Cardiopulmonary Bypass Priming Using a High Dose of a Balanced Hydroxyethyl Starch Versus an Albumin-Based Priming Strategy

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BACKGROUND: The optimal priming solution for cardiopulmonary bypass (CPB) is unclear. In this study, we evaluated the influence of high-volume priming with a modern balanced hydroxyethyl starch (HES) preparation on coagulation, inflammation, and organ function compared with an albumin-based CPB priming regimen.

METHODS: In 50 patients undergoing coronary artery bypass grafting, the CPB circuit was prospectively and randomly primed with either 1500 mL of 6% HES 130/0.42 in a balanced electrolyte solution (Na^+ 140 mmol/L, Cl^- 118 mmol/L, K^+ 4 mmol/L, Ca^{2+} 2.5 mmol/L, Mg^{++} 1 mmol/L, $acetate^-$ 24 mmol/L, $malate^-$ 5 mmol/L) ($n = 25$) or with 500 mL of 5% human albumin plus 1000 mL 0.9% saline solution ($n = 25$). Inflammation (interleukins [IL]-6, -10), endothelial damage (soluble intercellular adhesion molecule-1), kidney function (kidney-specific proteins α-glutathione *S*-transferase, neutrophil gelatinase-associated lipocalin), coagulation (measured by thrombelastometry [ROTEM®, Pentapharm, Munich, Germany]), and platelet function (measured by whole blood aggregometry [Multiplate® analyzer, Dynabyte Medical, Munich, Germany]) were assessed after induction of anesthesia, immediately after surgery, 5 h after surgery, and on the morning of first and second postoperative days.

RESULTS: Total volume given during and after CPB was 3090 ± 540 mL of balanced HES and 3110 ± 450 mL of albumin. Base excess after surgery was lower in the albumin-based priming group than in the balanced HES priming group (−5.9 ± 1.2 mmol/L vs +0.2 ± 0.2 mmol/L, $P = 0.0003$). Plasma levels of IL-6, IL-10, and intercellular adhesion molecule-1 were higher after CPB in the albumin-based priming group compared with the HES priming group at all time periods ($P = 0.0002$). Urinary concentrations of α-glutathione *S*-transferase and neutrophil gelatinase-associated lipocalin were higher after CPB through the end of the study in the albumin group compared with the balanced HES group ($P = 0.00004$). After surgery through the first postoperative day, thrombelastometry data (clotting time and clot formation time) revealed more impaired coagulation in the albumin-based priming group compared with the HES priming group ($P = 0.004$). Compared with baseline, platelet function was unchanged in the high-dose balanced HES priming group after CPB and 5 h after surgery, but it was significantly reduced in the albumin-based priming group.

CONCLUSION: High-volume priming of the CPB circuit with a modern balanced HES solution resulted in reduced inflammation, less endothelial damage, and fewer alterations in renal tubular integrity compared with an albumin-based priming. Coagulation including platelet function was better preserved with high-dose balanced HES CPB priming compared with albumin-based CPB priming.

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The ideal strategy for priming of the cardiopulmonary bypass (CPB) circuit in adult cardiac surgery is still a matter of debate.[1–6] In many institutions, either albumin or nonprotein synthetic colloids (gelatins, dextrans, hydroxyethyl starch [HES]) are added to the crystalloid-based prime. HES preparations are classified based on their mean molecular weight (MW; low MW HES: 70 kD; medium MW HES: from 130 to 260 kD; high MW [HMW] HES: >450 kD), their molar substitution (MS; high MS: >0.7; medium MS: >0.5; low MS: >0.5), and their ratio of the C_2:C_6 hydroxyethylation. The importance of the diluent solution of HES has been recently emphasized.[7,8] Most colloids (including albumin) are diluted in 0.9% normal saline that contains nonphysiologically high concentrations of sodium (154 mmol/L) and chloride (154 mmol/L) that might contribute to hyperchloremic acidosis.[9] Modern HES preparations are dissolved in an electrolyte solution closer in composition to plasma ("balanced" or "plasma adapted" solutions). The purpose

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of this study was to assess the effects of a high-volume CPB priming with a balanced modern HES preparation with a low MW and a low MS on inflammation, coagulation, and kidney function compared with an albumin-based priming strategy.

METHODS

Patients and Grouping

Fifty consecutive patients undergoing elective coronary artery bypass grafting were studied after approval of the IRB and after receiving individual written informed consent. Patients were excluded from study for kidney dysfunction (serum creatinine [sCR] concentration >2.0 g/dL; chronic oliguria/anuria requiring dialysis), liver insufficiency (aspartate aminotransferase >40 U/L, alanine aminotransferase >40 U/L), or current corticosteroid treatment.

The patients were prospectively randomized into one of the two groups by a computer-generated list and sealed envelopes. In group HES ($n = 25$), priming of the CPB circuit consisted of 1500 mL of balanced 6% HES 130/0.42 containing Na^+ 140 mmol/L, Cl^- 118 mmol/L, K^+ 4 mmol/L, Ca^{2+} 2.5 mmol/L, Mg^{++} 1 mmol/L, acetate$^-$ 24 mmol/L, and malate^{2-} 5 mmol/L (Tetraspan®, B. Braun, Melsungen, Germany). In the albumin group ($n = 25$), the CPB circuit was primed with 500 mL 5% human albumin dissolved in 0.9% normal saline (Na^+ 154 mmol/L, Cl^- 154 mmol/L) with an additional 1000 mL of normal saline. Perioperatively, IV volume was given when mean arterial blood pressure (MAP) was <60 mm Hg and pulmonary capillary wedge pressure (PCWP) or central venous pressure (CVP) was <10 mm Hg to a target of 12–14 mm Hg. In group HES, balanced HES and a balanced crystalloid containing Na^+ 140 mmol/L, Cl^- 127 mmol/L, K^+ 4 mmol/L, Ca^{2+} 2.5 mmol/L, Mg^{2+} 1 mmol/L, acetate$^-$ 24 mmol/L, and malate^{2-} 5 mmol/L (Sterofundin Iso®, B. Braun) was given in a 1:2 ratio. In the albumin group, albumin or saline solution was given in a 1:2 ratio.

Anesthesia induction and maintenance were performed with sufentanil (total dose: 5–7 μg/kg), midazolam (total dose: 0.3 mg/kg), and pancuronium bromide (total dose: 0.35–0.4 mg/kg). Desflurane was given and titrated based on clinical assessments. CPB was performed using nonpulsatile blood flow at 2.4 $L \cdot min^{-1} \cdot m^2$, a nonheparin coated circuit, and a membrane oxygenator (Terumo System 1™, Terumo, Leuven, Belgium). St. Thomas cardioplegic solution was used for myocardial preservation. The patients received tranexamic acid (2 g after anesthesia induction and then 6 $mg \cdot kg^{-1} \cdot h^{-1}$, with 1 g added to the CPB prime). During CPB, body temperature was kept >34°C (bladder temperature). Norepinephrine was given to maintain MAP >60 mm Hg during CPB. HES or albumin was added to maintain sufficient filling of the extracorporeal circuit. Leukocyte-depleted packed red blood cells (PRBCs) were given when hemoglobin was <7 g/dL. After termination of CPB, the blood from the CPB circuit was given to the patient without processing after sternal closure.

Table 1. Patient Demographic and Perioperative Data

	High-dose HES group ($n = 25$)	Albumin-based group ($n = 25$)	P
Demographics			
Age (yr)	69 ± 4	70 ± 5	0.8
Weight (kg)	83 ± 13	80 ± 11	0.9
Height (cm)	170 ± 5	167 ± 8	0.9
Gender (F/M)	14/11	12/13	0.7
Preoperative medication			
Aspirin	14	15	0.6
Beta-blockers	15	16	0.9
ACE inhibitors	12	12	
Nitrates	6	8	0.6
AT_1 inhibitors	10	9	0.9
Oral antidiabetics	5	4	0.7
Other antihypertonic drugs	5	6	0.6
Diuretics	9	6	0.2
Statins	10	12	0.3
Time of (min)			
Anesthesia	256 ± 57	253 ± 50	0.4
CPB	72 ± 25	73 ± 23	0.9
Cross-clamp	54 ± 16	59 ± 15	0.4
Intubation	400 ± 98	425 ± 101	0.5
Outcome			
ICU mortality (MOF)	1	1	

CPB = cardiopulmonary bypass; ICU = intensive care unit; MOF = multiorgan failure; ICU = intensive care unit; HES = hydroxyethyl starch.

All patients were transferred to the intensive care unit (ICU) where their lungs were mechanically ventilated. Tracheal extubation was performed when hemodynamics were stable, temperature was >36°C, and there was adequate spontaneous breathing (Pao_2 >80 mm Hg with FIO_2 0.3, breathing frequency <15/min). After surgery, PRBCs were given when the hemoglobin was <9 g/dL, and fresh frozen plasma (FFP) was given when there was excessive bleeding (>400 mL/h) in the presence of an activated partial thromboplastin time >60 s. Platelet concentrates were given when bleeding continued (>400 mL/h) despite a normal activated clotting time. Epinephrine or dobutamine was given when MAP was <60 mm Hg and cardiac index was <2.5 $L \cdot min^{-1} \cdot m^2$ despite administration of IV volume to reach PCWP (or CVP) >16 mm Hg (target for cardiac index: 2.5–3.0 $L \cdot min^{-1} \cdot m^2$). Norepinephrine was given when systemic vascular resistance was <600 $dyn \cdot s^{-1} \cdot cm^{-5}$ and MAP was <60 mm Hg.

Measurements

Hemodynamic measurements included heart rate, MAP, pulmonary artery pressure, PCWP, CVP, and cardiac output (by pulmonary artery catheter). sCR concentrations were measured using Jaffé reaction (Modular, Roche, Mannheim, Germany). Urine α-glutathione *S*-transferase (α-GST) was measured by

Table 2. Hemodynamics in the Two Groups

	Baseline	End of surgery	5 h after surgery	First POD	Second POD
MAP (mm Hg)					
High-dose HES	70 ± 9	72 ± 8	78 ± 10	82 ± 12	85 ± 12
Albumin	72 ± 10	75 ± 10	79 ± 9	78 ± 8	82 ± 10
HR (bpm)					
High-dose HES	66 ± 11	83 ± 11	88 ± 10	86 ± 10	89 ± 12
Albumin	62 ± 12	87 ± 14	85 ± 12	85 ± 14	87 ± 11
PAP (mm Hg)					
High-dose HES	20 ± 4	26 ± 6	24 ± 5	21 ± 7	
Albumin	22 ± 5	23 ± 7	26 ± 4	23 ± 4	
PCWP (mm Hg)					
High-dose HES	10 ± 3	14 ± 3	14 ± 4	12 ± 3	
Albumin	10 ± 2	13 ± 4	12 ± 4	13 ± 5	
CVP (mm Hg)					
High-dose HES	10 ± 4	12 ± 4	11 ± 4	12 ± 3	13 ± 3
Albumin	9 ± 3	13 ± 3	13 ± 3	13 ± 5	14 ± 3
CI ($L \cdot min^{-1} \cdot m^{-2}$)					
High-dose HES	2.19 ± 0.3	2.49 ± 0.3	2.68 ± 0.4	2.79 ± 0.3	
Albumin	2.15 ± 0.3	2.36 ± 0.2	2.44 ± 0.3	2.75 ± 0.4	

MAP = mean arterial blood pressure; HR = heart rate; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; CI = cardiac index; POD = postoperative day.

Table 3. Use of Catecholamines and Diuretics

	End of surgery	During CPB	5 h after surgery	First POD	Second POD
Norepinephrine (number of patients/ range [$\mu g \cdot kg^{-1} \cdot min^{-1}$])					
High-dose HES	9/2–12	9/2–6	7/2–8	1/2	1/3
Albumin	8/4–10	7/2–6	10/2–8	1/3	—
Epinephrine (number of patients/ range [$\mu g \cdot kg^{-1} \cdot min^{-1}$])					
High-dose HES	6/2–6	—	3/2–8	4/3–6	1/6
Albumin	5/2–6	—	4/2–6	4/2–4	1/6
Dobutamine (number of patients/ range [$\mu g \cdot kg^{-1} \cdot min^{-1}$])					
High-dose HES	11/3–8	—	4/3–6	8/2–6	3/2–6
Albumin	10/2–6	—	5/2–6	9/1–5	3/2–6
Furosemide (number of patients/ median cumulative [mg])					
High-dose HES	2/10	—	2/35	3/30	2/10
Albumin	2/40	—	2/30	4/25	2/10

POD = postoperative day; CPB = cardiopulmonary bypass; HES = hydroxyethyl starch.

enzyme immunoassay (Nephkit™-Alpha, Biotrin International, Sinsheim-Reihen, Germany). Normal values for this assay are 3.5 ± 11.1 μg/L (mean ± 2 SD). Urine neutrophil gelatinase-associated lipocalin (NGAL) was analyzed by sandwich enzyme-linked immonosorbent assay using microwells coated with monoclonal antibody against human NGAL (Kit 0236, Antibody Shop, Grusbakken, Denmark). Normal values are 0.7–9.8 ng/mL and the lowest sensitivity is 0.5 ng/mL.

Plasma interleukin-6 (IL-6) and IL-10 were measured using commercially available solid-phase two-site chemiluminescent enzyme immunometric assays (Diagnostic Product Corporation, Los Angeles, CA). Normal values for IL-6 are <5 pg/dL and 2–24 pg/mL for IL-10. The lower limit of detection for IL-6 is 0.5 pg/dL and for IL-10 is 1 pg/dL.

Plasma levels of soluble intercellular adhesion molecule-1 (sICAM-1) were measured from arterial blood samples using enzyme-linked immonosorbent assay (British Bio-technology Products, Abington, UK). Normal range for this assay is 200–300 ng/mL.

A four-channel analyzer was used to measure rotational thrombelastometry (ROTEM®, Pentapharm, Munich, Germany). ROTEM analysis relies on continuous measurement of clot firmness, allowing the determination of the onset of coagulation (coagulation time [CT], standard TEG®: reaction time), kinetics of clot formation (clot formation time [CFT], standard TEG: CT), and maximum clot firmness [MCF], standard TEG: maximal amplitude). Clot formation was measured after recalcification of 300 μL of whole blood (20 μL of calcium chloride 0.2 M) and adding thromboplastin-phospholipid (20 μL) to monitor the intrinsic system (IntrinsicROTEM). The contact activator is ellagic acid. Clot formation was monitored after addition of calcium chloride to 300 μL of whole blood

Table 4. Intravenous and CPB Prime Volume Administered for Groups 1 and 2

	Surgery	5 h after surgery	Until first POD	Until second POD
Crystalloids (mL)				
High-dose HES	1070 ± 220*	2010 ± 310*	3220 ± 400*	4010 ± 410*
Albumin	2490 ± 340	3380 ± 300	5000 ± 360	5450 ± 560
Colloids (mL)				
High-dose HES	2195 ± 280*	2210 ± 250	2870 ± 260	3090 ± 340
Albumin	1580 ± 240	1980 ± 230	2820 ± 210	3110 ± 350
Drainage blood loss (mL)				
High-dose HES	540 ± 70	790 ± 170*	1070 ± 260*	1200 ± 290*
Albumin	610 ± 120	1130 ± 220	1440 ± 230	1520 ± 210
Urine output (mL)				
High-dose HES	880 ± 320	2880 ± 400	4780 ± 420*	6500 ± 730*
Albumin	860 ± 300	2270 ± 410	4010 ± 410	5420 ± 700
Blood/blood products (units)				
PRBC (total number/group)				
High-dose HES	320 ± 300 (28)*	350 ± 290 (32)*	350 ± 290 (32)*	380 ± 300 (36)*
Albumin	520 ± 490 (46)	580 ± 480 (56)	600 ± 490 (60)	600 ± 490 (60)
FFP (total number/group)				
High-dose HES	60 ± 210 (8)	60 ± 210 (8)*	60 ± 210 (8)*	60 ± 210 (8)*
Albumin	100 ± 260 (12)	200 ± 319 (26)	250 ± 370 (32)	250 ± 370 (32)
Platelets (number/group)				
High-dose HES	—	—	—	—
Albumin	—	—	—	—

Data are mean ± SD.

High-dose HES: high-dose balanced HES; Albumin: albumin-based priming; blood loss postoperatively: chest tube drainage.

HES = hydroxyethylstarch; FFP = fresh frozen plasma; PRBC = packed red blood cells; POD = postoperative day; CPB = cardiopulmonary bypass.

* $P < 0.05$ different between the groups.

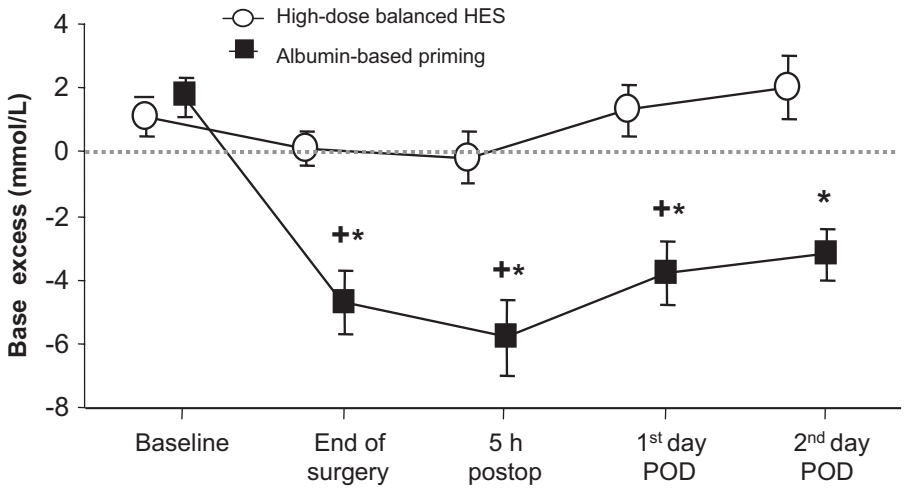

Figure 1. Changes in base excess (BE) in the albumin and hydroxyethyl starch (HES) cardiopulmonary bypass (CPB) priming groups. Mean (SD); POD = postoperative day. $+P < 0.05$ compared with baseline data; $*P < 0.05$ between the study groups. -○-: High-dose balanced HES; -■-: albumin-based priming.

and addition of liquid-stable thromboplastin reagent derived from rabbit brain (i.e., tissue factor + phospholipids) (20 μL) for monitoring the extrinsic system (ExtrinsicROTEM).

Platelet function was assessed with a whole blood platelet function analyzer (Multiplate®, Dynabyte Medical, Munich, Germany). This test measures electrical impedance between electrodes immersed in whole blood.[9] Blood is stirred using an electromagnetic stirrer at 800 rpm. The attachment of platelet aggregates on the electrodes increases impedance. The change of the impedance is transformed to arbitrary aggregation units and plotted against time. Three hundred microliters of blood was withdrawn into a tube containing hirudin and then mixed with 300 μL of prewarmed isotonic saline solution. After incubation for 3 min, 20 μL of activating substrate was added to the blood sample. Activated platelet function was recorded for 6 min. The area under the curve of the clotting procedure of each measurement was measured and averaged. Platelet function was assessed for each sample after the addition of adenosine diphosphate (ADPTest® 2 mM/mL, Instrumentation Laboratory, Munich, Germany), thrombin-activating protein (TRAPTest® 1 mM/mL, Instrumentation Laboratory), and collagen (COLTest® 100 μg/mL, Instrumentation Laboratory). Measurements were performed in duplicate within 30 min after blood withdrawal always by the same person who was blinded to the grouping.

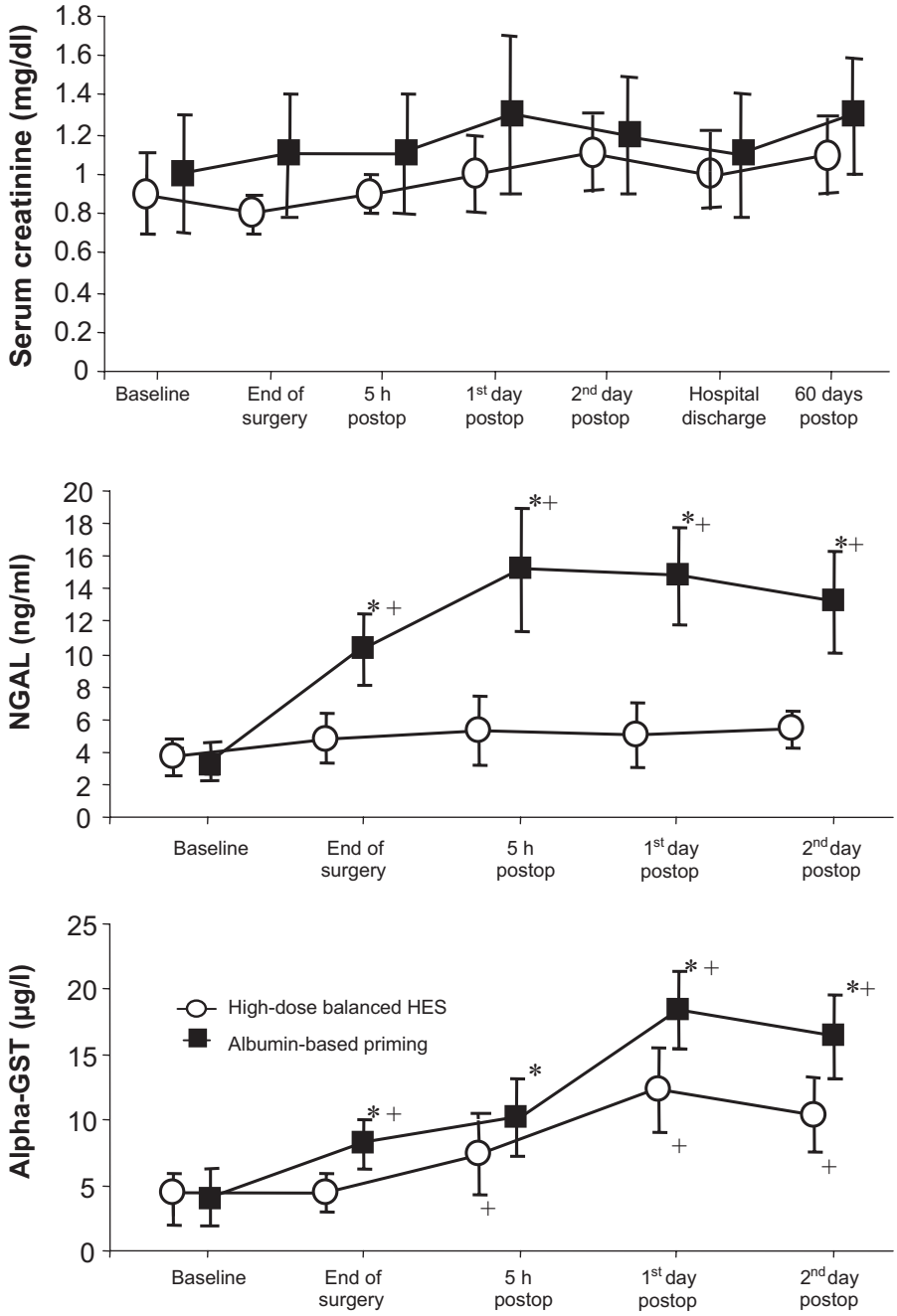

Figure 2. Changes in serum creatinine (sCr) and in α-glutathione *S*-transferase (α-GST) (normal value: 3.5 ± 11.1 µg/L [mean ± 2 SD]) and neutrophil gelatinase-associated lipocalin (NGAL) (normal value: 5.3 ng/mL [range, 0.7–9.8 ng/mL]). Data for sCr at discharge from the hospital and data after discharge from the hospital: $n = 24$ in both groups. Mean (SD); POD = postoperative day. $+P < 0.05$ compared with baseline data; $*P < 0.05$ between the study groups. -○-: High-dose balanced hydroxyethyl starch (HES); -■-: albumin-based priming.

Hemodynamic and all laboratory measurements were made after induction of anesthesia (before any IV volume was administered), at the end of surgery, 5 h after surgery (in the ICU), and at the morning of the first and second postoperative day (POD) in the ICU. A questionnaire was sent to the patients' primary physician to receive information on patients' sCr, renal failure requiring renal replacement therapy, and mortality approximately 60 days after hospital discharge.

Data Analysis

Data from Tamayo et al.[10] were used for power analysis. We hypothesized that the use of HES for CPB priming would reduce IL-6 levels after surgery by 30% compared with albumin priming. Based on this assumption, 20 patients in each group would be needed to detect this difference with an α of 0.05 and a power of 80%.

Data are expressed as mean and standard deviation unless otherwise indicated. χ^2 test was used to analyze categorical data. Normally distributed data (tested by Kolmogorov-Smirnov test) were analyzed using Student's *t*-test. Two-way analysis of variance with repeated measures and *post hoc* Scheffé test were used to determine the effects of group, time, and group-time interaction. When multiple comparisons were made, Bonferroni correction was done (serially measured data, e.g., for hemodynamics, biochemical data). Mann–Whitney *U*-test or the Kruskal–Wallis *H*-test was also

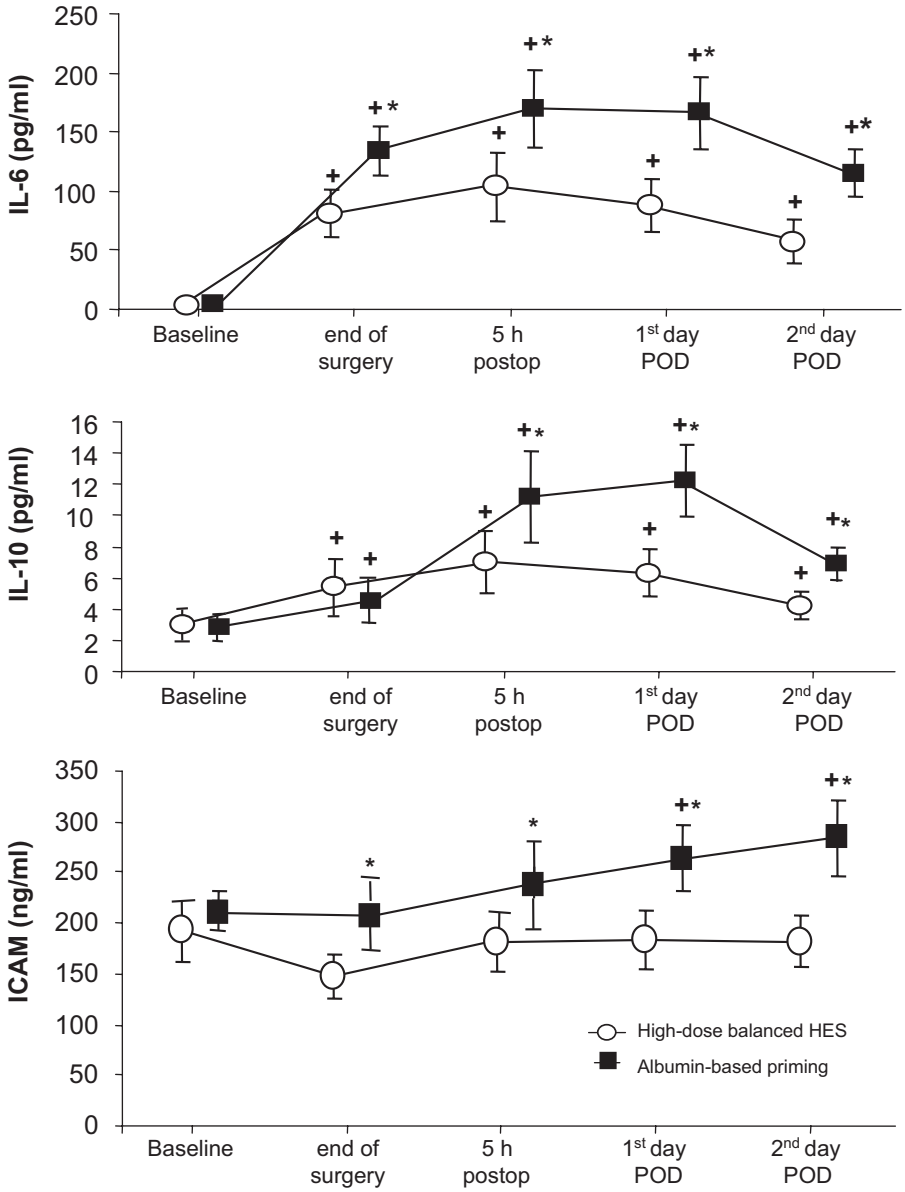

Figure 3. Plasma levels of interleukin-6 (IL-6; normal value: <5 pg/dL), interleukin-10 (IL-10; normal values: 2–24 pg/dL), and soluble intercellular adhesion molecule-1 (sICAM-1; normal range: 200–300 ng/mL). Mean (standard deviation); POD = postoperative day. $+P < 0.05$ compared with baseline data; $*P < 0.05$ between the study groups. -○-: High-dose balanced hydroxyethyl starch (HES); -■-: albumin-based priming.

used when appropriate. A MedCalc 4.30 (MedCalc Software, Mariakerke, Belgium) software package was used for statistical analyses. A P value <0.05 was considered significant.

RESULTS

Patient demographic and medical information are listed in Table 1. There were no differences between the groups in the listed variables. Hemodynamic results, use of diuretics, norepinephrine, and positive inotropes were not different between the two groups (Tables 2 and 3). No patient suffered from acute renal failure requiring renal replacement therapy during or after hospitalization (physicians' response rate, 80%). Duration of hospitalization in the ICU and on the postoperative ward did not differ between the two groups.

The total volume of colloid given was similar between the groups (3090 ± 540 mL of balanced HES and 3110 ± 450 mL of albumin) (Table 4). Total urine output was higher in the HES group than in the albumin group. Postoperative chest tube drainage was higher (P = 0.003), transfusion of PRBCs and FFP more frequent, and base excess lower in the albumin group compared with the HES group (Table 4 and Fig. 1).

Renal Function

sCR, α-GST, and NGAL results are shown in Figure 2. sCR did not change from baseline during the study period for either group. Even approximately 60 days after surgery, no differences in sCr were found between groups. Kidney-specific proteins α-GST and NGAL levels were within normal range at baseline in both groups. α-GST levels increased significantly from baseline in the albumin group at all measurement time points after surgery. This protein was higher on the first and second POD compared with baseline in the HES group. α-GST was higher after surgery in the albumin group compared with the HES group and remained significantly higher in the albumin than the HES group until the second POD.

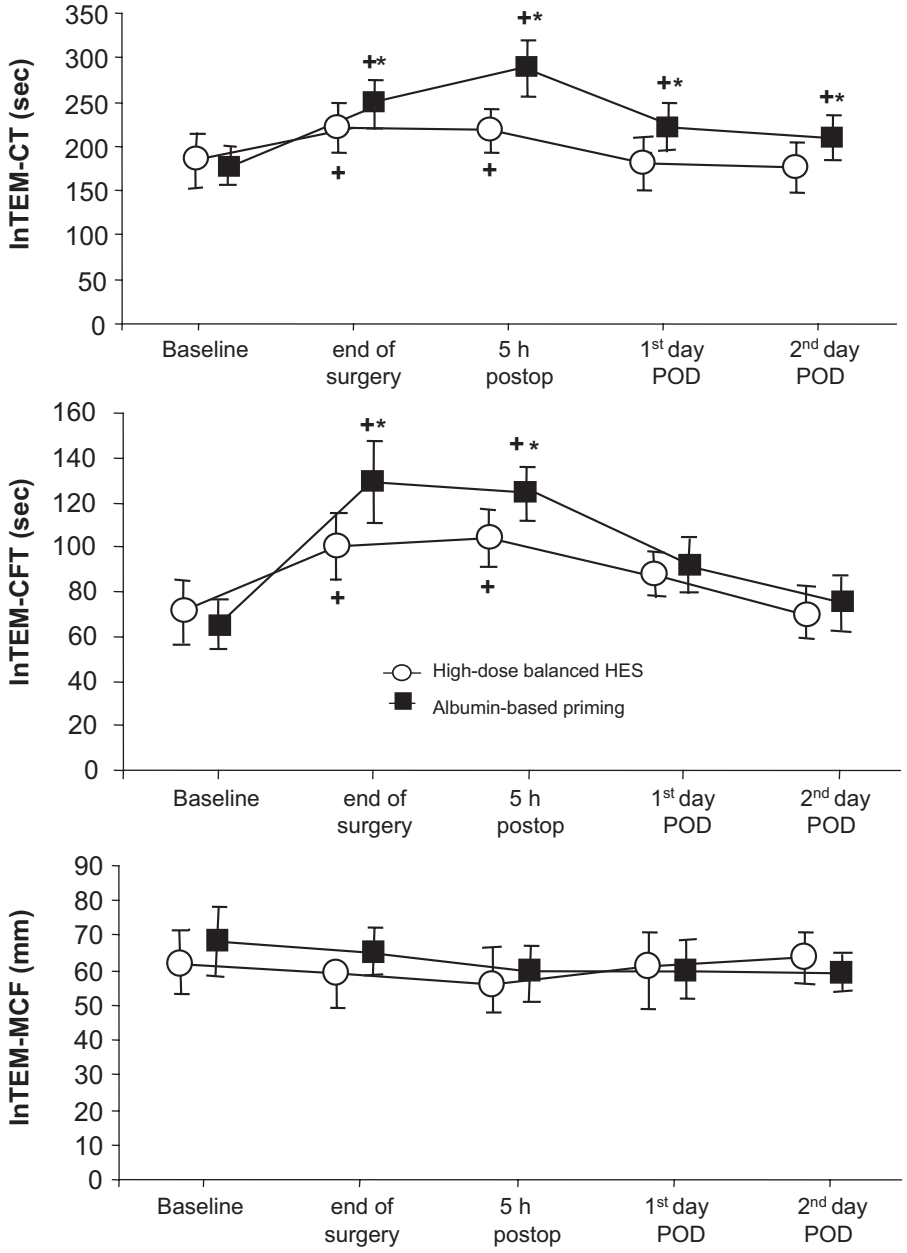

Figure 4. Perioperative changes in coagulation time (CT) (onset of coagulation; normal values: 137–246 s), clot formation time (CFT) (kinetics of clot formation; normal values: 40–100 s), and maximum clot firmness (MCF) (normal values: 52–72 mm) using extrinsic activation (IntrinsicROTEM®). Data are presented as mean ± SD. $+P < 0.05$ compared with baseline data; $*P < 0.05$ between the study groups. -○-: High-dose balanced hydroxyethyl starch (HES); -■-: albumin-based priming.

NGAL concentrations were higher after surgery compared with baseline in the albumin group but not the HES group. NGAL levels were higher through the end of the study in the albumin group compared with the HES group.

Inflammation/Endothelial Integrity

Plasma inflammatory and endothelial marker results are shown in Figure 3. IL-6, IL-10, and ICAM-1 plasma levels were normal at baseline in both groups. Plasma levels of IL-6 and IL-10 were higher after surgery compared with baseline in both groups. Plasma IL-6 and IL-10 levels were higher 5 h after surgery through the second POD in the albumin group compared with the HES group. Plasma levels of ICAM-1 were not different after surgery compared with baseline in the HES group. In contrast, ICAM-1 plasma levels were higher on the first and second POD in the albumin group compared with baseline. Plasma ICAM-1 levels were higher than those measured in the HES group at all measured time points after surgery.

Thrombelastometry

Thrombelastometry results are shown in Figures 4 and 5. At baseline, InTEG- and ExTEG-CT, CFT, and MCF were within the normal range in both groups. After CPB, CT and CFT increased from baseline in both groups. Compared with baseline, these measurements were higher at all postoperative measurements in the albumin group but only at the end of surgery and 5 h after surgery in the HES group. InTEG-CT and ExTEG-CT were higher in the albumin group compared with the HES group at all measurement periods. InTEG-CFT and ExTEG-CFT were higher in the albumin group compared with the HES group at the end of

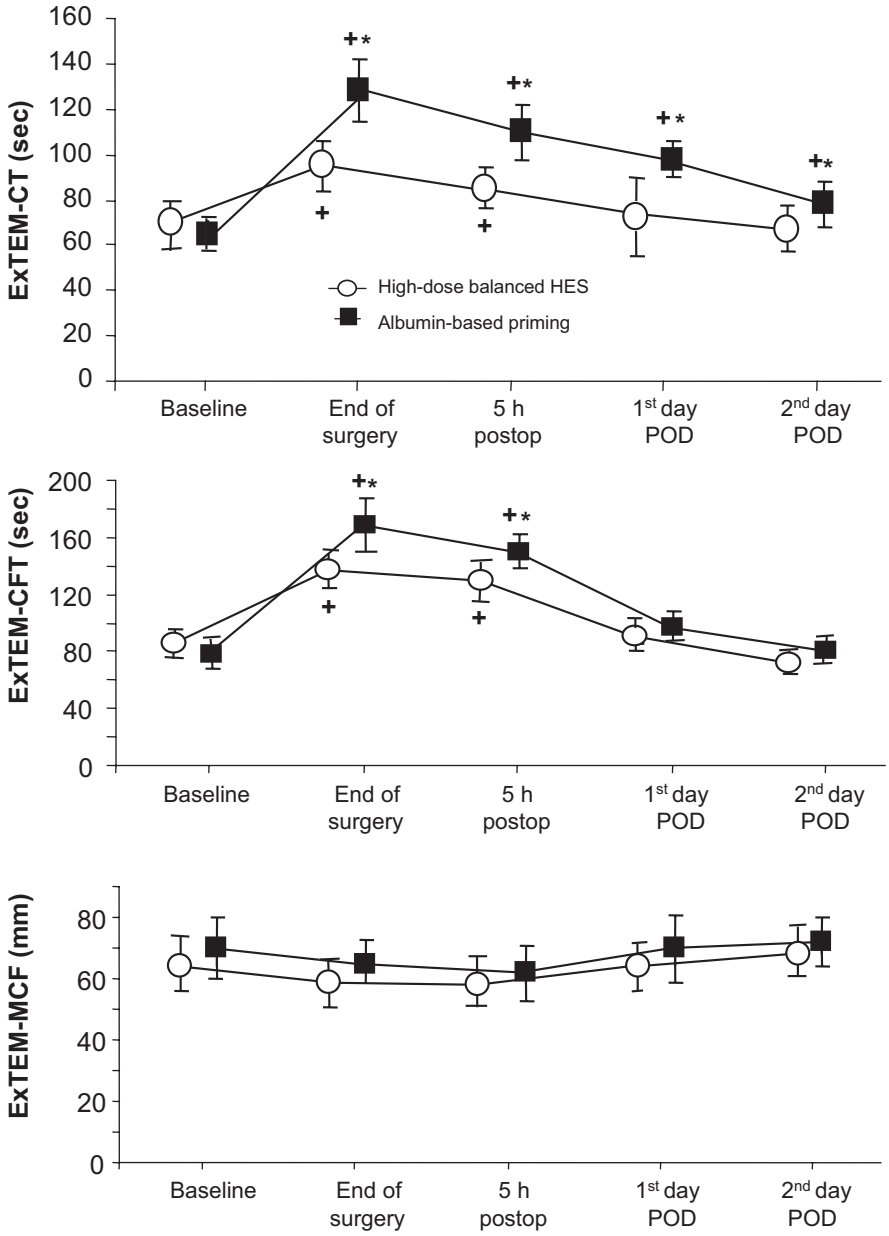

Figure 5. Perioperative changes of coagulation time (CT) (onset of coagulation; normal values: 42–74 s), clot formation time (CFT) (kinetics of clot formation; normal values: 46–148 s), and maximum clot firmness (MCF) (normal values: 49–72 mm) using extrinsic activation (ExtrinsicROTEM®). Data are presented as mean ± SD. $+P < 0.05$ compared with baseline data; $*P < 0.05$ between the study groups. -○-: High-dose balanced hydroxyethyl starch (HES); -■-: albumin-based priming.

surgery and 5 h after surgery. There were no differences in MCF from baseline in either group.

Whole Blood Aggregometry

Whole blood aggregometery data are shown in Figure 6. Platelet aggregation was normal at baseline in both groups. Platelet aggregation in response to all inductors remained unchanged compared with baseline in the HES group throughout the entire study. In contrast, platelet aggregation induced by all three inductors was reduced immediately after surgery and 5 h after surgery in the albumin group. Platelet function was not different between the two groups on the first and second POD.

DISCUSSION

In this study, we found that the use of high-dose CPB priming with a modern balanced HES preparation was associated with significantly less inflammatory response, tubular dysfunction, and coagulation alterations after surgery compared with an albumin-based priming regimen.

The influence of HES on renal function is of particular interest in light of data showing an increased incidence of acute renal failure in septic patients receiving an unbalanced hypertonic 10% HES 200/0.5.[11] In our study, we evaluated renal function with sCr as well with α-GST and NGAL because subclinical alterations in renal function have been reported in the absence of overt changes in sCr.[12] Urinary α-GST is a marker of proximal tubular injury.[12] NGAL, a member of the lipocalin superfamily, is a 25-kDa protein covalently bound to gelatinase from human neutrophils.[13] NGAL is usually barely detectable in human tissues including the kidney, but its levels are upregulated by ischemia predominantly in the proximal tubules. NGAL is, thus, suggested to be an early biomarker of acute renal injury.[14] We found no changes in sCr

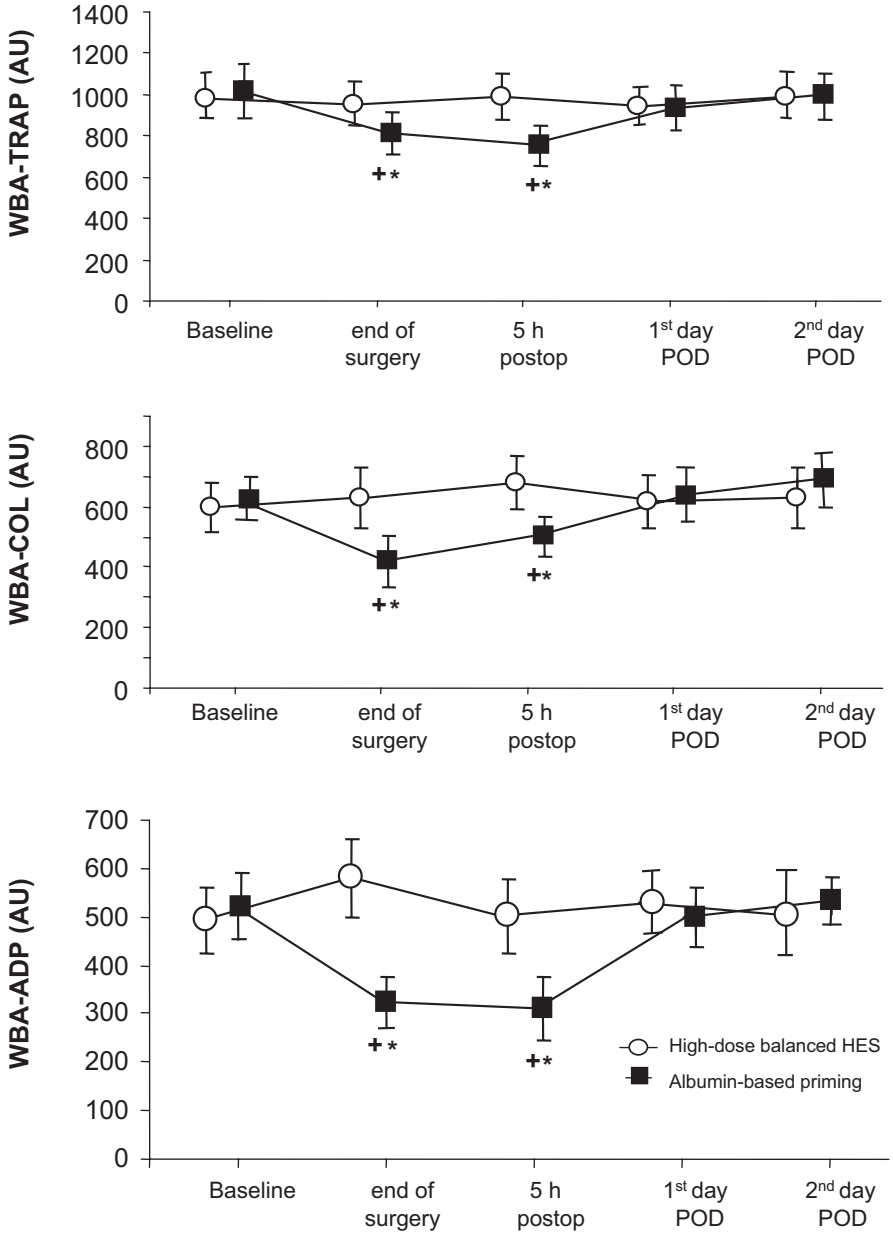

Figure 6. Perioperative changes in whole blood aggregometry using thrombin-activating protein (TRAP) (normal: 927–1565), collagen (COL) (normal: 546–1134), and adenosine diphosphate (ADP) (normal: 369–1180) as stimulators. AU = arbitrary aggregation units. Data are presented as mean ± SD. $+P < 0.05$ different from baseline data, $*P < 0.05$ between the study groups. ⊸: High-dose balanced hydroxyethyl starch (HES); ■: albumin-based priming.

perioperatively after approximately 60 days after hospital discharge in both groups indicating no long-term negative renal effects of this HES preparation compared with albumin CPB priming. Urinary concentrations of both NGAL and α-GST were significantly higher immediately after surgery and 5 h later in the ICU in the albumin group compared with the HES group. These findings suggest better preservation of tubular function with HES CPB priming. One reason for these findings might be that the high concentrations of chloride in the albumin and the saline solution might have had negative effects on kidney function and kidney integrity.[15]

Cardiac surgery using CPB results in an inflammatory response and activation of the coagulation system.[16] We found lower plasma levels of the proinflammatory cytokine IL-6, antiinflammatory cytokine IL-10, and adhesion molecule ICAM-1 after CPB in the HES group compared with the albumin group, suggesting less inflammation and less impaired endothelial integrity with the former CPB priming strategy. These findings are consistent with other investigations suggesting potential beneficial effects on inflammation and endothelial function from HES.[17,18] It has been shown in an experimental shock model that avoiding hyperchloremic acidosis reduced the levels of proinflammatory cytokines.[19,20] In our study, base excess in the HES priming group remained almost unchanged from baseline and remained higher than in the albumin-based priming group. These findings suggest that CPB priming with albumin dissolved in normal saline may have led to hyperchloremic acidosis.

Impaired blood coagulation is a major concern with the use of HES in patients undergoing cardiac surgery.[21] The Food and Drug Administration in the United States required a product labeling change for 6% HMW (>500 kD) HES with a high MS (0.7)

dissolved in saline specifically recommending that this solution be avoided in patients undergoing surgery with CPB.[22] The varying physical-chemical characteristics of the different HES preparations are of fundamental importance when considering the effects on coagulation.[23] Dissolving HES in a balanced, plasma-adapted solution may minimize coagulation perturbations.[8,24–26] Indeed, in our study, CPB priming with a balanced modern HES preparation resulted in fewer coagulation derangements shown by thrombelastometry than with albumin plus saline CPB priming. Nonetheless, larger studies are needed to confirm the safety of the former solution in this population of patients.

The effect of HES on platelet function during cardiac surgery is an additional concern.[3,27] HES has been described to adversely affect platelet function depending on the type of HES preparation. Franz et al.[28] studied the effects of IV infusion of saline solution and four HES preparations with different MW and MS on platelet function assessed by the Platelet Function Analyzer 100 (PFA-100™). HES 450/0.7, HES 200/0.6, and HES 70/0.5 prolonged PFA-100 closure times indicating impaired platelet function. These HES preparations all reduced platelet glycoprotein (GP) IIb/IIIa expression. In contrast, HES 130/0.4 was not associated with negative effects on platelet function. Stögermüller et al.[29] observed reduced adenosine diphosphate and thrombin-activating protein-induced expression of platelet GP IIb/IIIa after infusion of a nonbalanced medium MW HES (HES 200). By contrast, an *in vitro* study found increased GP IIb/IIIa expression with HMW, high MS HES in a balanced solution (Hextend®, BioTime, Inc., Berkeley, CA).[30] This unexpected platelet-stimulating effect of this HMW, high-MS HES preparation may have been induced by the solvent containing calcium chloride dihydrate (2.5 mmol/L). We also found better preserved platelet function in our balanced (Ca^{2+}-containing) HES group than in the albumin plus saline group.

In our study, the albumin group received significantly more PRBC and FFP transfusions than the HES group. Because allogeneic blood transfusion may be associated with increased inflammation,[31] this might have contributed to our findings of an increased inflammatory response in the albumin group. Only leukocyte-depleted blood, however, was given to patients in this study, which less likely modulated PRBC transfusion-induced inflammatory responses.[31] The higher use of FFP in the albumin group may have affected our coagulation and platelet function results.

In summary, a high-dose CPB priming strategy with a modern balanced HES preparation resulted in less inflammatory response, fewer alterations in endothelial integrity, more preserved coagulation function, and preserved kidney integrity than an albumin-based priming regimen. Further investigations are needed to confirm this beneficial effect of CPB priming with this HES solution for managing patients undergoing cardiac surgery.

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