Cold-induced fluid extravasation during cardiopulmonary bypass in piglets can be counteracted by use of iso-oncotic prime

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Objective: Hypothermic cardiopulmonary bypass is associated with increased fluid extravasation. This study aimed to compare whether iso-oncotic priming solutions, in contrast to crystalloids, could reduce the cold-induced fluid extravasation during cardiopulmonary bypass in piglets.

Methods: Three groups were studied: the control group (CT group; n = 10), the albumin group (Alb group; n = 7), and the hydroxyethyl starch group (HES group; n = 7). Prime (1000 mL) and supplemental fluid were acetated Ringer solution, 4% albumin, and 6% hydroxyethyl starch, respectively. After 1 hour of normothermic cardiopulmonary bypass, hypothermic cardiopulmonary bypass (cooling to 28°C within 15 minutes) was initiated and continued to 90 minutes. Fluid needs, plasma volume, changes in colloid osmotic pressure in plasma and interstitial fluid, hematocrit levels, and tissue water content were recorded, and protein masses and fluid extravasation rates were calculated.

Results: Colloid osmotic pressure in plasma decreased immediately after the start of cardiopulmonary bypass in the CT group but remained stable in the Alb and HES groups. Colloid osmotic pressure in interstitial fluid tended to decrease in the CT group and remained unchanged in the Alb group, whereas a slight increase was observed in the HES group. Immediately after the start of cooling, fluid extravasation rates increased from 0.15 ± 0.10 to $0.64 \pm 0.12 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the CT group, whereas no such increase was observed in the Alb and HES groups. The changes in fluid extravasation rates were reflected by corresponding changes in tissue water content.

Conclusion: The use of albumin or hydroxyethyl starch as prime to preserve the colloid osmotic pressure during cardiopulmonary bypass causes a reduction in the cold-induced fluid extravasation compared with that seen with crystalloids. Albumin seems more effective than hydroxyethyl starch to limit cold-induced fluid shifts during cardiopulmonary bypass.

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This study was financially supported by the Norwegian Research Council, the Norwegian Council on Cardiovascular Diseases, the Faculty of Medicine at the University of Bergen, The Frank Mohn Foundation, and the Laerdal Foundation for Acute Medicine. Marit Farstad is a research fellow of the University of Bergen, Norway.

Received for publication Aug 9, 2004; revisions received Sept 23, 2004; accepted for publication Oct 13, 2004.

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J Thorac Cardiovasc Surg 2005;130:287-94
0022-5223/\$30.00

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doi:10.1016/j.jtcvs.2004.10.006

The use of cardiopulmonary bypass (CPB) is associated with fluid accumulation and edema formation, occasionally causing organ dysfunction.^{1,2} The heart, lungs, gastrointestinal tract, and central nervous system might be affected. Together with hypothermia, hemodilution and a general inflammatory

Figure 1. Albumin mass in the respective groups at the start of and during bypass. *Dotted line, Start of hypothermic CPB.* Values are presented as means $\pm$ SEM. * $P < .05$ (calculated albumin mass after 30 minutes of CPB compared with initial value).

response syndrome related to contact between blood and tubing surface material have been held responsible.^{3,4}

In a recent study we evaluated the effect of anti-inflammatory agents on fluid homeostasis during normothermic and hypothermic CPB. None of the drugs tested (methylprednisolone, vitamin C, or α -trinositol) revealed any effect on the fluid leakage during CPB.⁵ In previous studies we found an abrupt and persisting increase in fluid filtration from circulation to the interstitial space after the start of cooling when acetated Ringer solution was used as prime.⁶⁻⁸ In these studies the colloid osmotic pressures (COP) in plasma remained low after the initial hemodilution at the start of CPB.⁵⁻⁸

We hypothesized that preservation of an iso-oncotic pressure in plasma could reduce or prevent the cold-induced fluid extravasation from circulation to the interstitial space during CPB. We designed our study to compare the effects on microvascular fluid exchange of 3 different priming solutions (pure crystalloid solution, albumin, and heta-starch) in piglets undergoing normothermic and hypothermic CPB.

Materials and Methods

Animal Handling and Anesthesia

Thirty-seven domestic piglets (Norwegian Landrace Norhybrid; Stend Agriculture College, Bergen, Norway) were studied. They were about 12 weeks old, about 30 kg, and received humane care in accordance with recommendations given by the Norwegian State Commission for Laboratory Animals. Food was withdrawn 12 hours before the study. Water was provided at all times. Twenty-four of the animals were instrumented and subjected to 150 minutes of CPB. In addition, a historic non-CPB control group ($n = 13$) was included.⁵ Premedication of the animals and induction and maintenance of anesthesia were carried out according to the methods of Farstad,⁵ Husby,⁹ and their associates.

Through a midline sternotomy, preparation for extracorporeal circulation was done after intravenous administration of heparin (6 mg/kg body weight plus 3 mg/kg after 1 hour). In parallel, arterial and venous lines for continuous monitoring of systemic mean arterial pressure (MAP) and central venous pressure (CVP) were placed in the left femoral artery and vein, respectively. A urinary bladder catheter was inserted through a midline laparotomy. Surgical intervention was normally completed within 20 minutes. All animals were thereafter allowed 60 minutes' stabilization before the start of CPB.

CPB

Cannulation for CPB was established in the ascending aorta and the right atrium, as recently presented.⁵ Pump flow was nonpulsatile and set to $2.7 \text{ L} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$. During CPB, 0.5% isoflurane was added to the machine oxygenator. Throughout the experiments, there was a constant fixed height difference ($73 \pm 3 \text{ cm}$) between the level of the machine reservoir and the site of venous drainage (the right atrium). Free venous drainage was controlled continuously.

Study Design and Groups

Three groups were studied: the control group (CT group; $n = 10$), the albumin group (Alb group; $n = 7$), and the hydroxyethyl starch group (HES group; $n = 7$). In addition, a non-CPB control group ($n = 13$) was included as a baseline for determination of total tissue water (TTW) content in the different study groups.⁵

In the CT group the CPB circuit was primed with acetated Ringer solution, and when needed, acetated Ringer solution was added to the machine reservoir. Blood loss was substituted for using Ringer solution in volumes of 3 times the blood loss volume. During CPB, blood loss into the open chest was returned to circulation through the extracorporeal machine reservoir.

In the Alb group the CPB circuit was primed with 4% albumin (batch no. 027006610/N; osmolality, 278 mOsm/kg; Octapharma AG, Vienna, Austria), and when needed, albumin was added to the reservoir. Blood losses were corrected by means of intravenous administration of 4% albumin in a 1:1 ratio.

In the HES group poly(O-2-hydroxyethyl) starch, 60 mg/mL (HES 200/05; batch no. NF 8501/07; osmolality, 308 mOsm/L; Fresenius Kabi AB, Uppsala, Sweden), was mixed with acetated Ringer solution to obtain a COP equivalent to the in vivo plasma COP in each animal. This mixture was subsequently used for priming of the CPB circuit, for fluid additions to the machine reservoir when needed, and to substitute for blood losses in a 1:1 ratio. In all 3 groups, 5 mL/kg body weight per hour of acetated Ringer solution was administered as maintenance fluid throughout the experiments.

The priming volume of the CPB circuit was 1000 mL of fluid in all groups, which regularly resulted in a filling of the machine reservoir to the 400-mL level. This level was used as a fluid gauge. Changes in this level indicated losses or gain of fluid from circulation to the interstitial space or changes in vascular tone. When the reservoir blood level decreased, fluid was supplied to restore the 400-mL level.

After stabilization for 60 minutes, normothermic CPB (38°C -

TABLE 1. Osmolality, mean arterial pressure, hematocrit level, serum albumin and serum total protein concentrations, protein mass, fluid additions, diuresis, blood loss, and plasma volume

Parameters	Group	Before bypass		Normothermic CPB				Hypothermic CPB		
		0 min	5 min	30 min	60 min	90 min	120 min	150 min		
Osmolality (mOsm/kg)	CT	283.7 (1.7)		286.7 (4.3)	283.7 (1.7)	283.2 (1.8)	283.4 (1.9)	283.8 (1.7)		
	Alb	279.0 (1.8)		282.6 (1.7)	285.3 (2.1)	285.7 (2.3)	284.9 (2.9)	286.4 (2.2)		
	HES	290.3 (2.7)#		296.1 (2.3)**	296.1 (1.8)#,	296.6 (1.7)#,	294.7 (1.7)§	293.6 (1.7)‡		
MAP (mm Hg)	CT	49 (2.8)		54 (2.8)	58 (3.8)	61 (5.0)	66 (6.5)	65 (6.4)		
	Alb	50 (2.8)		51 (3.0)	51 (2.9)	59 (2.3)	61 (2.9)	59 (4.0)		
	HES	52 (2.5)		55 (3.5)	54 (3.5)	65 (4.0)	71 (7.6)	72 (7.3)		
Hematocrit (%)	CT	30 (0.8)	22 (0.6)†	25 (0.5)	24 (0.6)	22 (0.5)	22 (0.5)	22 (0.5)		
	Alb	30 (0.7)	23 (1.1)†	23 (0.9)	23 (0.9)	22 (0.9)	22 (1.0)	22 (1.2)		
	HES	29 (1.3)	18 (0.9)	18 (1.1)	19 (1.2)‡	18 (1.2)	18 (1.3)	18 (1.4)		
Serum albumin (g/L)	CT	28.4 (0.9)		23.3 (0.9)††,‡	21.4 (0.7)†	18.6 (0.7)†	18.6 (0.7)†	18.4 (0.7)†		
	Alb	33.0 (0.9)		35.0 (0.8)	34.6 (0.6)	34.7 (0.8)	34.4 (0.8)	35.0 (0.9)		
	HES	29.0 (1.4)		17.6 (1.1)†	18.1 (1.1)†	16.7 (1.0)†	16.6 (1.4)†	15.6 (1.3)†		
Serum total protein (g/L)	CT	44.4 (1.2)		35.3 (0.3)†	33.4 (1.1)†	29.7 (1.1)†	29.2 (1.1)†	28.8 (1.0)†		
	Alb	46.9 (1.1)		45.4 (1.1)	44.7 (1.1)	44.0 (1.0)	43.6 (1.1)	44.1 (1.1)		
	HES	46.3 (2.0)		27.4 (1.8)†	28.1 (1.9)†	25.6 (1.8)†	25.6 (2.0)†	25.0 (2.1)†		
Serum protein mass (g)	CT	78.5 (3.7)		76.2 (2.5)	81.4 (3.9)	77.9 (3.6)	76.7 (3.1)	75.1 (4.3)		
	Alb	93.7 (9.3)		119.9 (9.3)	116.2 (9.1)	122.9 (10.6)§	124.9 (15.0)§	126.6 (16.5)		
	HES	74.5 (5.6)		75.9 (5.1)	74.0 (4.7)	71.6 (4.6)	70.0 (5.1)	69.4 (5.1)		
Fluid additions (mL · kg ⁻¹ · min ⁻¹)	CT			0.70 (0.18)	0.18 (0.07)	0.84 (0.08)§§	0.52 (0.09)	0.67 (0.08)‡‡		
	Alb			0.07 (0.07)	0.01 (0.05)§	0.39 (0.08)	0.01 (0.04)‡	0.16 (0.04)‡		
	HES			-0.16 (0.17)‡	0.22 (0.10)	0.56 (0.09)	0.32 (0.04)	0.38 (0.06)		
Diuresis (mL · kg ⁻¹ · min ⁻¹)	CT	0.02 (0.01)		0.03 (0.01)	0.02 (0.01)	0.17 (0.09)	0.20 (0.06)*	0.33 (0.08)*		
	Alb	0.02 (0.01)		0.02 (0.01)	0.01 (0.01)	0.01 (0.01)	0.02 (0.01)	0.04 (0.01)		
	HES	0.03 (0.01)		0.02 (0.01)	0.02 (0.01)	0.04 (0.02)	0.07 (0.03)	0.07 (0.02)		
Blood loss (mL)	CT			4.7 (0.7)	6.8 (1.6)	13.1 (4.6)	23.5 (6.6)	17.8 (7.7)		
	Alb			17.0 (3.4)	18.1 (4.0)	15.6 (4.1)	20.1 (5.4)	28.6 (8.9)		
	HES			8.0 (2.5)	5.3 (0.8)	8.7 (2.3)	19.3 (6.3)	16.9 (4.6)		
Plasma volume (mL/kg)	CT	55.8 (3.8)		46.9 (2.7)	51.1 (4.3)	58.9 (4.6)	58.8 (5.2)	58.2 (5.9)		
	Alb	56.5 (3.9)		48.3 (3.2)	46.4 (3.3)	53.7 (4.1)	57.4 (6.1)	57.6 (7.2)		
	HES	56.4 (3.1)		60.2 (7.1)	58.8 (6.9)	70.2 (6.8)	69.6 (7.1)	72.1 (8.2)		

Values for diuresis and additions refer to the last 30 minutes. The values are presented as means, with SEMs in parentheses. CPB, Cardiopulmonary bypass; CT, control group (n = 10); Alb, albumin group (n = 7); HES, hydroxyethyl starch group (n = 7). **P* < .05 and †*P* < .001 compared with time 0. ‡*P* < .05, §*P* < .01, and ||*P* < .001 compared with control value at same time. ¶*P* < .01 compared with values at 30 minutes. #*P* < .05 and ***P* < .01 compared with the Alb group at same time. ††n = 3. ‡‡*P* < .05 and §§*P* < .001 compared with the values at 60 minutes.

39°C) was initiated and continued for 60 minutes followed by 90 minutes of hypothermic CPB (28°C). By setting the water temperature of the CPB heat exchanger to 5°C, a decrease in the core temperature from 39°C to 28°C was achieved within 15 to 20 minutes. During CPB, nasopharyngeal and rectal temperatures were measured continuously.

Hemodynamic Variables and Blood Analysis

Heart rate, MAP, CVP, hematocrit (Hct) level, plasma colloid osmotic pressure (COPp), and serum concentrations of albumin, total protein, and electrolytes, as well as acid-base parameters, were recorded as recently described.⁵

COP and Plasma Volume Determination

COP was measured as previously described⁵ in plasma and interstitial fluid, with a specially designed colloid osmometer accepting sample volumes of 5 µL.¹⁰ Fluid for determination of interstitial colloid osmotic pressure (COPi) was sampled by using multifilamentous nylon wicks.¹¹ Wick fluid from 3 implantation periods (before CPB, during normothermic CPB, and during hypothermic CPB) was analyzed.

Red blood cell volume was determined by using carbon monoxide as a label^{5,12} just before the start of CPB. Subsequent blood and plasma volumes were calculated from determination of the changes of the Hct values and corrected for blood loss. The

Figure 2. COP in plasma (A) and interstitial fluid (B). Values are presented as means $\pm$ SEM. *Open circles*, Albumin as prime; *closed circles*, acetated Ringer solution as prime (CT group); *triangles*, HES as prime. A, Values at start of and during CPB. *Dotted line*, start of cooling. $\bullet\bullet\bullet P < .001$ compared with CT group, $***P < .001$ compared with initial value. B, Sampling number: 1, before CPB; 2, after 1 hour of normothermic CPB; 3, after 90 minutes of hypothermic CPB. $\bullet\bullet P < .01$ compared with CT group.

calculated plasma volumes were corrected according to the following equation to assess the real in vivo plasma volume of the animals during CPB:

$$\text{Real volume} = \text{Calculated volume} - \text{Volume in CPB circuit.}$$

Fluid Loss and Supplementation and Fluid Extravasation

Urine output was recorded every half hour through a suprapubic catheter. Fluid balance (ie, fluid input and output) was recorded continuously. After the start of CPB, fluid additions to the machine reservoir and net fluid balance (NFB) (ie, all fluid additions and losses, including diuresis) were calculated on a half-hour basis. The fluid extravasation rate (FER) was subsequently calculated for

each individual experiment on a half-hour basis as the net fluid balance corrected for changes in plasma volume (PV) per 30 minutes (ΔPV), according to the following formula:

$$\text{FER (mL/kg/30 min)} = \text{NFB (mL/kg/30 min)} - \Delta \text{PV (mL/kg/30 min)}$$

Albumin Mass, Protein Mass, and Albumin and Protein Extravasation

Total intravascular albumin and protein masses (in grams within the animal, tubing, and machine reservoir) were determined as the product of PV (in liters within the animal, tubing, and reservoir) and the serum albumin (ie, measured albumin mass; Figure 1) or serum total protein concentrations in grams per liter.

In addition, we calculated the albumin mass in the Alb group as follows:

$$\begin{aligned} \text{Calculated albumin mass (g)} &= \text{Albumin (g/L)} \times \text{PV (L)} \\ &+ \text{Albumin added (g)/Time interval (30 min)} \end{aligned}$$

If the measured albumin mass was less than the calculated albumin mass, we could conclude that albumin was lost from circulation.

End of Experiment and TTW

At the end of each experiment, the pigs were killed with an intravenous injection of 20 mL of saturated KCl solution.

Immediately after the animals were killed, tissue samples (3 parallel pieces) were taken simultaneously from the left quadriceps muscle, abdominal skin, colon, ileum, stomach, liver, pancreas, kidney, lung, and heart (left and right ventricular myocardium) and placed in preweighed vials, reweighed, and placed in a drying chamber at 70°C. The vials were weighed repeatedly until a stable weight was obtained. TTW was recorded as grams per gram of dry weight.

Statistical Methods

The results are presented as the mean and SEM. All data were analyzed by means of the Graph Pad InStat (version 3.02; Graph Pad Software Inc, San Diego, Calif).

Repeated-measures analysis of variance (ANOVA) with one grouping variable was used to test the relationship of the outcome variable at different times. If a significant between-group P value was found, a 1-way ANOVA was applied, followed by using the Tukey-Kramer multiple comparisons test. Furthermore, when finding a significant within-group P value, a post hoc paired t test was used. The level of significance was adjusted according to the number of comparisons. The 1-way ANOVA was also used when comparing the non-CPB and CT groups and in each of the interventional groups. This test was followed by the Tukey-Kramer multiple comparisons test when necessary.

Results

All animals studied were comparable with respect to age (CT group, 12.8 ± 0.6 ; Alb group, 13.9 ± 0.5 ; HES group, 12.0 ± 0.8 ; and non-CPB group, 13.5 ± 0.4 weeks), weight (31.9 ± 1.3 , 35.3 ± 2.1 , 28.5 ± 1.5 , and 32.7 ± 1.0 kg, respectively), and sex (male/female: 9/1, 5/2, 6/1, and 11/2, respectively). Variations in serum

osmolality (Table 1) and acid-base parameters were similar in all groups, and the values remained within normal ranges throughout the study. The serum osmolality in the HES group was significantly higher than in the CT and Alb groups, as displayed in Table 1.

Hemodynamics

All animals remained cardiovascularly stable with beating hearts during the experiments. CVP remained essentially unchanged in all groups at a level of 7 ± 1 mm Hg, as measured in the femoral vein. No venous obstruction at the site of drainage (right atrium) was present during the studies. MAP tended to increase slightly in all groups without reaching significance (Table 1). Values for blood losses and diuresis are given in Table 1. In the CT group a significant increase in diuresis was seen after the start of cooling. No such increase was observed in the interventional groups.

Albumin and Protein Concentrations, Masses, Plasma Volume, and COPs

Initiation of CPB resulted in a 25% hemodilution in the CT and Alb groups ($P < .001$) and a 40% hemodilution in the HES group judged on the basis of the changes in Hct levels ($P < .001$, Table 1). This degree of hemodilution is also reflected by a decrease in both the serum albumin and serum protein concentrations after the start of CPB in the CT and HES groups ($P < .001$), whereas the albumin and protein concentrations remained unchanged in the Alb group throughout the experiments related to the prime composition (Table 1).

Plasma volume remained essentially unchanged, with no significant within-group or between-group differences throughout the experiments, although a slight increase could be observed in the HES group (Table 1).

The albumin masses remained stable at about 50 g in the CT and HES groups during the experiments (Figure 1). In the Alb group an increase in the mass was seen immediately after initiation of CPB ($P < .05$), with a slight initial difference between the measured and calculated values (Figure 1). After 60 minutes of CPB, the calculated and measured values became equal. The protein mass showed a similar pattern for the respective groups, as demonstrated in Table 1.

COPp decreased significantly immediately after the start of CPB in the CT group ($P < .001$) but remained isoncotic throughout the experiments both in the Alb and HES groups (Figure 2, A). COPi decreased slightly in the CT group ($P > .05$) and remained unchanged in the Alb group, whereas a slight insignificant increase was present in the HES group (Figure 2, B). Consequently, the changes in the COPp-i gradients were most pronounced in the CT group (8.1 ± 0.8 to 2.5 ± 0.6 mm Hg, $P < .001$), followed by the HES group (7.5 ± 0.8 to 6.0 ± 0.3 mm Hg) and the Alb group (9.4 ± 0.3 to 8.3 ± 0.6 mm Hg).

Figure 3. FER during normothermic (NT-CPB) and hypothermic CPB (HT-CPB). Values are presented as means $\pm$ SEM. ** $P < .01$ compared with NT-CPB. • $P < .05$ and •• $P < .01$ compared with CT group at same time.

Fluid Additions, Net Fluid Balance, and Fluid Extravasation

Fluid additions to the CPB circuit reservoir are presented in milliliters per kilogram per minute half hourly in Table 1. FERs are displayed in Figure 3.

Immediately after the start of CPB, the FERs were 0.99 ± 0.12 mL $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$ in the CT group and 0.33 ± 0.11 and -0.24 ± 0.16 mL $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$ ($P < .001$ compared with the CT group at same time) in the Alb and HES groups, respectively. The values rapidly leveled off within 5 to 20 minutes to a new steady state. This new level (ie, the last 30 minutes of normothermic CPB; Figure 3) was used as baseline for all subsequent changes during induction of hypothermic CPB.

Immediately after the start of cooling, the FER increased significantly in the CT group ($P < .01$), from 0.15 ± 0.10 to 0.64 ± 0.12 mL $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$, whereas no such increase was observed in the interventional groups (Alb and HES groups, Figure 3). In fact, in the Alb group FER was significantly lower at 90 minutes ($P < .05$) and 120 minutes ($P < .01$) compared with that seen in the CT group. In the HES group FER remained at about 0.3 mL $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$ during normothermic and hypothermic CPB (Figure 3).

TTW

Table 2 displays the TTW in the different tissues and organs. The values were compared with those of a reference group ($n = 13$) that never underwent bypass (the non-CPB control group). When acetated Ringer solution was used as prime, TTW increased in most organs compared with the non-CPB control group (Table 2). When albumin or HES was used as prime, the TTW was greater than that of the non-CPB control group in a series of tissues and organs but

TABLE 2. Total water content (gram per gram of dry weight) in different tissues after hypothermic extracorporeal circulation

Tissue	Non-CPB (n = 13)	CT (n = 10)	Alb (n = 7)	HES (n = 7)
Right myocardium	4.17 (0.02)	4.54 (0.06)‡	4.22 (0.06)¶	4.30 (0.03)
Left myocardium	4.00 (0.04)	4.26 (0.05)†	4.10 (0.05)	4.11 (0.08)
Lung	4.16 (0.07)	5.68 (0.31)‡	5.00 (0.39)	4.94 (0.34)
Liver	2.89 (0.05)	3.28 (0.04)‡	3.25 (0.07)‡	3.24 (0.05)‡
Left kidney	4.48 (0.07)	4.68 (0.08)	4.47 (0.05)	4.36 (0.07)
Right kidney	4.56 (0.08)	4.58 (0.08)	4.43 (0.04)	4.32 (0.05)
Stomach (muscularis)	4.03 (0.09)	4.94 (0.12)‡	4.46 (0.06)*,§	4.74 (0.04)†
Stomach (mucosa)	4.41 (0.08)	4.67 (0.15)	4.30 (0.23)§	4.38 (0.16)
Pancreas	3.40 (0.10)	4.53 (0.11)‡	3.67 (0.12)*,¶	4.02 (0.24)*
Ileum (muscularis)	3.65 (0.18)	4.52 (0.24)†	4.34 (0.09)*	4.44 (0.17)*
Ileum (mucosa)	4.72 (0.05)	5.53 (0.22)†	4.74 (0.06)§	5.28 (0.23)*
Colon	3.85 (0.19)	5.05 (0.18)‡	4.38 (0.17)	4.23 (0.18)§
Skeletal muscle	3.43 (0.04)	3.98 (0.05)‡	3.74 (0.09)†,§	3.89 (0.12)†
Skin	1.93 (0.07)	2.45 (0.18)*	2.65 (0.09)†	2.31 (0.10)
Brain	3.74 (0.09)	3.84 (0.15) (n=3)	3.89 (0.05)	3.71 (0.09)

Values are presented as means $\pm$ SEM and compared with a control group that never went through CPB (non-CPB group). CPB, Cardiopulmonary bypass; CT, control group; Alb, albumin group; HES, HES group. * $P < .05$, † $P < .01$, ‡ $P < .001$ compared with non-CPB; § $P < .05$, ¶ $P < .01$, and || $P < .001$ compared with control.

significantly less than the values of the CT group, in which acetated Ringer solution was used as prime (Table 2).

Discussion

A variety of priming solutions for the extracorporeal circuit have been proposed. Albumin is one of the most common prime additives, although alternative colloids, such as dextran, HES, and gelatins, are used. The ideal colloid is still debated, and the controversy concerning crystalloids versus colloids is still ongoing.

Edema formation during and after CPB is well known to occur as a result of reduced COP in plasma. This might lead to myocardial fluid accumulation with cardiac dysfunction,¹³ an increase in extravascular lung water,¹⁴ and gastrointestinal edema.⁵ Edema of the central nervous system has also been reported.^{15,16} The rationale for adding colloids to the priming solution is to boost the plasma COP and thereby to prevent fluid leakage and edema formation.

In recent studies⁵⁻⁸ we presented data supporting a cold-induced extravasation of fluid from the circulation to the interstitial space during hypothermic CPB when acetated Ringer solution was used as prime. The present study was carried out to evaluate whether preservation of the plasma oncotic pressure could prevent or reduce this temperature-dependent fluid leakage during CPB. In brief, our hypothesis was confirmed.

Prime Solutions and Fluid Extravasation

HES or albumin was used as CPB prime, as supplemental fluid to the CPB circuit reservoir, and for blood loss substitution before and during bypass. Both solutions resulted

in stable iso-oncotic pressures in plasma throughout the experiments. Although COPp remained stable and similar in the Alb and HES groups, fluid intravasation occurred immediately after the start of CPB with HES as prime, whereas fluid was shifted out of the circulation with albumin. One possible explanation for the differences might be sought in the higher serum osmolality in the HES group compared with the 2 other groups. Consequently, the HES-induced fluid intravasation after the start of CPB resulted in a 40% decrease in Hct levels compared with a 25% decrease in the CT and Alb groups, respectively. The changes in Hct levels were not related to more pronounced bleeding in the HES group, as indicated in Table 1.

As reported in previous studies,⁵⁻⁸ the start of cooling abruptly increased the FER in the CT group. In the present study no such increase could be observed either in the HES or Alb group. In fact, in the Alb group FER remained less than that of the CT group during hypothermic CPB, whereas FER remained stable at a level in between in the HES group. To conclude, albumin and HES reduced the cold-induced fluid shift effectively. This is in line with other studies pointing out reduced weight gain after CPB, when colloids are added to the machine prime.¹⁷⁻²⁰ In a meta-analysis of 17 prospective randomized clinical trials,¹⁷ no differences could be demonstrated between albumin and artificial colloids for fluid balance across 7 studies (260 patients) and oncotic pressures across 5 studies (248 patients). In our study albumin seems to prevent fluid extravasation more effectively than HES, despite similar COPp values. The differences between albumin and HES are, however, not significant.

HES, which was used in the present study, is characterized by its mean molecular weight of 200,000 d, with 80% of the particles ranging from 13,000 to 780,000 d and with a 10% bottom fraction of less than 13,000 d. It is likely that the low-molecular-weight fraction of HES leaks from the intravascular to the extravascular space. If so, that could explain the slight increase in CO_{PI} throughout the experiments in the HES group and also the constant FER values seen both during normothermic and hypothermic CPB.

Finally, when comparing the changes in TTW, the use of albumin as prime reduced tissue edema more effectively than HES. One exception was the tendency toward lower TTW values in the brain obtained in the HES group. This might be related to the higher serum osmolality in this group and requires further investigation.

Albumin Versus Artificial Colloids

A number of authors have recommended the use of artificial colloids instead of human albumin as a cost-containment measure. However, concerns still remain about the potential adverse effects of artificial colloids, such as allergic-anaphylactic reactions, effects on hemostasis, and effects on viscosity.

The use of HES in a CPB setting has been associated with excessive postoperative bleeding and increased transfusion requirements. Postoperative bleeding was evaluated in a meta-analysis of 653 patients recruited from 16 studies. In 88% of the randomized comparisons, postoperative bleeding was lower among albumin recipients compared with HES recipients.²¹ Similar results were recently presented by Kuitunen and coworkers.²²

In a study by Sade and associates²³ comparing crystalloids with colloids (albumin and HES), differences were obtained with a substantially higher viscosity in the HES group than in the albumin and crystalloid groups, in which blood viscosity was nearly the same. This finding might be of special significance during hypothermic CPB because hypothermia per se also contributes to increased blood viscosity.

It has been hypothesized that albumin might minimize activation of blood platelets and the complement system through coating of the CPB circuit.²⁴ In addition, albumin possesses properties like antioxidant and free radical-scavenging activity, binding affinity for lipids, drugs, toxic substances, and other ligands and the ability to inhibit apoptosis in the microvascular endothelium.^{21,25} Thus far, albumin therefore should theoretically be our first-choice colloid with limited effects on viscosity and blood hemostasis and might be, by preventing fluid leakage, more effective.

Albumin Mass

The albumin mass of the CT and HES groups remained stable, indicating no net loss of albumin from the circulation

throughout the study. In the Alb group, however, an initial increase of the albumin mass was seen after the start of bypass related to the priming solution. The discrepancy between the calculated and measured albumin masses indicates a net albumin loss of about 20 g during the initial 30 minutes, which is half of the amount present in the prime. One explanation could be an initial trapping of albumin at the surfaces of the CPB circuit.²⁶ The initial albumin loss in our study was 10-fold of that reported²⁶ and could also be explained by a short-lived albumin extravasation. In human subjects plasma volume expansion with albumin led to a 50% loss during an observation period of 3 hours.²⁷ To what extent the use of alien human albumin in this porcine model influenced the transvascular shift of albumin is, to our knowledge, unknown.

Methodologic Considerations

In the present animal study a degree of hemodilution above that normally accepted in a clinical setting was used to obtain significant differences in COP_P in the interventional groups compared with in the control group.

Conclusion

Preservation of COP effectively reduces the cold-induced fluid extravasation during CPB. Albumin seems to be superior to HES in reducing tissue edema.

The Board of the Faculty of Medicine, University of Bergen, has authorized the "Locus for Circulatory Research" as an officially recognized research group within the faculty. We greatly acknowledge this support. We also acknowledge the support and fruitful discussions with Stein-Erik Rynning, MD, PhD, and Henning Onarheim, MD, PhD. The technical assistance of Finn Eliassen, RP; Arve Mongstad, RP; Lill Andreassen; Gry Hilde Nilsen; and Cato Johnsen is greatly appreciated. Support from the laboratory of clinical biochemistry is appreciated.

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