Impact of hetastarch on the intestinal microvascular barrier during ECLS

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Smith and colleagues (21) established the gut as an ideal model for the evaluation of alterations in microvascular permeability with CPB. Furthermore, there is a growing body of evidence that the gastrointestinal tract is integral to the inflammatory response associated with ECLS (7). Specifically, the loss of gut barrier function has been associated with post-CPB septic complications (5, 10). Moreover, gut edema, as measured in our study, is a marker of organ injury that has been associated with gut barrier dysfunction in numerous clinical scenarios and laboratory models (2, 4, 6). Recent work has shown that gut lymph from animals that have undergone ischemia-reperfusion primes PMNs for superoxide release and upregulates the vascular endothelial intercellular adhesion molecule ICAM-1 (26). Thus gut microvascular barrier injury may be an effect of a systemic insult, and the increased volume/alteration character of mesenteric lymph after initiation of CPB/ECLS may cause an amplified inflammatory response and distant organ injury.

We have demonstrated that ECLS without a prior inflammatory stimulus is associated with a moderate gut microvascular barrier injury and the development of gut edema (4). Hetastarch has been used to minimize edema after CPB, and these effects have been attributed principally to the maintenance of plasma colloid osmotic pressure (COP). In contrast, in vitro studies have demonstrated that hetastarch minimizes endothelial injury in response to ischemia-reperfusion (16). Ex vivo and in vivo studies also pointed to a direct effect of hetastarch on the microvasculature independent of its COP effects. Therefore, we hypothesized that addition of the large-molecular-weight colloid hetastarch to an ECLS priming solution would decrease the transvascular fluid flux and edema formation associated with ECLS via maintenance of the COP and preservation of the microvascular barrier.

METHODS

Animal preparation. All procedures were approved by the University of Texas Animal Welfare Committee and were consistent with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. To minimize the excessive use of large animals, our laboratory uses a moving control group for interventional studies. Specifically, we include two to five new control animals and drop the most remote two to five animals as the study is performed. This ensures a contemporary group for comparison, while scientific validity is maintained. However, there is overlap in

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control animals from previous and future reports. Conditioned mongrel dogs of either gender [31 ± 2 and 33 ± 1 kg for lactated Ringer (LR) and hetastarch (HS) groups, respectively] were anesthetized with thiopental sodium (25 mg/kg iv; Abbott Laboratories, North Chicago, IL), intubated, and mechanically ventilated at a tidal volume of 15 ml/kg body wt, positive end-expiratory pressure of 5 cmH2O, and respiratory rate of 10 breaths/min with 100% oxygen with a volume-cycled respirator (model 900C, Siemens-Elema). Anesthesia was maintained with intravenous infusion of 1% thiopental sodium in Ringer solution.

Fluid-filled catheters were placed into the left femoral artery and vein and connected to pressure transducers to monitor mean arterial pressure, sample arterial blood, and administer fluid, respectively. A 7-Fr Swan-Ganz thermodilution catheter was inserted into the pulmonary artery via the left jugular vein for central venous pressure, pulmonary arterial pressure, and cardiac output (CO) determination. The right femoral artery was exposed for subsequent CPB cannulation. The pressure-monitoring catheters were connected to pressure transducers (Isotec, Heathlyne Cardiovascular, Irvine, CA), and data were recorded on an eight-channel chart recorder (Grass Instrument, Quincy, MA). We used a CO computer connected to a Swan-Ganz thermodilution pulmonary artery catheter (Baxter-Edwards Critical Care, Irvine, CA) to determine CO in duplicate. Ice-cold Ringer solution (10 ml) was used as the injectate. A urinary drainage catheter was placed in the bladder at the time of laparotomy, and urine output was measured every 30 min. Arterial blood gas measurements were made using an automated blood-gas analyzer (model IL-BGE, Instrumentation Laboratories, Lexington, MA).

Lymphatic fistula preparation and capillary pressure measurements. Transcapillary fluid filtration rate ($J_τ$) is determined by the Starling forces as calculated from the following equation

$$\dot{Q}_L = J_τ \cdot K_f \cdot (P_c - P_i) - \alpha (\pi_c - \pi_i)$$

(1)

where $\dot{Q}_L$ is lymph flow, $K_f$ is capillary filtration coefficient, $P_c$ is capillary pressure, $P_i$ is interstitial pressure, $\alpha$ is reflection coefficient, $\pi_c$ is plasma oncotic pressure, and $\pi_i$ is interstitial oncotic pressure. The $\alpha$ was calculated by simultaneously measuring plasma and lymph protein concentrations ($C_i$ and $C_p$, respectively) after interstitial protein "washdown" was induced by elevated mesenteric venous pressure. When $C_i / C_p$ reached filtration independence

$$\alpha = 1 - \frac{C_i}{C_p}$$

(2)

The $\alpha$ represents the ability of the membrane to selectively limit the passage of macromolecules and is a surface area-independent coefficient. A $\alpha$ of 1 represents an impermeable membrane, and a $\alpha$ of 0 represents no barrier function. $K_f$ is a surface area-dependent coefficient that describes the fluid conductance properties of the capillary membrane. Transvascular protein clearance was calculated as $Q_L \times C_i / C_p$, and was used in conjunction with $\alpha$ as a marker of microvascular permeability to protein.

To obtain the measurements of $Q_L$ and $C_i$, a midline laparotomy was performed and a mesenteric lymphatic was cannulated with 0.025-in.-ID tubing and attached to a pressure transducer that was interfaced with a physiological recorder (model 7D polygraph, Grass Instrument). This was used to estimate $P_c$ according to the method of Granger et al. (9). $P_c$ was measured using the venous occlusion technique, which results in a rapid rise in the venous pressure to $P_c$, and then a more gradual increase. This was graphically measured by increasing the chart speed on the chart recorder, and the inflection point represents $P_c$. We used a calibrated semipermeable membrane (3 x 10^4 mol wt) in a colloid osmometer (model 4100, Wescor, Logan, UT) to measure the plasma and lymph COP.

$C_i$ and $C_p$ were determined using a refractometer (Leica). Because of concerns that hetastarch may affect the $C_i$ and $C_p$ determinations, we studied the effects of adding 6% hetastarch in a 1:4 ratio with plasma on $C_p$ determinations with the refractometer: 6% hetastarch alone gave a reading of 2.6 g/dl. The $C_p$ of 2.0–4.5 g/dl was tested. There was a 0.15 g/dl decrease in the 2.2–2.6 g/dl range. With the 4.6 g/dl $C_p$, there was a 0.3 g/dl decrease in $C_p$. Presumably, the effect of 6% hetastarch on $C_p$ in the 3.5–3.8 g/dl range would be between 0 and 0.3 g/dl and, most likely, a decrease of ~0.15 g/dl. This does not significantly affect the calculations of $\alpha$ (a potential change from 0.73 to 0.72) in the HS group, nor does it significantly affect the between-group comparisons. These differences are within the accepted ~3–5% error range with the refractometer technique (24).

Intestinal water content determination. For intestinal water content determination, we modified a gravimetric technique originally developed for cerebral tissue (19). Intestinal water content was determined by specific density measurement of small ileal tissue samples by use of a linear density gradient. With knowledge of the specific density of an ileal tissue sample, the percent gram water per gram tissue can be calculated. For preparation of the density gradient, we used two mixtures: kerosene (specific gravity 0.773) and bromobenzene (specific gravity 1.484). The specific gravities of these mixtures were adjusted to 0.983 and 1.073, respectively, and the density column was generated using a gradient former (model GC-0971, Bethesda Research Laboratories, Bethesda, MD). We then used various K2SO4 solutions with known specific gravities of 1.086, 1.079, 1.072, 1.067, 1.044, 1.035, 1.031, and 1.027 to calibrate the gradient. We carefully placed 10-µl drops of the K2SO4 solutions in the gradient and recorded the equilibration depth after 1 min. We then plotted equilibration depth vs. specific gravity and confirmed the linearity of the gradient by linear least-squares regression analysis. The mean correlation coefficient was 0.983 ± 0.002 (SD); n = 15.

To determine specific gravity of the ileum, we sharply excised full-thickness ileal tissue samples (6–8 mm²). These samples were gently placed into the density gradient, and the equilibration depth was recorded after 1 min. The grams of water per gram of ileum, or ileal water content (IWC, %), was calculated as follows

$IWC = 1 - [(SG_{ileal} - 1)/(1 - 1/SG_{dry})] \cdot 100\%$ (3)

where $SG_{ileal}$ and $SG_{dry}$ are the specific gravities of the ileal tissue sample and dry ileum, respectively. At the end of the experiment, we euthanized the dog with an intravenous thiopental sodium overdose and saturated potassium chloride. The bowel was then weighed, and a sample was stored in an oven and dried to a constant weight at 60°C. We calculated $SG_{dry}$ as follows

$$SG_{dry} = 1/(1 - [(SG_{ileal} - 1) \cdot W/ID \cdot SG_{ileal}])$$ (4)
where W and D are wet and dry weights of the ileum, respectively. We assumed that S_{Gdry} did not change over the experimental period. All ileal tissue water content measurements were performed in triplicate.

ECLS techniques. After preparation, heparin (300 IU/kg iv) was given for systemic anticoagulation. Additional doses of 75 IU/kg heparin were administered every 60 min throughout the experiment. We introduced a 16-F arterial perfusion cannula into the prepared right femoral artery. A two-stage (34/38-F) venous cannula (model TAC2, DLP, Grand Rapids, MI) was inserted into the right atrium/inferior vena cava via median sternotomy. No cardioplegia, left ventricular vent, or aortic cross clamp was used. We primed the extracorporeal circuit and the membrane oxygenator (model HVRF-3700, Cobe Cardiovascular, Arvada, CO) with 800 ml of Ringer solution and 1,000 IU of heparin (LR group). Hetastarch was added to the priming solution to achieve a 6% final concentration in the HS group. A rectal temperature probe was placed, and the body temperature was maintained at 37°C during extracorporeal circulation with a heat exchanger (Sarns heater-cooler, Ann Arbor, MI). We maintained ECLS flow between 60 and 80 ml·kg⁻¹·min⁻¹ and mean systemic perfusion pressure between 60 and 80 mmHg. There is a marked reduction in pulse pressure from ~40–50 to 10–20 mmHg with the initiation of ECLS. As such as the left ventricle was not arrested and the arterial waveform was not obliterated, there was some contribution of the heart to CO. Thus pump flow should not be viewed as total CO during ECLS. Lactated Ringer solution was added to the reservoir to maintain a constant level of 100 ml.

Experimental protocol. Two groups of animals were studied: the LR group (n = 9) received only lactated Ringer priming solution, and the HS group (n = 6) received a 6% hetastarch priming solution. After instrumentation, we recorded baseline measurements of CO, mean arterial pressure, pulmonary arterial pressure, and right atrial (central venous) pressure. Q_l, lymph and plasma protein determinations, and P_c were measured. Once baseline measurements were completed, mesenteric venous pressure was elevated in one step to 33 ± 0 and 32 ± 1 mmHg in the LR and HS groups, respectively, to obtain a minimum C_l /C_p. Once a steady state was achieved, as evidenced by two similar C_l measurements 15 min apart, ECLS was initiated. This was typically at 120 min. Previous experiments of 3–4 h failed to demonstrate further washdown with reduction in C_l. All other variables were measured at 30-min intervals for 2 h of ECLS. At the conclusion of the ECLS period, the ECLS flow was reduced, and the dog was weaned and separated from ECLS. Ileal tissue samples were taken at baseline and steady state and every 30 min for gravimetric tissue water determinations.

Statistical analysis. Values are means ± SE. We used ANOVA for repeated measures and Fisher's least significant difference test to examine the time courses of each measured parameter. Time point comparisons were made using unpaired Student's t-test. P < 0.05 was considered significant.

RESULTS

The primary hemodynamic and Starling data are shown in Tables 1 and 2. Q_l data are shown in Fig. 1. After initiation of ECLS, there was a small increase in Q_l in the LR group; there was no increase in Q_l in the HS group. There was no statistically significant difference in Q_l between the groups. The σ is shown

### Table 1. Hemodynamic data

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<th>60 min</th>
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<th>90 min</th>
<th>120 min</th>
<th>120 min</th>
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<tr>
<td>LR</td>
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<td>37.8 ± 1.5</td>
<td>34.2 ± 2.5</td>
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Values are means ± SE. MAP, mean arterial pressure; PAP, pulmonary arterial pressure; CVP, right atrial (central venous) pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; P_aO_2, and P_aCO_2, arterial P_O_2 and P_CO_2; Hct, hematocrit; ECLS, extracorporeal life support; LR, lactated Ringer priming-solution; HS, hetastarch. *P < 0.05 vs. washdown (by ANOVA and Fisher's least significant difference test for within-group comparisons); †P < 0.05 vs. LR at same time point (by t-test).
in Fig. 2. Initiation of ECLS resulted in a statistically significant decrease in \( \sigma \) in both groups. The \( \sigma \) recovered in the HS group by the end of the ECLS period, whereas it trended downward in the LR group. Concomitantly, transvascular protein clearance (\( Q_T \times C_L / C_P \)) increased to a significantly greater degree in the LR than in the HS group (Fig. 3). This corresponded to a decrease in \( \sigma \), and both indicate an increased permeability to protein. Ileal tissue water was shown in Fig. 4. Ileal tissue water was significantly greater in the LR than in the HS group. Both groups were in an isogravimetric steady state before initiation of ECLS. The final wet weight = dry weight/dry weight of the ileum was significantly lower in the HS than in the LR group: 4.32 ± 0.15 and 4.93 ± 0.27, respectively (\( P < 0.03 \)). Total fluid balance (fluid infused − urine output) was significantly less in the HS than in the LR group: 901 ± 120 min of ECLS and 30 min after ECLS.

![Fig. 1. Lymph flow (\( Q_L \)) as a function of time. Mesenteric pressure elevation is initiated after baseline measurements (BL). WD, "washdown" (i.e., steady-state plateau of \( Q_L \) and minimum lymph protein concentration (\( C_L \)). \( Q_L \) increases to high flows, and there is no significant further increase with initiation of extracorporeal life support (ECLS). LR, group treated with lactated Ringer solution; HS, group treated with 6% hetastarch. pECLS, post-ECLS.](image)

![Fig. 2. Reflection coefficient (\( \sigma \)) as a function of time. \( \sigma \) is calculated from \( 1 - C_L / C_P \) (where \( C_P \) is plasma protein concentration) and is an accurate measure of microvascular permeability to protein. There is an acute drop in \( \sigma \) (indicating an increase in membrane permeability) with initiation of ECLS that further decreases in LR group. In HS group, \( \sigma \) recovers and is significantly different from \( \sigma \) in LR group at 120 min of ECLS and 30 min after ECLS. *Within-group significant change from WD; †significant difference between groups at an individual time point.](image)
contrast to the drop in plasma COP in the LR group from 13.7 ± 0.3 to 8.5 ± 0.7 mmHg. The increase in plasma COP in the HS group accounts for an increase in the plasma-to-lymph COP gradient of 5 mmHg in the HS compared with the LR group at 30 min of ECLS. When Δπ (Δπ) is calculated at the period of greatest change in permeability (120 min), the effective COP gradient is 3.8 and 6.2 mmHg in the LR and HS groups, respectively.

**DISCUSSION**

Our data demonstrate that a hetastarch priming solution decreases intestinal edema associated with ECLS. With initiation of ECLS, there is a modest decrease in Δπ, indicative of increased microvascular permeability to protein. The observed reduction in intestinal edema with the hetastarch priming solution can be explained by two factors: 1) the maintenance of the plasma-to-interstitial COP gradient and 2) the lessening of the decrease in Δπ.

Hetastarch is an artificial colloid with an average molecular weight of 4.5 × 10^5 (1 × 10^4–3.5 × 10^6) (17). The physiological colloidal properties of hetastarch are comparable to those of albumin, the primary colloid in blood, which has a molecular weight of 6.9 × 10^4. Previous work by two groups helps explain our data. Microvascular leak is thought to be due, in part, to endothelial cell contraction, resulting in large intercellular junctions. This increase in intercellular junctional space results in the flow of macromolecules and fluid into the interstitium, leading to tissue edema. Zikria et al. (28) demonstrated that hetastarch minimized tissue edema in an ischemia-reperfusion model of increased vascular permeability, independent of the COP effect. They hypothesized that this finding was related to a biophysical effect of hetastarch effectively sealing the separated endothelial junctions. Similar results have been shown using isolated jejunal loops (27). Oz et al. (16) demonstrated another explanation for the effect of hetastarch involving decreased PMN-endothelial adherence. Numerous studies implicate the PMN as the mediator of microvascular barrier injury associated with ischemia-reperfusion, ECLS, and numerous inflammatory conditions. In a striated muscle model, Oz et al. found that hetastarch treatment was associated
with a twofold decrease in PMN binding to the stimulated endothelium.

McGrath and colleagues (13) compared starch-based macromolecules and their effects on lung fluid balance. They noted that the oncotic effectiveness of the starch-based plasma volume expanders correlated with their range of molecular weights. Solutions without low-molecular-weight components maintained the plasma-to-interstitial COP gradient better than the lower-molecular-weight compound (dextran). In our study, the hetastarch priming solution effectively maintained the plasma-to-interstitial COP gradient, similar to the data presented by McGrath et al. As with the study of McGrath et al., ours is not a model of severe microvascular barrier injury with marked changes in microvascular permeability (π). Thus increases in plasma COP, as seen with hetastarch, effectively contribute to the COP gradient. Conversely, we would expect a very transient augmentation of the oncotic gradient in high-permeability states such as sepsis/bacteremia. We also noted a transient increase in the lymph COP in the HS group at 30 min of ECLS. This probably represented the acute movement of the low-molecular-weight fraction of hetastarch across the microvascular barrier with the institution of ECLS. We can infer that hetastarch decreased Jv, inasmuch as Ql was not significantly changed, whereas tissue water was decreased in the HS group compared with the LR group. This may be a preparation artifact, since mesenteric venous pressure was elevated in both groups, such that Ql was at or near maximum, which can be limited by cannula resistance. Thus highly significant changes in Jv would be required to demonstrate a difference in Ql.

The acute reduction of plasma proteins with hemodilution acutely increases the net filtration pressure. This is reflected by a reduction in plasma COP with a proportional increase in transmicrovascular fluid flux. As fluid moves into the interstitium, P, rises and Ql increases. Hemodilution occurs during our experimental preparation, but only after a number of responses to elevated venous pressures have occurred: Ql is at or near maximum, P, is elevated, and interstitial COP and Cl are reduced. Thus some of the “edema safety factors” of Ql and an interstitial COP are already near capacity. Thus a reduction in plasma COP may increase the net filtration pressure, resulting in greater edema than in a preparation without elevated venous pressure. However, the preparation allows a precise determination of the microvascular permeability changes to protein by measurement of σ. So, as demonstrated in our data, hemodilution or, more specifically, loss of the plasma-to-interstitial COP gradient with a modest decrease in σ can result in edema formation. Also, minimizing the effects of “hemodilution”/reduction of the plasma COP can reduce edema formation.

Cardiac surgery requiring CPB is well tolerated by most patients, and a mild systemic inflammatory response is usually well compensated by adequate myocardial protection and circulatory support. However, inasmuch as the practice of cardiac surgery extends to more complicated and higher-risk patients, there is increased probability of clinical manifestations of the postpump syndrome with higher rates of morbidity and mortality. Although much attention has focused on the blood-foreign surface interactions that cause the systemic inflammatory response, the importance of the gut in relation to these systemic disorders after CPB has become increasingly evident. Gut edema and microvascular barrier injury have been associated with gut and lung dysfunction in numerous clinical scenarios and experimental models (12, 23). Gut dysfunction has been correlated with complications after CPB. The model used in this study allows a precise evaluation of the degree of gut microvascular barrier injury and edema formation in an intact, whole organ preparation. This permits an analysis of the factors associated with edema formation and insight into potential mechanisms of injury.

In contrast to CPB for cardiac surgery, long-term ECLS (or extracorporeal membrane oxygenation) is initiated in response to cardiopulmonary failure, and a significant number of patients have experienced a prior inflammatory insult, e.g., meconium aspiration syndrome, sepsis, and gut ischemia-reperfusion. In these circumstances, we would expect much greater changes in microvascular permeability to protein and large molecules (decreased σ). Therefore, we would predict that colloid priming solutions would result in variable effects on transvascular fluid flux and edema formation. The heterogeneous colloid solutions could result in a greater plasma-to-lymph COP gradient that would be offset by the migration of the smaller-molecular-weight fractions into the interstitium. Thus estimation of the degree of microvascular barrier damage and the future availability of colloids with a narrower spectrum of molecular weights (e.g., pentastarch and pentafracta) would allow the development of an effective fluid strategy during ECLS to minimize edema.

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