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Institutional report - Cardiopulmonary bypass

Clinical performance and biocompatibility of hyaluronan-based heparin-bonded extracorporeal circuits in different risk cohorts☆

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Abstract

This prospective randomized study compares novel hyaluronan-based heparin-bonded circuits vs. uncoated controls across EuroSCORE patient risk strata including biomaterial evaluation. Over a two-year period, 90 patients undergoing coronary artery bypass grafting were prospectively randomized to one of the two perfusion protocols: Group 1 was treated with hyaluronan-based heparin-bonded preconnected circuits (Vision HFO-GBS™, Gish, CA, USA) and Group 2 with identical uncoated controls. Each group was composed of three subgroups ($n=15$) with respect to preoperative evaluation of low (EuroSCORE 0–2), medium (3–5) and high (6+) risk patients. Blood samples were collected after induction (T1) and heparinization (T2), 15 min after cardiopulmonary bypass start (T3), before cessation of CPB (T4), 15 min after reversal (T5), and the first postoperative day (T6). In high-risk patients, platelet counts demonstrated significant preservation at T4, T5 and leukocyte counts were lower at T5 in hyaluronan group ($P \leq 0.05$ vs. control). C3a ($ng \cdot ml^{-1}$) levels were significantly lower at T3 (0.2 ± 0.04 vs. 0.31 ± 0.05), T4 (0.25 ± 0.04 vs. 0.51 ± 0.05), T5 (0.38 ± 0.04 vs. 0.56 ± 0.05) and interleukin-6 ($pg \cdot ml^{-1}$) at T4 (91 ± 18 vs. 124 ± 20), T5 (110 ± 20 vs. 220 ± 25) in coated group vs. control ($P \leq 0.05$). Protein desorption (microalbumin) on fibers ($mg \cdot mm^{-3}$) was less in hyaluronan vs. control groups ($P \leq 0.05$). Hyaluronan coating reduced platelet adhesion and cell adsorption, and modulated inflammatory response in high-risk patients.

Keywords: Cardiopulmonary bypass; Hyaluronic acid; Coronary artery bypass grafting

1. Introduction

Implementation of heparin coated cardiopulmonary bypass (CPB) circuits in cardiac operations has proved to attenuate the activation of biologic cascades and the presence of thromboresistant heparinized surfaces has further allowed better perioperative outcomes [1, 2]. However, clinical benefits have not been demonstrated in most studies on surface heparinized circuits when employed in low-risk patients [3, 4].

The patient population referred for coronary artery bypass grafting (CABG) has become more challenging. The results of this displacement could be altered to the benefit of the patients undergoing open heart surgery by continual improvement of the operative techniques as well as the technology of CPB systems.

Researchers focus on factors associated with patient risk, develop and test strategies designed to improve the margin of safety and lead to risk neutralization.

Hyaluronan is a polysaccharide of the glycosaminoglycans class. It is a unique biopolymer which is found in all tissues and body fluids in every mammalian species as well as in microorganisms. It is very hydrophilic; its viscous solutions have most unusual rheological properties and are exceedingly lubricious [5].

Hyaluronan-coated extracorporeal circuits, commercially known as GBS™ Coating (Gish Biomedical Inc, CA, USA), is a novel heparin-based covalent bonding consisting of a polycarbonate backbone with hydrophilic as well as hydrophobic groups.

In this report, the powerful precept of preoperative risk assessment has been applied to examine prospectively the relative benefits of hyaluronan-coated extracorporeal circuits across patient risk strata for three different cohorts with the documentation of broad indicators of systemic inflammation, platelet function as well as biomaterial evaluation.

2. Patients and methods

2.1. Patients

This study was approved by the Medical Ethics Committee of the Institution. Informed consent was obtained from each patient included in the study.

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Over a two-year period, 90 patients undergoing CABG were evaluated according to the EuroSCORE before the operation and then prospectively randomized (closed envelope allocation) to one of the two perfusion protocols with the investigators blinded to the allocation: Group 1 was treated with tip-to-tip hyaluronan-based heparin-bonded circuits (Vision HFO-GBS™, Gish Biomedical, CA, USA) and Group 2 with identical uncoated controls (Vision HFO™, Gish, CA, USA). Each group was further divided into three subgroups ($n=15$) with respect to low (EuroSCORE 0–2), medium (3–5) and high (6+) risk patients.

CPB was instituted on roller pump (System 1, TCM Heat exchanger, Terumo) via closed system with a softshell venous reservoir and no cardiotomy-suction connection into the circuit (SVR11S-uncoated and SVR11S-GBS-coated, Gish, USA).

Anticoagulation or antiplatelet therapy was discontinued seven days before the operation in all patients. Exclusion criteria consisted of known coagulopathy, endocarditis, inability to obtain informed consent. The rest of the patients that did not correspond to exclusion criteria were enrolled in the study with respect to preoperative EuroSCORE classification.

2.2. Operative technique

Anesthesia was induced by fentanyl (35 μg/kg) and muscle relaxation was established with pancronium (0.1 mg/kg). The patients were intubated endotracheally and ventilated with 100% oxygen. A Swan–Ganz catheter was placed via internal jugular vein. Patients were administered full dose – 300 IU/kg heparin (Liquemine, Roche) with target activated clotting time (ACT) over 480 s. ACT was measured by Hemochron 801 (International Technodyne Corporation, Edison, NJ). The set-up of the circuits in the study was designed to exclude as much parameter as possible interfering inflammatory reactions attending CPB. Cardiotomy, suction and left ventricle decompression lines were not connected to the circuit. Shed blood was not retransfused and processed in cell-saver (Dideco-Shiley Therapeutic Autotransfusion System). The ascending aorta was cannulated for arterial inflow, and the right atrium for venous return. Patients were cooled down to 30 °C. Blood flow was maintained 2.0–2.4 l/min/m² during CPB. After cross-clamping of aorta, the heart was arrested with 4:1 blood cardioplegia, 10–15 ml/kg and maintained at 20-min intervals. Warm blood cardioplegia was administered before the aortic cross-clamp was released. Bilateral internal mammary artery or radial artery grafts were used for coronary artery lesions, if not utilized in the first operation and saphenous vein grafts were used as alternative in other instances. Rewarming was initiated during last grafting. At 36.5 °C, CPB was discontinued and heparin was reversed by protamine sulphate (Protamine, Roche, Istanbul, Turkey), 3.1 mg/kg. The adequacy of protamine reversal was checked by ACT and corrected, when necessary. Prime for CPB was identical for all patient groups; 60 ml of mannitol 20%+1000 ml of hydroxyethyl starch (Voluven 130.4, Fresenius, Turkey) and 300 ml of crystalloid (Plasmalyte A, Eczacibasi, Turkey) with a total of 1360 cc.

2.3. Perioperative follow-up

For each patient, the following factors were evaluated before discharge and documented: hemodynamic parameters, perfusion and cross-clamp duration, intubation period, postoperative hemorrhage, the use of blood (as units) and fresh frozen plasma (blood product – as units) during the hospital stay, incidence of arrhythmia, use of inotropic support, complications and infection, the duration of intensive care unit (ICU) stay and hospital stay, perioperative mortality, New York Heart Association (NYHA) classification, and Doppler echocardiography were evaluated before discharge and documented. Comparison between groups was performed retrospectively.

2.4. Blood samples and assays

Complete blood count [hemoglobin, hematocrit, erythrocyte, white blood cell (WBC) and platelet counts] was recorded. Results of standard blood and urine chemistry; especially serum albumin and globulin fractions were documented. Complement fragment, C3a anaphylatoxin levels were measured by ELISA, via turbidimetric method (Dade-Behring, Deerfiled, IL). Serum interleukin 6 (IL-6) levels were measured by enzyme linked immunosorbent assay (Bender Medsystems, Vienna, Austria) (coefficient of variation $<10\%$ and sensitivity <1.4 pg/ml). Creatine kinase MB (CKMB) and lactate levels were measured in the samples obtained from retrograde cardioplegia catheter (coronary sinus blood) before and at the end of CPB before protamine infusion.

Blood samples were collected in potassium-EDTA (ethylene diaminetetra acetic acid) tubes using a radial or femoral artery catheter at the following intervals:

Baseline: After induction of anesthesia (before administration of heparin) (T1).
Thromboelastography (TEG) control: After heparin administration before CPB (T2). (T2 was not evaluated in statistical analysis).
On-CPB: 15 min after initiation of CPB (T3).
Off-CPB: Before cessation of CPB (T4) (before protamine infusion).
Protamine: 15 min after reversal with protamine (T5)
ICU: First postoperative day at 8:00 a.m. (T6).

2.5. TEG

Platelet function was evaluated by TEG (ROTEG®, Pentapharm, GmbH, Germany) during the operation. Coagulation time (CT), clot formation time (CFT), α-angle, mean clot firmness (MCF) and A5 were measured in samples T1 up to T5.

2.6. Flow cytometry

Neutrophil CD11b/CD18 expressions were determined at T1 up to T5 by flow cytometry (EPICS Elite ESP, Coulter Corporation, Hialeah, FL) as previously described [6]. Cursors were set to measure the mean relative fluorescence intensity (RFI) and the values were expressed as a percentage of the baseline.

2.7. Spectrophotometry

At the termination of CPB, the complete circuit was rinsed with saline solution. The oxygenator was removed, treated with glutaraldehyde solution and dismantled by a saw under sterile conditions. Hollow fibers were collected for later protein desorption studies [7]. The amount of desorbed protein (microalbumin) in each specimen for every patient was evaluated quantitatively with a COBAS MIRA Spectrophotometer (Roche Diagnostics Systems Inc, Branchburg, NJ) with its range adjusted to >0.01.

2.8. Statistical analysis

Based on data from a previous study [8], a sample size of 15 patients in each subgroup would have a power of 90% and a type 1 error of 0.05 to detect a 25% difference in IL-6 levels. Data are expressed as the mean $\pm$ the standard error (S.E.) of the mean. Mann–Whitney *U*-test was used to compare demographic and non-parametric data. Two-way analysis of variance with factor group and repeated factor time was used to analyze differences over time in each group and for differences between groups. Post hoc test (Bonferroni correction) was applied whenever a significant difference was detected. A $P<0.05$ was considered significant. Data were analyzed using SPSS program.

3. Results

Four patients were excluded from the study and not included in statistical evaluation. Three of them refused to participate in this study and one was reported to have a history of coagulation factor insufficiency. Preoperative demographic data were comparable among groups.

3.1. Clinical evaluation

General overview and clinical outcome of patients ($n=90$) in two different groups are summarized in Table 1. Perioperative laboratory outcome in two groups are demonstrated in Table 2.

No statistically significant differences were observed between two groups in low-risk cohorts with respect to hemodynamic evaluation, perioperative follow-up, blood sampling and assays. Clinical outcome of all patient groups was thoroughly uneventful.

Percentage expression of neutrophil CD11b/CD18 levels in medium risk cohort were significantly lower in hyaluronan-coated group at T4 (off-CPB) and T5 (protamine reversal) ($P<0.05$).

Respiratory support time ($P=0.0001$) and atrial fibrillation incidence ($P=0.032$) were significantly lower in hyaluronan-coated group vs. control in medium-risk cohorts.

In high-risk cohorts, serum IL-6 levels were significantly lower in hyaluronan-coated group at T4 (off-CPB), T5 (protamine reversal) ($P<0.01$) (Fig. 1). C3a levels showed significant differences in hyaluronan-coated group at T3 (on-CPB), T4 (off-CPB), T5 (protamine reversal) ($P<0.01$) (Fig. 2). CKMB levels in coronary sinus blood demonstrated well preserved myocardium in hyaluronan-coated group (Fig. 3). Flow cytometric analysis was demonstrated in Fig. 4. Percentage expression of neutrophil CD11b/CD18 levels were significantly lower in hyaluronan-coated group at T3 (on-CPB) and T4 (off-CPB) ($P<0.05$).

Table 1
Overall clinical evaluation of patients in two different groups

	Group 1 (Hyaluronan)	Group 2 (Control)	*P*-value
Duration of CPB (min)	71.57±4.72	78.2±4.74	>0.05
Duration of X-clamp (min)	51.4±3.97	55.2±4.1	>0.05
t-intub (h)	9.18±0.31	12.7±0.8	0.0001
Postoperative hemorrhage (ml)	493.8±15.4	602.7±31.2	0.002
Arrhythmia (*n*)	3	15	0.001
Blood transfusion (U)	1.2±0.16	1.5±0.2	>0.05
Blood products (U)	1.6±0.19	1.8±0.2	>0.05
Inotropic support (*n*)	11	17	>0.05
ICU stay (day)	2.57±0.14	3.4±0.19	0.001
Postoperative NYHA class	2.7±0.84	2.6±0.86	>0.05
IABP (*n*)	2	4	>0.05
Postoperative EF (%)	48.6±0.96	47.7±1.4	>0.05
Hospital stay (day)	7.2±0.23	8.7±0.48	0.006
Mortality (*n*)	2	5	>0.05

CPB, cardiopulmonary bypass; X-clamp, aortic cross-clamp; t-intub, respiratory support time; ICU, intensive care unit; NYHA, New York Heart Association class; EF, ejection fraction.

Perioperative follow-up for high-risk cohorts is summarized in Table 3. TEG evaluation did not demonstrate any significant difference among groups in any evaluation period.

3.2. Biomaterial evaluation

Protein (microalbumin) desorption on fibers was significantly higher in high-risk cohort on uncoated surfaces (Fig. 5).

4. Discussion

Despite early promise as a means of reducing the inflammatory response to surgery and subsequent organ damage, the evidence of the clinical value of surface modification remains equivocal [9, 10]. Therefore, we have studied various risk cohorts as a population that adds far more confounding variables than uncomplicated routine, first time coronary bypass operation. Greater homogeneity may be achieved by identifying those patients at greater risk of exaggerated responses to CPB in larger study groups.

We have studied hyaluronan-coated circuits in reoperation for coronary revascularization and documented better results for surface coated group [11]. Also, feasibility of reducing heparin dosage on hyaluronan-coated surfaces has also been verified by our group [12].

Lowering dose of heparin was related to thrombin generation.

In our study on hyaluronan-based heparin-bonded circuits, the preventive effects on systemic inflammatory response dominated WBC counts, IL-6, C3a levels and integrin expression in coated group of high risk. Only CD11b/CD18 measurements were documented up to the end of operation but all other parameters up to postoperative first day. CD11b/CD18 is a very sensitive marker for acute SIRS and we have observed that levels decrease to the baseline in a few hours postoperatively [13].

Coated circuits preserved platelets during CPB in medium and high-risk groups, provided better perioperative period

Table 2
Overall laboratory evaluation of patients in two different groups

	T1		T3		T4		T5		T6		*P*-value			
	Group 1 (Hyaluronan) $n=45$	Group 2 (Control) $n=45$	Group 1 (Hyaluronan) $n=45$	Group 2 (Control) $n=45$	Group 1 (Hyaluronan) $n=45$	Group 2 (Control) $n=45$	Group 1 (Hyaluronan) $n=45$	Group 2 (Control) $n=45$	Group 1 (Hyaluronan) $n=45$	Group 2 (Control) $n=45$	Within group		Between groups	Interactive
											Group 1 (Hyaluronan)	Group 2 (Control)		
WBC	7272±130	7214±134	6637±121	6894±119	7808±120	7646±122	7854±134	8630±226	7086±121	7193±111	T1–T3=0.000 T1–T4=0.000 T1–T5=0.000 T3–T4=0.000 T3–T5=0.000 T3–T6=0.000 T4–T6=0.000 T5–T6=0.000	T1–T3=0.000 T1–T4=0.000 T1–T5=0.000 T3–T4=0.000 T3–T5=0.000 T3–T6=0.013 T4–T5=0.000 T4–T6=0.001 T5–T6=0.000	T3=0.43 T5=0.006	0.019
PLT count (×1000)	161.7±2.9	166.2±3.1	118.2±3.8	119.8±3.5	140.8±2.2	126±2.7	142.4±2.4	122.9±3.4	141±2.4	140.5±2.7	T1–T3=0.000 T1–T4=0.000 T1–T5=0.000 T1–T6=0.000 T3–T4=0.000 T3–T5=0.000 T3–T6=0.000	T1–T3=0.000 T1–T4=0.000 T1–T5=0.000 T1–T6=0.000 T3–T6=0.000 T4–T6=0.000 T5–T6=0.000	T4=0.000 T5=0.000	0.001
IL-6	16.3±0.4	15.8±0.5	24.3±1.3	23.4±1.4	43.6±5.3	52.5±7.6	83.4±3.2	121.7±10	19.1±0.8	17.6±0.5	T1–T3=0.000 T1–T4=0.000 T1–T5=0.000 T3–T4=0.000 T3–T5=0.000 T3–T6=0.001 T4–T5=0.000 T4–T6=0.000 T5–T6=0.000	T1–T3=0.000 T1–T4=0.000 T1–T5=0.000 T3–T4=0.000 T3–T5=0.000 T3–T6=0.000 T4–T5=0.000 T4–T6=0.000 T5–T6=0.000	T4=0.003 T5=0.000	0.000
C3	0.4±0.008	0.39±0.01	0.2±0.01	0.23±0.01	0.38±0.007	0.43±0.01	0.4±0.01	0.47±0.02	0.38±0.01	0.39±0.01	T1–T3=0.000 T3–T4=0.000 T3–T5=0.000 T3–T6=0.000	T1–T3=0.000 T1–T5=0.000 T3–T4=0.000 T3–T5=0.000 T3–T6=0.000 T5–T6=0.000	T3=0.013 T4=0.016 T5=0.000	0.000
CD11b/CD18	1.2±0.17	1.3±0.2	10.9±0.98	13.7±1.5	10±0.6	12.6±0.9	6.3±0.4	7.4±0.4	–	–	T1–T3=0.000 T1–T4=0.000 T1–T5=0.000 T3–T5=0.000 T4–T5=0.000	T1–T3=0.000 T1–T4=0.000 T1–T5=0.000 T3–T5=0.000 T4–T5=0.000	T3=0.01 T4=0.001 T5=0.002	0.000

WBC, leukocyte count; PLT, platelet; IL-6, interleukin-6; C3, complement-3; CD11b/CD18, integrin.

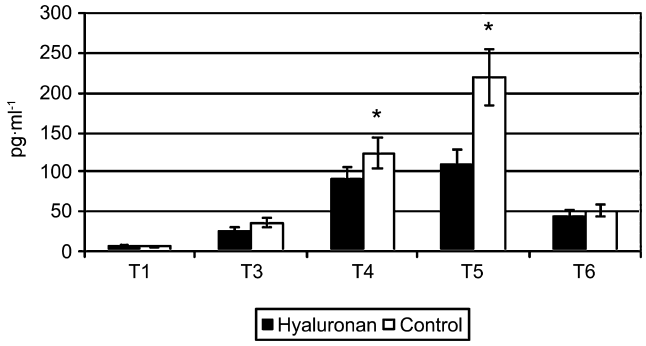

Fig. 1. IL-6 levels (pg/ml) throughout the procedure in patients with high risk. *$P<0.05$ vs. control. IL-6, interleukin-6.

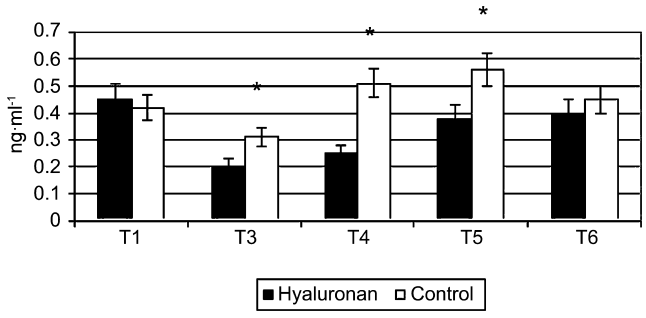

Fig. 2. C3a (ng/ml) levels throughout the procedure in patients with high risk. *$P<0.05$ vs. control.

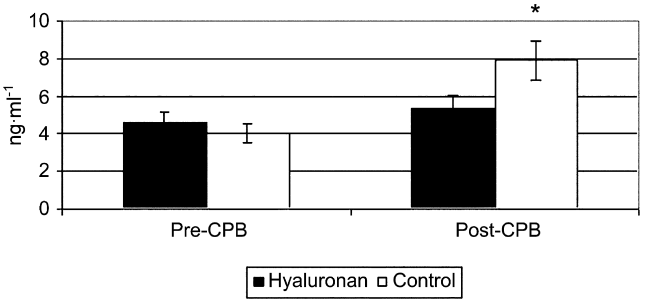

Fig. 3. Coronary sinus CKMB (ng/ml) evaluation before (T1) and post-CPB (T4) in patients with high risk. *$P<0.05$ vs. control. CPB, cardiopulmonary bypass; CRMB, creatine kinase MB.

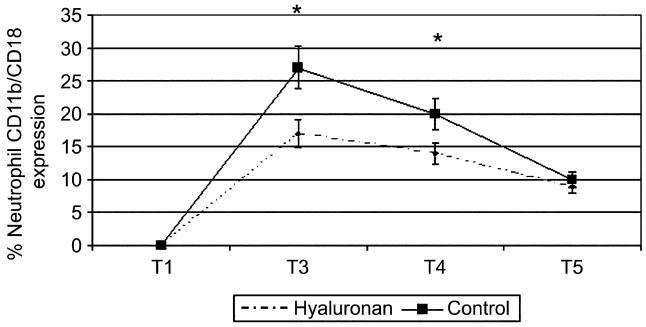

Fig. 4. Neutrophil CD11b/CD18 upregulation detected by flow cytometry in high-risk patients. *$P<0.05$ vs. control.

Table 3
Perioperative follow-up of patients with high risk

	Group 1 (Hyaluronan)	Group 2 (Control)	*P*-value
Duration of CPB (min)	108±4.2	114±3.7	>0.05
Duration of X-clamp (min)	80.3±3	87.2±3.2	>0.05
t-intub (h)	10±0.6	17±1.5	0.0001
Postoperative hemorrhage (ml)	590±23	857±30	0.0001
Arrhythmia (*n*)	AF:3	AF:9	0.025
Blood transfusion (U)	2.1±0.22	2.8±0.26	0.044
Blood products (U)	2.2±0.35	2.9±0.3	>0.05
Inotropic support (n)	6	8	>0.05
Postoperative NYHA class	3.1±0.1	2.9±0.1	>0.05
IABP (*n*)	2	4	>0.05
ICU stay (day)	2.9±0.24	4.6±0.27	0.0001
Postoperative EF (%)	44±1.5	39.4±1.4	>0.05
Hospital stay (day)	7.5±0.5	12±1.1	0.004
Mortality rate (*n*)	2	4	>0.05

CPB, cardiopulmonary bypass; X-clamp, aortic cross-clamp; t-intub, respiratory support time; ICU, intensive care unit; NYHA, New York Heart Association class; EF, ejection fraction.

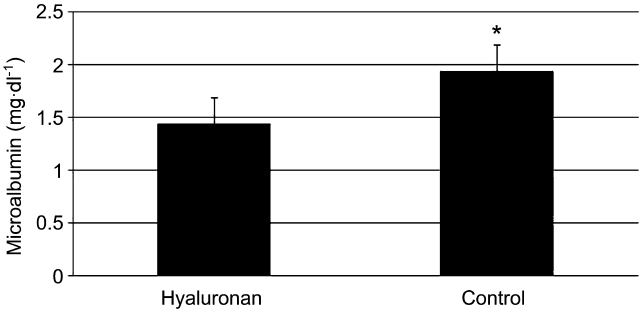

Fig. 5. Desorbed protein amount (microalbumin) on oxygenator fibers. *$P<0.05$.

via decreasing mechanical ventilation time and hemorrhage in high-risk group, reduced cell adsorption on fibers and circuits in cell culture. Proinflammatory and hematologic responses were better controlled in coated high-risk group and resulted in significantly less ICU and hospital stay. No clinical, technical or laboratory evidence of undesired thrombogenicity was observed, and there were no signs of increased fibrinolysis or consumption of coagulation factors documented by TEG.

The coated group's impact on blood conservation was clearly delineated by the significantly lower postoperative hemorrhage and blood use. The effects of coating on postoperative bleeding are not unexpected because of platelet preservation. The additional effects of hyaluronan on the incidence of atrial fibrillation are not easy to explain.

Consequently, we have demonstrated that hyaluronan treated surfaces were able to reduce the risks associated with CPB in selected patients, especially those at high risk.

Obviously, very many different factors may contribute to post-CPB morbidity and mortality in each patient, not all of which are related to biocompatibility. The present knowledge about pathogenesis is probably fragmentary rendering it difficult to find efficient measures to reduce risk. Inflammatory response to CPB is multifactorial and com-

bined therapies may be more efficient than a single intervention to improve outcome.

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