give a larger volume of labeled albumin to maintain the same level of administered activity, although the actual albumin dose given was never $> 0.5$ g. A dose of $0.1 \mu$Ci/kg body wt was used, in an attempt to obtain initial counts of $\sim 2,000$ counts-min$^{-1}$.1-ml plasma sample$^{-1}$. This ensured that, when measuring activity over a 4-h period in even the most “leaky” patients, there was still activity of $> 10,000$ decays/10-min counting period in the final specimens, such that errors due to variability in counts were kept below 1%. After the administration of $^{125}$I-albumin, arterial blood samples of 4 ml were collected at 1, 3, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 min into lithium heparin gel-separator tubes. These samples were spun down for 10 min at 2,000 rpm, and duplicate 1-ml plasma samples were collected for later estimation of gamma activity in an automated scintillation counter.

A bolus of 200 ml of 20% albumin was then infused via the same central venous line, again over a period of 90 s, and the blood sampling was repeated at the same time intervals over a further 1.5 h. Albumin measurements were performed on samples taken before and then at 1, 5, 15, 30, 60, 120, and 240 min after the albumin infusion. Hematocrit was calculated from full blood counts taken with each albumin sample to enable correction for the dilutional changes secondary to the fluid shifts caused by the hyperoncotic 20% albumin. The hematocrit and serum albumin samples were measured in the hospital hematology and clinical chemistry departments, by a STAKS Coulter counter for hematocrit and a bromocresol purple dye-binding technique on a Hitachi 911 multichannel analyzer for albumin (Boehringer, Mannheim, Germany).

As part of routine management, the blood pressures of all patients were monitored with indwelling arterial and central venous catheters, and continuous ECG and pulse oximetry were displayed in real time and recorded for off-line analysis. To ascertain the effects of the albumin bolus on cardiovascular dynamics in these septic patients, we analyzed changes in heart rate, mean arterial pressure, and central venous pressure (CVP) over the 30 min after the rapid infusion. Because of the theoretical risk of volume overload and acute ventricular dysfunction, the CVP was observed continuously during the administration of the albumin. It was decided that, if the pressure rose by 8 mmHg or more during the infusion of albumin, it would be stopped and the study aborted, but in no patient was this necessary.

Sample Analyses

The analyses of the radiolabeled specimens were performed in the Department of Nuclear Medicine where the $^{125}$I-albumin boluses had been prepared. Scintillation counting took place over a period of 10 min/sample or until 10,000 counts were reached; thus a complete series of 50 samples took up to 8 h to count and could only be run overnight.

Activity was reported as counts per second, and the mean of the two 1-ml plasma samples was recorded for each time point. Mean activity was plotted against time on a natural log-linear plot to allow measurement of slope and hence calculation of plasma half-life of labeled albumin, and from the same plot the proportion of reduction in activity over a 1-h period was taken to allow calculation of the transcapillary escape rate (TER). These calculations were performed for the baseline period before and then the study period after the infusion of the 20% albumin bolus.

The initial steep curve over the first 10–15 min after the injection of radiolabeled albumin, which is demonstrated in the present study and has been reported previously (1) but is of unclear etiology, was ignored when the slopes and TER were calculated. The possible causes of this early steep slope, in previous studies attributed to a mixing phenomenon, will be addressed in the DISCUSSION.

The studies ran over a period of 10 mo and took place in the intensive care unit of the Chelsea and Westminster Hospital (London, UK).

Statistical Analyses

Comparison of the changes in albumin concentration and cardiovascular parameters before and after the albumin bolus was by Student’s $t$-test. The measured TER and the slopes of the log-linear decay plot were similarly compared by using the $t$-test.

The intravascular half-life of the radiolabeled albumin before and after the bolus was compared by using Wilcoxon’s signed-rank test.

Ethical Considerations

The purpose and risks of the study, the nature and dose of the administered radiolabeled albumin, and the blood sampling that was required were explained to immediate relatives, and approval (assent) was sought. Approximately one-third of the patients’ families approached refused to take part. All patients in whom investigation was commenced were included in the final analyses.

There were several issues regarding the perceived risks to patients from this investigative procedure, and they are detailed below. The effective dose of administered radiation was $\sim 0.35$ mSv, a dose equivalent to 6 wk of background radiation in London and less than one-twentieth of the dose received from a computed tomography scan of the chest. The administered dose of 200 ml of 20% albumin is the standard pharmaceutical preparation, heat treated and screened for viral infection, and it was infused under continuous CVP monitoring as described earlier, such that volume overload could be instantly recognized, in which case the infusion would have been stopped. The investigation was not performed in patients with a previous history of cardiac failure or evidence of significant left ventricular dysfunction. We have previously given 200 ml of 20% albumin as a 2-min infusion to $> 100$ patients without a single episode of pulmonary edema or hypotension (unpublished observations). The risk of anaphylactic reaction was always present but very low, particularly because all patients were on continuous infusions of $\alpha$-adrenergic agonists and because the patients were being fully monitored at all times and could have been immediately treated if a reaction had occurred.

The study was approved by the Local Ethics Committee. All patients were sedated and ventilated in the intensive care unit, and they had arterial and central venous lines 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. However, in every case, an explanation of the procedures and
risks was given, and approval and consent by proxy (assent) were sought from relatives before the commencement of the study.

RESULTS

Patient Demographics

The median age of the 12 patients studied was 64 yr (range 38–96 yr), and the median weight was 78 kg (range 50–130 kg). The median Acute Physiology and Chronic Health Evaluation (APACHE II) score on the day of study was 18 (range 8–35). Details of the underlying disease process and precise data for each individual are shown in Table 1.

Serum Albumin and Hematocrit Changes

The administration of 200 ml of 20% albumin in these patients led to a near doubling of the serum albumin concentration, such that the mean level rose from 10.3 ± 3.8 to 20.1 ± 4.0 g/l at 1 min postinfusion. There was a subsequent fall in the serum albumin concentration, with a mean level of 18.5 ± 3.7 g/l at 30 min, i.e., halfway through the second period of TER measurement. This fall is in part due to hemodilution, as the intravascular compartment expands secondary to the hyperoncotic effect of the 20% albumin, and in part due to transcapillary albumin escape. The degree of hemodilution was reflected by changes to the hematocrit after the albumin infusion and is shown in Fig. 1.

To compensate for hemodilution and its effect in reducing activity in the serum samples, all activity and serum albumin values were corrected by using the equation

\[
\text{Alb}_{0} = \text{Alb}_{1} \left( \frac{1 - 100/\text{Hct}_{0}}{1 - 100/\text{Hct}_{1}} \right)
\]

where \(\text{Alb}_{0}\) and \(\text{Alb}_{1}\) are albumin concentrations before and after administration of albumin, respectively, and \(\text{Hct}_{0}\) and \(\text{Hct}_{1}\) are hematocrit before and after administration of albumin, respectively.

Changes to the total serum albumin concentrations, both uncorrected and corrected for hemodilution, are shown in Fig. 2.

Table 1. Individual patient demographics and results

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<th>Weight, kg</th>
<th>Disease Process</th>
<th>APACHE II Score</th>
<th>CVP0, mmHg</th>
<th>CVP15, mmHg</th>
<th>Alb0, g/l</th>
<th>Alb15, g/l</th>
<th>TER Pre, mmHg</th>
<th>TER Post, mmHg</th>
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AAA, abdominal aortic aneurysm; APACHE II, Acute Physiology and Chronic Health Evaluation; CVP0 and CVP15, central venous pressure measured at 0 and 15 min after infusion of albumin bolus, respectively; Alb0 and Alb15, albumin concentration measured at 0 and 15 min after infusion of albumin bolus, respectively; TER Pre and TER Post, transcapillary escape rate before and after albumin bolus infusion, respectively; GI, gastrointestinal.

Fig. 1. Change in hematocrit (Hct) after bolus administration of 200 ml of 20% albumin. Values are means ± SE for 12 septic patients. For each patient, the 125I-labeled albumin plasma volume (PVpre) and the Hct (Hctpre) were measured before administration of the albumin. The new Hct after a 200-ml dilution (Hct200) was calculated for each patient; the mean was 0.296. The following equation was used to calculate Hct200:

\[\text{Hct}_{200} = [1 - (\text{PV}_{\text{pre}} + 0.2)]/(1 - \text{PV}_{\text{pre}}/\text{Hct}_{\text{pre}} + 0.2)].\]
Cardiovascular Changes

In each patient, there was an immediate rise in the systemic arterial pressure and CVP after the 200-ml albumin bolus, with a return toward the preinfusion level over the next 30 min. These changes are shown in Fig. 3. At 30 min after the albumin bolus, CVP was an average of 2 mmHg above the baseline level (range of change 0–5 mmHg).

In no patient did the percutaneous oxygen saturation fall after the albumin bolus, and there was no clinical evidence of pulmonary edema in any patient. Colloid osmotic pressure rose in every patient, by a mean of 4.9 ± 0.9 mmHg. The trend in colloid osmotic pressure over 4 h in 11 of the 12 patients (incomplete data collection in 1 patient) is shown in Fig. 4.

TER

Log-linear plots of change in serum activity and calculated TER before and after the 40-g albumin bolus were calculated for each patient, and a typical plot is shown in Fig. 5. Individual transcapillary escape rates for each patient before and after the administration of the 40-g albumin bolus are shown in Table 1. Grouped results, that is, mean TER, median half-life, and mean slope of decay curve before and after the 40-g albumin bolus, together with statistical analyses are shown in Table 2.

In the final three patients studied, additional specimens for counts of activity were taken over the first 15 min to more accurately delineate the apparent biexponential nature of the early curve, and the plot of the final patient is shown as Fig. 6.

DISCUSSION

Clinical Significance

Our results (10, 14, 17) do not agree with previously described observations from in vitro studies. In this study, we were unable to demonstrate a significant decrease in microvascular permeability after the ad-
ministration of albumin. This may have been because of a fault in the study design and our inability to detect a genuine change in permeability or because that the change is very small. It may also be a genuine result and reflect that there is no significant change in permeability over the rise in serum albumin concentration we produced.

Previous Studies

Humans. Increased microvascular permeability to proteins and other macromolecules is a well-recognized effect of critical illness. In the healthy individual, there is an escape of albumin from the intravascular compartment to the interstitium of ~6 g/h or ~4–5% of the intravascular albumin mass. In critically ill patients, this transcapillary escape rate may be up to 20%/h (7). No previous clinical studies have specifically investigated the effect of altering albumin concentrations on permeability characteristics. The study of Payen et al. (15) of preoperative hemodilution using 4% albumin suggested that the extravasation rate of albumin and fluid to the interstitial tissues was increased. However, these patients were undergoing elective surgical procedures and were not hypoalbuminemic, and the plasma albumin level did not change after the administration of albumin.

Whole animal models. Studies in an unanesthetized sheep model with chronic lung and soft tissue lymph fistulas have shown a reversible two- to threefold increase in lymph flow after acute protein depletion by plasmapheresis (9). This effect was seen when plasma protein levels were reduced to only 50% of normal. It was further noted that, on reinfusion of stored plasma, lymph flow took 24 h to return to normal levels. The authors suggested this observation was most likely explained by changes to flow resistance at the level of the interstitial matrix secondary to a washout of interstitial protein.

If this were the predominant mechanism affecting transcapillary flux of albumin in sepsis, then the 90-min observation period of our study would be too short to identify a delayed reduction in permeability.

Nonalbumin colloidal solutions. There are several studies looking at the effects of starches and other colloidal solutions on microvascular permeability. An effect of starches on transcapillary fluid flux in an ischemia-reperfusion model was demonstrated by Zikria et al. (18), who hypothesized that this finding was related to a biophysical effect of hetastarch effectively sealing the separated endothelial junctions. A recently published study by Holbeck et al. (11), from London, showed that infusing dextran, gelatin, or starch into cats had no effect on permeability to (human) albumin in the denervated cat hindlimb, as measured by plethysmography.

Cox et al. (4), from Houston, Texas, compared the effects on microvascular permeability of Ringer lactate against 6% hetastarch in the circuit prime of dogs that then underwent extracorporeal life support, by using direct cannulation of lymphatic vessels with lymph analysis and direct weight of excised segments of the ileum. They found that tissue edema was greater with Ringer lactate compared with hetastarch. They described a reduction in the measured microvascular permeability coefficient (σ) that was less pronounced in the hetastarch group. This study is of great interest but not directly comparable to ours. One would clearly expect greater fluid shifts when comparing a crystalloid with a colloidal solution in an extracorporeal circuit prime; additionally, the starch was administered before the insult and may have attenuated the inflammatory response. In our study, there is no question of the albumin affecting the pathological process that lead to the increased microvascular permeability.

Limitations of the Study

There is a recirculation of radiolabeled albumin back from the tissues via the lymphatics, and the precise degree cannot be measured. It could be argued that this recirculation would maintain plasma activity and
mask a change in permeability. However, one can model the pharmacokinetics of albumin if one makes assumptions of the compartment sizes, albumin concentrations, and the fractional escape rate (i.e., the TER). In a septic edematous patient, typical values would be an intravascular compartment size of 4 liters with a plasma albumin concentration of 20 g/l, an interstitial compartment size of 16 liters with a concentration of 10 g/l, and a 10% transcapillary albumin loss per hour. One must assume that the extravascular compartment is effectively homogenous and that concentrations throughout this compartment are equal.

In this situation, there will be a recirculation over the first 1 h of ~0.25%, and, after the first 4 h, ~5% of the albumin escaping into the interstitium will return to the plasma. In most of our patients the TER was <10%, and it is probable that the interstitial compartment was larger than the 16 liters suggested in this model. Our studies were all completed in a little over 3 h, so the effect of recirculation on altering slopes of decay in activity was minimal, and, most importantly, if it were to occur it would appear to accentuate the reduction in permeability. Despite any effect of recirculation, we were not able to show a significant reduction in TER after the albumin bolus.

Transcapillary solute loss is increased in the face of increased fluid flux, such as occurs with increased hydrostatic microvascular pressures. After the infusion of albumin, there was a rise in CVP, which, at 30 min postinfusion, was a mean of 2.1 mmHg higher than preinfusion. The rise in CVP probably reflects a rise in microvascular hydrostatic pressure, and an increased transcapillary fluid flux with associated solvent drag might mask any reduction in permeability. In addition, the volume expansion effect might recruit additional capillary beds, increasing the area available for transcapillary escape, but we were unable to measure this effect in our study.

In total, ~100–120 ml of blood per patient were withdrawn for analyses, ~2% of the total blood volume. This in itself is a source of error because it leads to dilution and reduction in the absolute intravascular activity. However, because the error is only ~1–2% in the final samples, it can probably be ignored. This potential error is in the opposite direction to that which would be caused by a recirculation effect.

Cardiovascular Effects

There is extensive literature on small-volume resuscitation with markedly hypertonic solutions but relatively little on the effects of hyperoncotic colloidal solutions in septic patients. We were initially concerned that giving 200 ml of 20% albumin over 90 s would overload the circulation in these patients with sepsis-related myocardial dysfunction who were requiring inotropic support. Albumin is known to bind calcium ions, and we were worried about causing significant reductions in ionized calcium affecting contractility and reducing cardiac outputs.

We previously measured arterial blood-gas PO2 before and over the 30 min after an identical albumin bolus in similarly ventilated septic patients, and we demonstrated an unexpected rise in arterial PO2 (unpublished observations). In a total of 47 patients, the arterial PO2 rose from a prealbumin mean of 12.6 to 13.5 kPa at 1 min after the bolus, falling back to 13.2 kPa at 30 min. The immediate improvement in oxygenation most likely represents an improvement in perfusion, possibly increasing mixed venous oxygen saturation, because there is very little early hemodilution and therefore minimal fluid shifts to improve gas transfer by a reduction in pulmonary edema, as demonstrated by the hematocrit changes shown in Fig. 1.

Serial Barrier Hypothesis

After administration of labeled albumin, there is a biexponential decay curve, with an inflection point at ~10 min. Although this initial phase of rapid decay is possibly due to mixing alone, and possibly due to early rapid redistribution into the hepatic and splenic interstitium, it has been hypothesized that it may also represent serial barriers to efflux. Evidence for serial barriers is not convincing, but it has been suggested that the rate-limiting step to albumin efflux occurs not at the pores and slit junctions of the endothelium, but at the subendothelial and interstitial gel level (1, 2).

The transcapillary escape rate measures the second (steady-state) phase of redistribution. If this reflects permeability of the subendothelial and matrix layers, it may explain why the positive results from in vitro studies on endothelial cell monolayers (without matrix) are not carried over to the clinical setting. Although we have not shown any significant change to the TER after the infusion of albumin, the TER is measured from 15 min onward. In pharmacokinetic terms, we are showing that altering the serum albumin concentration does not affect the second component of the redistribution half-life, rate constant k2 (see Fig. 7). However, it may be that altering the serum albumin concentration affects the early efflux characteristics (during the first 15 min), by decreasing the immediate transendothelial permeability, and that this may change the slope of the first component of the redistribution half-life curve. We have not been able to quantify the early rate constant k1.

If there were an effect of albumin in reducing endothelial permeability, this would be in keeping with many in
vitro physiological experiments (10, 14, 17). To demonstrate that raising the serum albumin concentration had an effect on this early transendothelial escape rate, a dual-tracer technique with use of a second labeled albumin would be necessary. Unfortunately, \(^{131}\)I-labeled albumin (human) is no longer commercially available in the United Kingdom, and other labels such as technetium have such short half-lives that collection and analysis of specimens would be impracticable. Therefore, this line of investigation has been discontinued.

An alternative explanation for the lack of effect of supplemental albumin in altering permeability is that the concentration of albumin required to reduce permeability to a maximal extent is very low, below the level that any of these patients reached. This seems very likely. In vitro work performed in a pig vena caval endothelial model (17) and work by Huxley and Curry (14) in the United States and by Michel (14) in the United Kingdom showed that changes in permeability with low albumin concentrations occur in the range 0.1–3 g/l. Further studies (11a, 12a, 14a) have suggested that, when very low concentrations of albumin are added to protein-free perfusates of rat renal glomerulus and rat, cat, and dog perfused hindlimbs, microvascular permeability is reduced and that raising the albumin concentrations above these low levels has no further effect.

The modulating effect of albumin appears to depend on the ionization of its arginine residues (16) and seems to be mediated through a reduction in intracellular calcium concentrations (10).

Furthermore, other plasma proteins also affect permeability, including immunoglobulin G, orosomucoid, and cationized ferritin, and there is strong evidence that plasma is more effective than albumin alone in modulating permeability (8).

There is thus a fairly extensive pure physiology literature suggesting that, at least at the endothelial level, a reduction in the serum albumin level to \(~10\) g/l should have little effect on permeability. This clinical study does not support the suggestion that there is any other significant albumin effect at a subendothelial level.

**Conclusion**

Despite a near doubling of the serum albumin concentration, it was not possible to demonstrate a significant reduction in the any of the three parameters of microvascular leak measured. This clinical study would appear to confirm the prediction from in vitro work that albumin supplementation does not affect vascular permeability.

Although the precise physiology of capillary leak in sepsis remains to be elucidated, the clinical message is clear. In septic patients, the administration of 200 ml of 20% albumin does not lead to a clinically significant reduction in microvascular protein leakage.

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