Artificial
Organs

Clinical Evaluation of New Generation Oxygenators With Integrated Arterial Line Filters for Cardiopulmonary Bypass

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Abstract: New generation oxygenators with integrated arterial line filters have been marketed to improve the efficacy of cardiopulmonary bypass (CPB). Differences in designs, materials, coating surfaces, pore size of arterial filter, and static prime exist between the oxygenators. Despite abundant preclinical data, literature lacks clinical studies. From September 2010 to March 2011, 80 consecutive patients were randomized to CPB using Terumo Capiox FX25 (40 patients, Group-T) or Sorin Synthesis (40 patients, Group-S) oxygenators. Pressure drop and gas exchange efficacy were registered during CPB. High-sensitivity C-reactive protein (hs-CRP), white blood cells (WBCs), fluid balance, activated clotting time, international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, platelets (PLTs), serum albumin, and total proteins were measured perioperatively at different timepoints. Clinical outcome was recorded. Repeated measure analysis of variance and nonparametric statistics assessed between-groups and during time differences. The two groups showed similar baseline and intraoperative variables. No differences were recorded in pressure drop and gas exchange (group-P and group*time-P = N.S. for all) during CPB. Despite similar fluid balance (P = N.S. for static/dynamic priming and ΔVolume administered intraoperatively), Group-T showed higher hs-CRP (group-$P = 0.034$), aPTT (group-$P = 0.0001$), and INR (group-$P = 0.05$), with lower serum albumin (group-$P = 0.014$), total proteins (group-$P = 0.0001$), fibrinogen (group-$P = 0.041$), and PLTs (group-$P = 0.021$). Group-T also showed higher postoperative bleeding (group-$P = 0.009$) and need for transfusions ($P = 0.008$ for packed red cells and $P = 0.0001$ for fresh frozen plasma and total transfused volumes). However, clinical outcome was comparable (P = N.S. for all clinical endpoints). Both oxygenators proved effective and resulted in comparable clinical outcomes. However, Sorin Synthesis seems to reduce inflammation and better preserve the coagulative cascade and serum proteins, resulting in lower transfusions and post-CPB inflammatory response. **Key Words:** Cardiopulmonary bypass—Oxygenators—Integrated arterial filters—Arterial filter.

Since the beginning of cardiac surgery, it was recognized that cardiopulmonary bypass (CPB) induces a systemic inflammatory reaction that results in increased postoperative morbidity and hospital stay (1,2). Accordingly, several studies have focused on the systemic inflammatory response syndrome (SIRS), and progressive technical refinements to the CPB machine have been suggested to attenuate SIRS (1,2). It has been suggested that coated circuits improve postoperative outcome compared with the traditional uncoated ones (2). It has been reported that different types of coating attenuate inflammatory response (2), platelet (PLT) activation (3), fibrinolysis (4), need for transfusions (5), postoperative cerebral dysfunction (6), and myocardial damage (7) compared with the "uncoated" technology. Thus, the overall concordance of the literature on this topic has led to the general recommendation to use coated circuits in the daily surgical practice (2). Similarly, published guidelines have concluded that "heparin-coated bypass circuits (oxygenator alone or the entire circuit) are not unreasonable for blood conservation"

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(Class IIb-Level of Evidence B) (8) and that "reduction of circuit surface and the use of biocompatible surface-modified circuits might be useful—effective in reducing the systemic inflammatory response" (Class IIa- Level of Evidence B) (1).

Similarly, gaseous microemboli (GME), generated during CPB by perfusionist interventions, surgical manipulations, temperature changes as well as by the CPB circuit components, have been promptly recognized as important contributing factors to embolic organ damage and, consequently, as specific triggers of SIRS (9). Accordingly, arterial line filters have been proposed (and afterward proved) to significantly reduce the load of gaseous and particulate emboli (10). A systematic review of the data related to the arterial line filtration strategy has reported that the level of evidence supporting this practice was as high as Class I-Level of Evidence A (1). Finally, miniaturization of the CPB machine has proved to be effective in reducing pump-priming, inflammation, blood loss, and donor blood usage (11–13).

Innovative CPB settings have been developed in order to integrate the above-mentioned concepts of "surface-coating," "blood-filtration," and "miniaturization." Indeed, the integration of arterial line filters with oxygenators fulfill these principles. However, although these innovations have been often compared with traditional CPB equipment, no study—to the best of our knowledge—has ever evaluated the clinical impact of the dissimilar "coating" and "filtering properties" offered by the available oxygenators with integrated arterial line filters. Therefore, it was the aim of this study to investigate the clinical and biochemical outcome related to the use of two different "coated" oxygenators with integrated arterial filter in routine surgical practice.

PATIENTS AND METHODS

Patients and technical equipments

From September 2010 to March 2011, 80 consecutive adult patients undergoing isolated primary aortic valve replacement (AVR) under CPB were prospectively randomized to undergo extracorporeal circulation using the Terumo Capiox FX25 oxygenator (40 patients, Group-T [Terumo Italia Srl, Rome, Italy]) or the Sorin Synthesis oxygenator (40 patients, Group-S [Sorin Group Italia, Mirandola, Modena, Italy]). Briefly, the Terumo Capiox FX25 woven hollow-fiber oxygenator sustains up to 7 L/min of blood flow, requires a static prime of 250 mL, has a surface area of 2.5 m^2, a biocompatible coating with poly-2-methoxyethylacrylate (so-called X-coating), and an integrated polyester arterial line filter of 32 μm pore size. However, the Sorin Synthesis oxygenator has a microporous polypropylene membrane requiring a static prime of 430 mL with a surface of 2.0 m^2, sustains up to 8 L/min of blood flow, and has a biocompatible phosphorylcholine coating with an integrated polyester arterial line filter of 40 μm pore size. Complete technical properties of both oxygenators are available online at http://www.terumo-cvs.com/doc/819820_FXFamilyBrochure_2009.pdf and http://www.sorin.com/sites/default/files/product /files/2010/10/07/09330-37_Synthesis.pdf, respectively (accessed October 27, 2011).

The study protocol was approved by the Institution's Ethical Committee/Institutional Review Board. Informed consent was obtained from each patient. Due to the investigation of both the clinical and the biochemical response to two different oxygenators, strict enrollment criteria and standardized protocols were defined.

Inclusion/exclusion criteria

Only patients scheduled for low-risk primary elective isolated AVR because of calcified degenerative aortic valve stenosis were enrolled in the study. In order to avoid potential bias related to prolonged CPB, this choice was dictated by the low-risk and rapid nature of these procedures (14).

All factors potentially interfering with the myocardial and/or the systemic inflammatory responses were considered exclusion criteria. In particular, in order to avoid the risk of bias related to an uneven distribution of cardioplegic solutions, patients with coronary disease were excluded from the study. Other exclusion criteria were: age <18 or >85 years, emergent/urgent/salvage procedures, left ventricular ejection fraction <35% at preoperative echocardiography, associated cardiac or vascular surgical procedures, redo surgery, recent (<8 weeks) acute myocardial infarction, preoperative intra-aortic balloon pump assistance, severe chronic obstructive pulmonary disease (≥Stage IIIa of Global Initiative for Chronic Obstructive Lung Disease [GOLD] classification), obesity (body mass index >30 kg/m^2), renal disease (Kidney Disease Outcome Quality Initiative class ≥2), previous irradiation, previous thoracic surgery, previous transfusions (within 6 months), recent (<30 days) infections, liver dysfunction, ongoing steroids or statins, drug abuse, neurologic diseases or recent (<3 months) stroke, acquired/congenital deficits of the immune system, autoimmune diseases, and cancer. On the day of surgery, patients were randomized by lottery, drawing preprepared sealed envelopes containing the group assignment. With the exception of the main investi-

gator and of the CPB technician, all other physicians (surgeons, anesthesiologists, intensivists, biochemists, etc.) dealing with perioperative patient care, biological sampling, and/or collection and analysis of clinical data were blinded to the group assignment until the end of the study.

Anesthesia and surgery

Anesthesia was standardized. No steroids were administered throughout the procedure. Anesthetic induction consisted of intravenous propofol infusion at 2 mg/kg combined with fentanyl administration at 0.010 mg/kg. Propofol infusion (150–200 μg/kg/min) and isoflurane (0.8% inspired concentration) maintained anesthesia in the operating room. Neuromuscular blockade was achieved by 4 mg/h of vecuronium bromide, and lungs were ventilated to normocapnia with a volume-controlled ventilation, at a frequency of 12/min, a tidal volume of 8 mL/kg of ideal body weight, and an administered oxygen fraction (FiO_2) of 0.5. A positive end-expiratory pressure (PEEP) was set at 5 cm/H_2O. During CPB, mechanical ventilation was discontinued. Arterial and central venous catheters were the standard. During intensive care unit (ICU) stay, lungs were ventilated mechanically for at least 4 h after termination of surgery, with volume-controlled ventilation, at an initial frequency of 12/min, a tidal volume of 8 mL/kg of ideal body weight, and a PEEP maintained at 5 cm/H_2O during the entire study period. FiO_2 and ventilation rates were then adjusted to keep arterial partial oxygen pressure (PaO_2) >120 mm Hg and arterial partial carbon dioxide pressure ($PaCO_2$) between 30 and 35 mm Hg. Airway clearance was maintained by means of closed routine tracheal suctioning. Anesthesia was maintained with continuous propofol infusion (180–200 μg/kg/min), plus intravenous fentanyl administration if requested, until the start of the weaning from mechanical ventilation. Mechanical ventilation (FiO_2 and ventilation rate) was adjusted during ICU stay to keep acid–base balance and $PaCO_2$ between 40 and 45 mm Hg. Analgesia was guaranteed by routine opioid administration.

Surgery was always performed through a median sternotomy. Bioprosthetic or mechanical AVRs were accomplished according to conventional guidelines. In all cases, supra-annular prosthetic anchorage was achieved by interrupted pledgeted noneverting sutures.

CPB was accomplished always by the same two senior perfusionists, through strict adherence to the established standardized protocol. Heparin was given at a dose of 300 IU/kg to achieve a target activated clotting time of 480 s or above. Left ventricular venting through the right superior pulmonary vein and cardiotomy suction, until protamine administration, were routinely employed. Returned blood was always reinfused to the patient. Blood recovery with an autotransfusion device (Autotrans Dideco, Mirandola, Modena, Italy) was also performed intraoperatively in all cases. A level of hemoglobin lower than 8 g/dL prompted blood transfusion. The extracorporeal circuit was primed with NaCl 0.9% solution and 5000 IU of heparin. A nonpulsatile CPB flow was established at 2.4 L/min/m^2. All patients were cooled to moderate hypothermia, ranging from 32 to 34°C. Cardiac arrest and myocardial protection were accomplished by means of aortic cross-clamping coupled with intermittent antegrade and retrograde hyperkalemic cold blood cardioplegia (1:4 ratio), followed by a retrograde "hot shot" immediately before aortic declamping, as already reported (15). Repeated doses were administered every 20 min.

Composition of the crystalloid solutions mixed with blood in a 1:4 ratio for antegrade bolus, retrograde maintenance, and predeclamping "hot shot" are reported in Table 1. CPB circuit was similarly standardized. It included a Terumo X-coated tubing set (Terumo Italia Srl) or Sorin phosphorylcholine-coated tubing set (Sorin Group SpA, Milano, Italy) for patients randomized to Group-T and Group-S, respectively, and a Jostra roller pump (Jostra, Maquet Cardiopulmonary, Hirrlingen, Germany). Blood gas management during CPB aimed at a pH between 7.35 and 7.40 and $PaCO_2$ between 35 and 40 mm Hg. PaO_2 was maintained higher than 200 mm Hg. Alpha-stat was chosen for blood gas management.

Following surgery, patients received anticoagulation with enoxaparin, starting when the postoperative bleeding was controlled (usually within 6 h), until the

TABLE 1. *Composition of each unit of crystalloid solution used for myocardial protection*

	Glucose 50% (mL)	CPD (mL)	NaCl 30% (mL)	NaCl 0.9% (mL)	Trometamol (mL)	KCl 3 mEq/mL (mL)	Energy (kJ)	Osmolarity
Bolus	55	50	6.5	500	200	20	481	748
Maintenance	55	50	6.5	500	200	7	481	651
Hot shot	225	225	250	40	225	9	611	701

CPD, citrate-phosphate-dextrose.

third postoperative day, associated to a daily dose of 100 mg acetylsalicylic acid. Oral anticoagulation with warfarin was started on the first postoperative day with a target INR of 2.5–3.5. When target INR was reached, warfarin was continued as the only anticoagulation strategy (lifelong in patients receiving mechanical valves or in those with longstanding persistent atrial fibrillation, limited to the first 3 months followed by 150 mg/day of acetylsalicylic acid in all the others).

Endpoints

Due to the fact that the two oxygenators differ in the technical refinements aimed at reducing the CPB-related SIRS, the inflammatory response was set as the primary endpoint of the study. In this perspective, the perioperative change of high-sensitivity C-reactive protein (hs-CRP) levels between the two groups was the primary efficacy endpoint of the study. hs-CRP was measured at three different timepoints (T0: preoperative, before anesthetic induction; T1: at the end of surgery; and T2: 24 h postoperatively).

Secondary endpoint related to the "systemic" response to CPB was the variation of perioperative white blood cell (WBC) count, collected at T0 (preoperative), T1 (at the end of surgery), T2 (3 h postoperatively), and T3 (24 h postoperatively).

Other data prospectively collected and considered as secondary endpoints were the following:

1. PaO_2, FiO_2, and $PaCO_2$, derived from blood gas analysis (RapidLab1265 AutomaticQC Cartridge, Siemens Healthcare Italia, Milan, Italy) and sampled from the arterial line during CPB and from the cannulated peripheral radial artery thereafter, at T0: preoperative, T1: at the start of CPB, T2: immediately before CPB discontinuation, T3: at the end of surgery, T4: 3 h, T5: 24 h postoperatively.
2. Blood hematocrit (Ht) was collected at T0 (preoperative) and at T1–T5 as for PaO_2.
3. Red blood cells (RBCs), PLT count, INR, activated partial thromboplastin time (aPTT), fibrinogen (FBG), and creatinine (Creat) were derived from peripheral blood sampling at T0–T3 as for WBC.
4. Serum albumin and total plasma proteins were assayed at T0 (preoperative), T1 (end of CPB), T2 (end of surgery), and T3 (24 h postoperatively).
5. Pressure drop (in mm Hg) across the two different oxygenators was measured at 10 (T1), 20 (T2), 40 (T3), and 60 (T4) min of CPB run.
6. Static and dynamic priming of the two groups.
7. Total intraoperative volume load, defined as the total amount of volume administered to the patients (Volume-In), the total amount of volume lost by the patient (Volume-Out), and the delta (ΔVolume) between Volume-In and Volume-Out during the intraoperative time course.
8. Postoperative bleeding, defined as the total amount of chest drain loss at 3 (T0), 6 (T1), 12 (T2), and 24 h (T3) postoperatively
9. Transfusions, defined as the volume of allogeneic red packed cells, plasma, PLTs, and total volume of transfusions per patient.
10. Clinical outcome was defined by intubation time (expressed in hours), ICU length of stay and hospital length of stay (expressed in days), hospital mortality, incidence of perioperative acute myocardial infarction, acute lung injury, acute respiratory insufficiency, acute renal insufficiency, acute renal failure, and type II neurologic complications, as already reported elsewhere (15). All these outcome variables were defined according to the current literature (15).

Statistical analysis

Between–within interactions of three-time hs-CRP measurement in 40 patients for each study group gave a power (1-β error probability) of 92.0% with an α-error probability of 0.05, given a partial eta-squared of 0.19, and an estimated effect size f of 0.48.

Pre- and perioperative data were summarized as mean and standard deviation (SD) or median and 25th–75th percentile if continuous and as counts and percent if categorical. Continuous variables were tested for normality with the Shapiro–Wilk test and compared between the two treatment groups with the Student's *t*-test or the Mann–Whitney *U*-test accordingly. Categorical variables were compared with the Fisher exact test. Ordinal variables were also compared with Mann–Whitney *U*-test. Repeated measures analysis of variance with Bonferroni correction for multiple measurements was used to compare serial data. Violations of sphericity were Greenhouse–Geisser corrected if $\varepsilon < 0.75$, or Huynh–Feldt corrected if $\varepsilon > 0.75$. Reported *P* values include group-*P*, assessing level of difference between groups; time-*P*, assessing change over time of measured variables; and group*time-*P*, assessing group–time interaction. Comparisons were considered significant if $P < 0.05$, unless otherwise dictated by Bonferroni correction. Statistical analysis was performed by the SPSS program for Windows, version 15.0 (SPSS, Inc., Chicago, IL, USA).

TABLE 2. *Baseline characteristics*

	Group-T—40 pts	Group-S—40 pts	*P*
Age (yr)	76.4 ± 11.1	78.6 ± 4.6	0.257
Male gender	26 (65.0%)	23 (57.5%)	0.647
Diabetes mellitus	20 (50.0%)	13 (32.5%)	0.173
Hypertension	24 (60.0%)	28 (70.0%)	0.482
LVEF	54.8 ± 7.4	52.3 ± 5.6	0.092
Log EuroSCORE	6.9 ± 2.1	7.9 ± 2.4	0.067
Debubbling time (mins)	4.4 ± 0.5	4.6 ± 0.6	0.090
ACC time (mins)	52.0 ± 7.1	50.1 ± 7.1	0.241
CPB time (mins)	70.3 ± 8.2	73.0 ± 8.8	0.162

ACC, aortic-cross clamping; CPB, cardiopulmonary bypass; LVEF: left ventricular ejection fraction.

RESULTS

Baseline characteristics of the two groups were comparable, as reported in Table 2. Pressure drops across the two types of oxygenators were also similar, as shown in Table 3.

Inflammatory response

hs-CRP values at the end of surgery were similar to those preoperative but showed a significant augmentation at 24 h postoperatively (time-$P = 0.0001$ for both groups). This augmentation was significantly higher in Group-T (group-$P = 0.034$; group*time-$P = 0.0001$, Fig. 1A). However, WBC count significantly rose since T1–T3 (time-$P = 0.0001$ for both groups) but did not reach the level of statistical significance between the two study groups (group-$P = 0.673$; group*time-$P = 0.097$; Fig. 1B).

Gas exchange

When the respiratory function was considered, both oxygenators proved to be highly effective in achieving adequate oxygenation (PaO_2: group-$P = 0.067$; group*time-$P = 0.069$), although a slight decline in this function was detected since T3 in both groups (time-$P = 0.0001$ for both; Fig. 2A). Likewise, comparable PaO_2 values were reached with similar FiO_2 administrations (group-$P = 0.992$; group*time-$P = 0.489$; Fig. 2B). Finally, a comparable good CO_2-scavanging effect was demonstrated with both oxygenators (group-$P = 0.323$; group*time-$P = 0.154$; Fig. 2C).

TABLE 3. *Pressure drops measured across the two oxygenators, postoperative bleeding, and serum creatinine at different timepoints (T0 to T3 values of each variable are specified in the text)*

	Group	T0	T1	T2	T3	Time-*P*	Group-*P*	Group*time-*P*
Pressure drop (mm Hg)	T	98.6 ± 45.0	101.8 ± 33.6	112.8 ± 45.4	119.1 ± 40.5	0.016	0.980	0.468
	S	98.5 ± 38.7	110.3 ± 29.1	110.1 ± 24.9	112.4 ± 20.9	0.020		
Bleeding (mL)	T	267.1 ± 169.0	360.3 ± 218.7	449.7 ± 231.4	553.0 ± 415.9	0.0001	0.009	0.001
	S	166.5 ± 105.8	235.0 ± 140.3	324.2 ± 161.7	430.0 ± 223.5	0.0001		
Creatinine (mg/dL)	T	1.0 ± 0.2	0.9 ± 0.2	1.0 ± 0.3	1.2 ± 0.3	0.851	0.421	0.290
	S	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	1.2 ± 0.4	0.985		

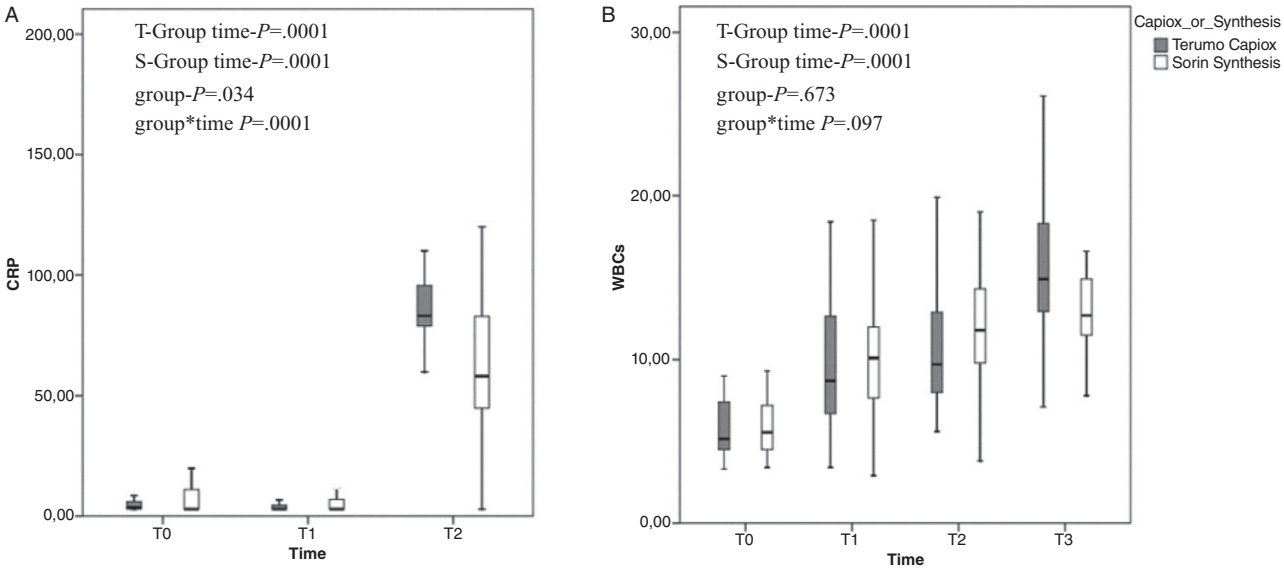

FIG. 1. Inflammatory response: perioperative leakage of hs-CRP (A) and WBC (B) count in the two groups. CRP, C-reactive protein.

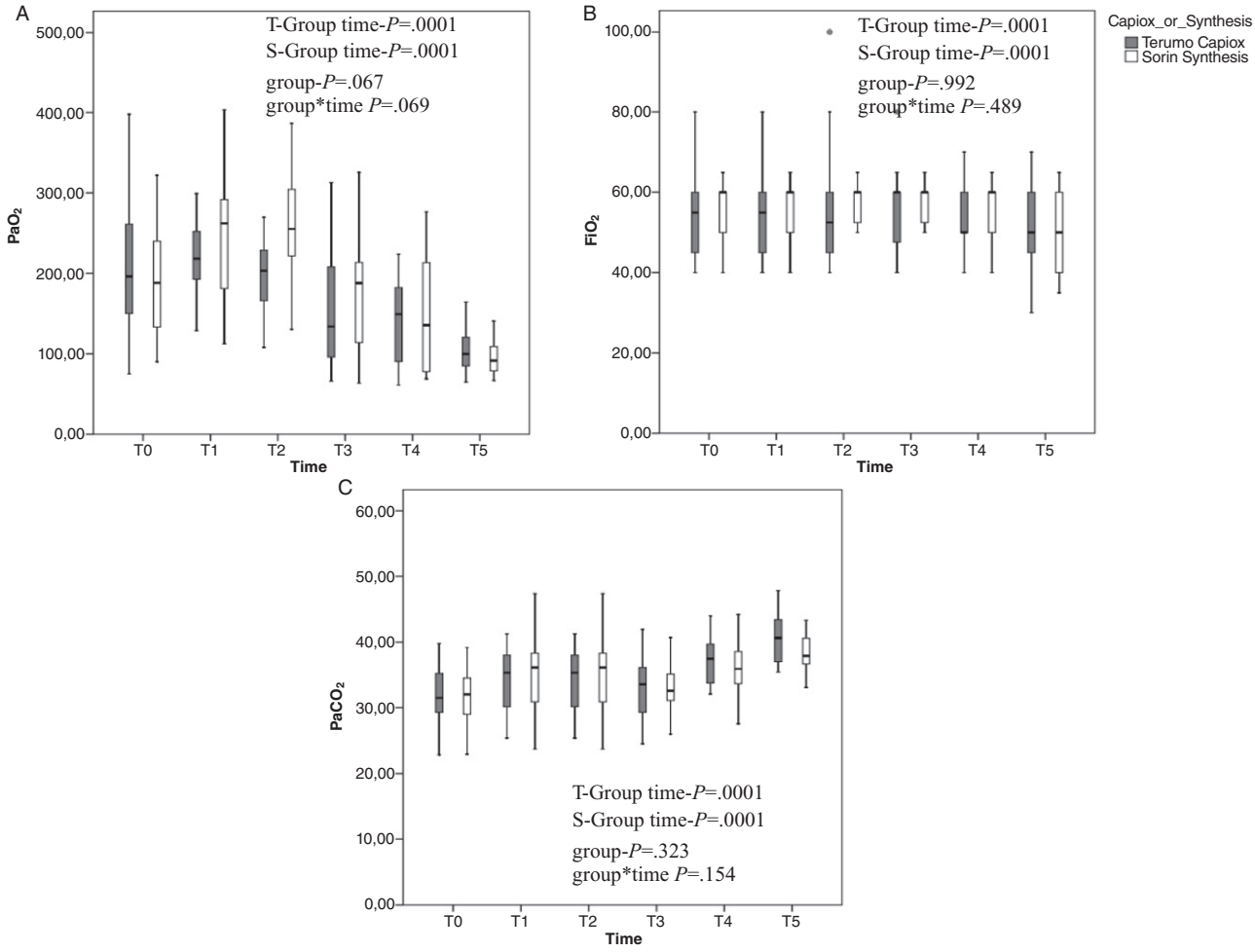

FIG. 2. Gas exchange: perioperative values of PaO_2 (A), FiO_2 (B), and $paCO_2$ (C) in the two groups.

Hemodilution

Both groups showed a comparable "volume load" administered by the CPB technicians, in terms of both static (Group-T = 920.1 ± 90.9 mL vs. Group-S = 973.7 ± 200.2 mL; $P = 0.284$) and dynamic priming (Group-T = 508.5 ± 508.7 mL vs. Group-S = 488.9 ± 571.7 mL; $P = 0.911$). Similarly, the entire intraoperative administration of fluids was comparable (Group-T Volume-In = 4609.6 ± 1055.8 mL vs. Group-S = 4573.4 ± 992.1; $P = 0.875$) as well as the intraoperative fluid loss (Group-T Volume-Out = 1602.0 ± 555.9 mL vs. Group-S = 1630.5 ± 457.3; $P = 0.803$) and the intraoperative ΔVolume (Group-T = +3007.6 ± 1114.2 mL vs. Group-S = +2942.9 ± 804.0 mL; $P = 0.767$).

In spite of the comparable fluid balance, Group-S showed significantly higher values of serum albumin (group-$P = 0.001$, group*time-$P = 0.0001$; Fig. 3A), and total proteins (group-$P = 0.0001$, group*time-$P = 0.0001$; Fig. 3B).

Ht values and RBC count—first declining at T1, rising since T3, and finally reaching the preoperative values at T5—proved comparable between the two groups (Ht: group-$P = 0.625$, group*time-$P = 0.152$; Fig. 3C—RBC count: group-$P = 0.646$, group*time-$P = 0.703$, Fig. 3D), possibly because of a higher transfusion rate in patients belonging to Group-T (see later "Hemocoagulative function" section)

Hemocoagulative function

When the hemocoagulative function was considered, an overall better profile could be detected in patients belonging to Group-S (Fig. 4). In detail, PLT count showed a progressive decline in both groups at T1 and T2, followed by a slight rise at T3 (time-$P = 0.0001$ for both). However, Group-S always showed a higher PLT count compared with Group-T (group-$P = 0.021$, group*time-$P = 0.0001$; Fig. 4A). Similarly, aPTT significantly prolonged at T1 and T2 in both

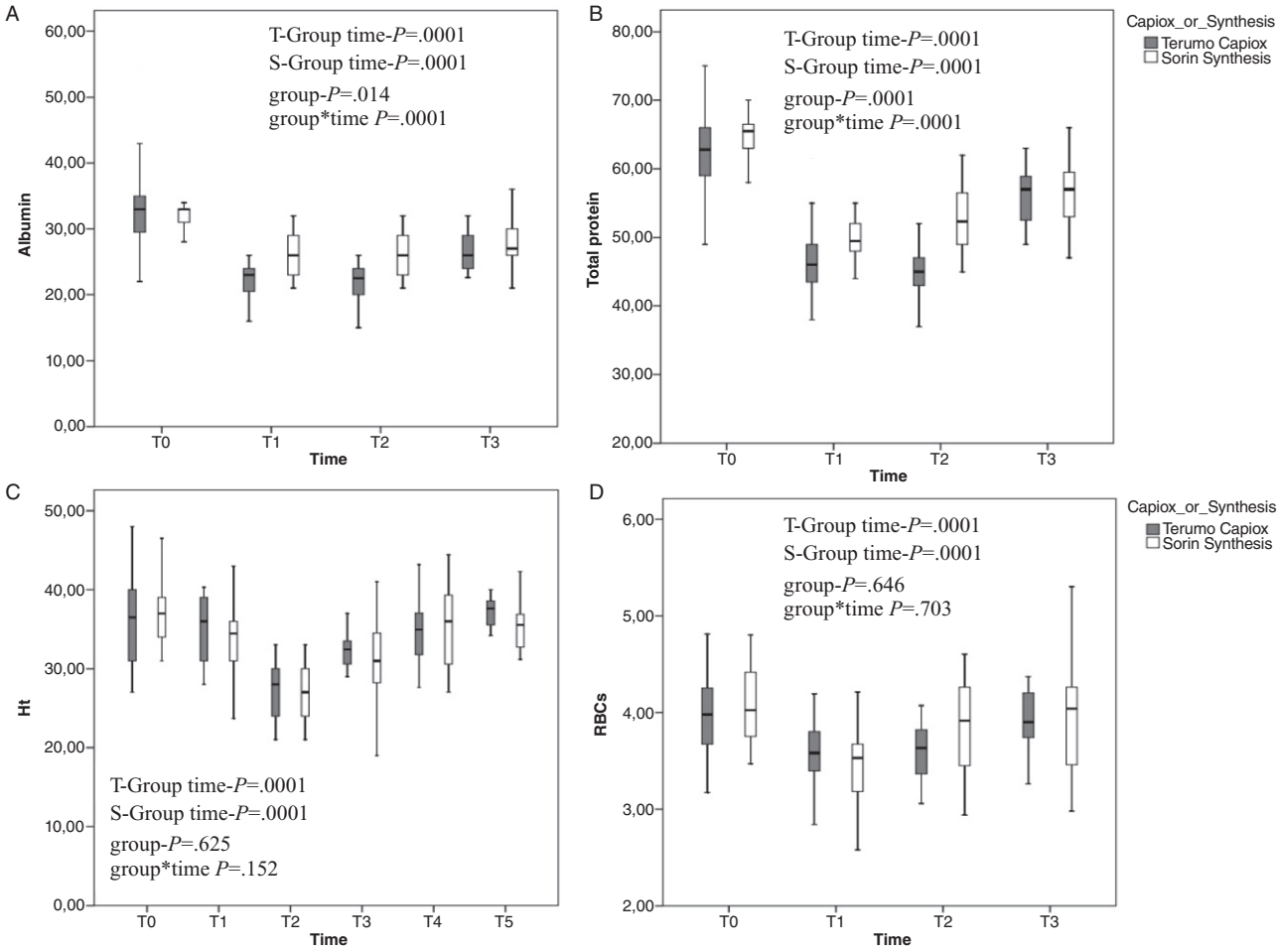

FIG. 3. Hemodilution: perioperative values of serum albumin (A), total proteins (B), Ht (C), and RBCs (D) in the two groups.

groups (time-$P = 0.0001$) but likewise proved to be better preserved in Group-S (group-$P = 0.0001$, group*time-$P = 0.0001$; Fig. 4B). FBG levels also declined at T1 and T2 in both groups (time-$P = 0.0001$), but higher values were found in Group-S (group-$P = 0.041$), also as a function of time (group*time-$P = 0.0001$; Fig. 4C). Finally, INR prolonged perioperatively in both groups, reaching the preoperative values only at T3 (time-$P = 0.0001$); again, INR prolongation was exacerbated in Group-T (group-$P = 0.05$, group*time-$P = 0.05$; Fig. 4D).

Patients undergoing Terumo Capiox FX25 showed a higher postoperative bleeding (group-$P = 0.009$, group*time-$P = 0.001$; Table 3) and a higher transfusion rate (Table 4). However, no patient underwent re-exploration for bleeding (Table 4).

Clinical outcome

Despite the above-mentioned differences in various biochemical assays, the two groups did not differ in all the major clinical outcome variables (Table 4). Similarly, serum creatinine—regarded as a marker of perioperative splanchnic perfusion—proved comparable in the two groups (group-$P = 0.421$, group*time-$P = 0.290$; Table 3).

DISCUSSION

Post-CPB SIRS still accounts for a large part of the mortality and the major morbidity observed after cardiac surgery (1,2). Recent technological refinements to the CPB machine include the miniaturization of the circuits, the integration of different components (i.e., the arterial filters to minimize priming and surface exposure to the circulating blood elements), and the less recent coating of the surfaces of the CPB machine with heparin (so-called "bioactive" coating) or different types of polymers (so-called "biopassive" coating), thus mimicking the endothelial surfaces (1–13).

Indeed, it was since the early 1990s that heparin-coated circuits were recognized to reduce blood cell

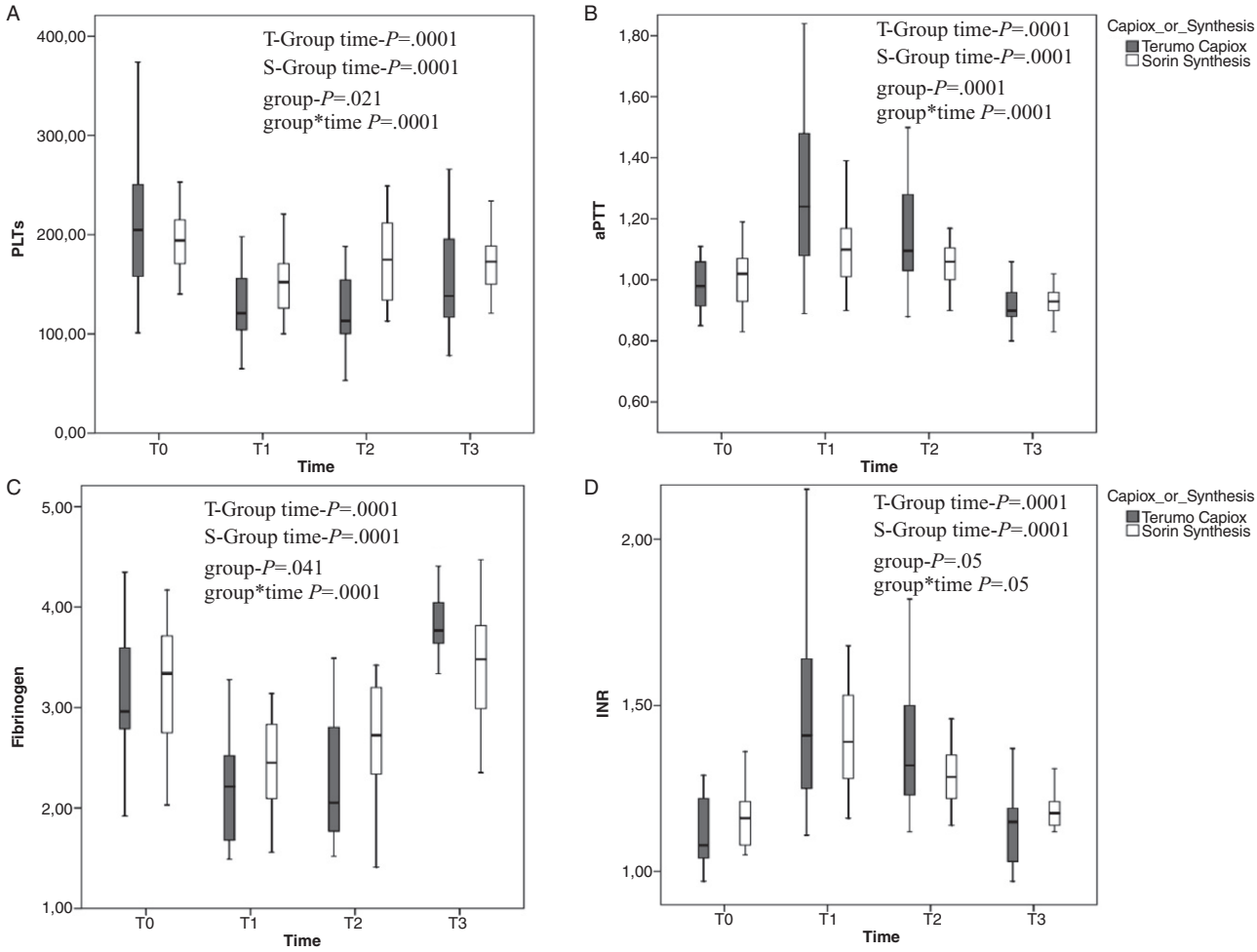

FIG. 4. Hemocoagulative function: perioperative PLT count (A), aPTT (B), fibrinogen levels (C), and INR (D) in the two groups.

TABLE 4. *Transfusions rate/patient and clinical outcome*

	Group-T—40 pts	Group-S—40 pts	*P*
RPCs (mL/pt)	411.7 ± 195.5	66.2 ± 15.0	0.008
PLTs (mL/pt)	15.0 ± 66.2	—	0.156
Plasma (mL/pt)	367.1 ± 217.5	—	0.0001
Total transfusions (mL/pt)	658.9 ± 448.0	66.2 ± 15.0	0.0001
Re-exploration for bleeding	—	—	—
Intubation time (h)	11.6 ± 4.8	10.5 ± 5.2	0.332
ICU-LOS (days)	1.9 ± 0.9	1.9 ± 1.0	0.947
Hospital LOS (days)	6.0 ± 1.4	5.2 ± 1.3	0.112
Mortality	—	—	—
Perioperative AMI	—	—	—
Perioperative ALI	—	—	—
Perioperative acute respiratory insufficiency	1/40 (2.5%)	1/40 (2.5%)	1.0
Perioperative acute renal insufficiency	3/40 (7.5%)	4/40 (10.0%)	1.0
Perioperative acute renal failure	2/40 (5.0%)	1/40 (2.5%)	1.0
Type II neurologic complications	1/40 (2.5%)	—	1.0

ALI, acute lung injury; AMI, acute myocardial infarction; ICU, intensive care unit; LOS, length of stay; PLTs, platelets; RPCs, red packed cells.

trauma in experimental and clinical scenarios (2). A more recent paper by Lorusso et al. demonstrated phosphorylcholine coating to reduce the intraoperative oxygenator inlet pressures, the perioperative PLT consumption, and the postoperative blood loss, when compared with uncoated circuits (3). Similarly, Myers et al. found a better PLT protection after phosphorylcholine-coated versus uncoated oxygenators (16). X-coating has proven: (i) to reduce the absorption of plasma proteins (17), (ii) to improve the entrapment of circulating WBCs with the potential benefit to attenuate SIRS (18), and (iii) to optimize the hemostasis and to reduce homologous blood transfusions (19) when compared to uncoated circuits. Accordingly, the recent 2011 update to the Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines incorporated these evidences and stated that "the use of biocompatible CPB circuits may be considered as part of a multimodality program for blood conservation," having this statement a Level of Evidence A (20).

Although the majority of the studies on the topic have proven that these technological improvements ameliorate the biochemical and clinical outcome when compared with the traditional CPB machine (i.e., uncoated circuits, uncoated oxygenators, not integrated arterial filters, etc.), few studies have compared the different types and settings of these new technologies (1–13). In the present study on a relatively low risk cohort, we demonstrated that no clinical difference emerged after CPB with either the Sorin Synthesis oxygenator with phosphorylcholine-coated circuits or the Terumo Capiox FX25 with X-coated circuits. Similarly, the two different oxygenators showed similar gas exchange capabilities and similar results in terms of pressure gradients generated across the system unit. However, although no clinical benefit could be demonstrated, patients belonging to Group-S showed less systemic inflammatory reaction (as demonstrated by the lower circulating levels of hs-CRP), together with higher serum albumins and plasma proteins, in spite of a comparable hemodilution induced by both the perfusion technicians (i.e., static and dynamic priming) and the anesthesiologists (i.e., Volume-In, Volume-Out, and ΔVolume). Similarly, Group-S showed a better preserved hemostasis, resulting in reduced postoperative bleeding and less need for transfusions.

A possible explanation for these observed outcomes can be attributed to the different "coating" of the two CPB settings. To the best of our knowledge, this is the first article aimed at comparing two different oxygenators, employed with the same manufacturer's circuits and similar surface coatings. Despite literature lacking direct comparison of the two coating systems, a recent study by Eisses et al. demonstrated that pediatric patients undergoing CPB with X-coated oxygenators, when compared with the uncoated ones, showed similar thrombin generation and comparable levels of tissue-plasminogen activator and plasminogen-activator inhibitor, thus concluding that no differences existed between the two systems in the activation of both the coagulation and the fibrinolytic pathways (21). Similarly, a study by Izuha et al. in adult patients demonstrated that changes in overall PLT function associated with the X-coating were similar to those associated with heparin coating, although the PLT aggregation threshold index slightly prolonged after X-coating—when compared with heparin coating—from 60 min to 2 h of CPB run (22). Another study by Marcoux et al. investigating five different coated surfaces underscored that X-coating CPB correlated with hs-CRP levels similar to those after the uncoated CPB and that X-coating failed to achieve shorter ventilation time or ICU length of stay compared with the uncoated circuits (23). The same study showed that X-coating achieved the worst clinical results—when compared with the other four different coating technologies—in terms of transfusion requirements, intubation time, and ICU length of stay (23). However, literature on phosphorylcholine coating uniformly proves its superiority when compared with the uncoated circuits. A study in children by De Somer et al. showed that phosphorylcholine coating had a favorable effect on PLTs, given a steady increase of thromboxane-B2 and beta-thromboglobulin during CPB in the control group, with an opposite "plateau effect" in the phosphorylcholine-coated group, a reduced complement activation after coating, and a resulting reduced blood loss (24). Another study by the same group in adult patients confirmed reduced PLT factor-4 and beta-thromboglobulin levels after phosphorylcholine coating versus uncoating, resulting in a 30% reduction in blood loss (25). Myers et al. showed that PLT protection with phosphorylcholine-coated oxygenators was significantly better than with uncoated oxygenators, regardless of the employed perfusate (16). Finally, a recent randomized controlled trial by Pappalardo et al. demonstrated that after complex cardiac procedures, phosphorylcholine-coated oxygenators reduce the intraoperative thrombin formation and the associated consumption of PLTs, FBG, and antithrombin (26).

Another possible explanation to our findings can be related to GME. We know from the literature that once GME enter the bloodstream, they are coated

with protein (resulting in larger wall thicknesses) and are more difficult to break (27). The significance of protein-coated GME lies in the fact that they have the ability to create morbidity as solid microemboli (28). Given the direct link between GME and multiorgan ischemia-reperfusion injury and the consequent inflammatory response (1), it can be hypothesized that Group-T patients in our study experienced a higher rate of postarterial GME. Indeed, an in vitro study by Myers et al. comparing five different integral cardiotomy reservoirs found a significant increase in postarterial GME count whenever a vent was employed (as in the aortic surgery of our patient population) and that GME count was significantly higher in the Terumo Capiox RX systems than in the Sorin one (27). Similarly, in another in vitro study evaluating the air separation ability of four different extracorporeal circuit designs, Dickinson et al. proved that the Terumo system showed an attenuated efficacy in GME removal (29). Undeniably, the different coating techniques utilized in an oxygenator may result in different capability in GME removal from the circulation (30). Furthermore, despite in vitro demonstration that the smaller the filter's pores, the higher the GME entrapment, researchers have also clearly demonstrated that the smaller the filter's pores, the higher the risk for fragmentation of large bubbles into microemboli, thus resulting in a higher rate of postarterial filter GME count (27). Therefore, due also to the demonstration in vivo that large amounts of microbubbles tend to fuse with others after the arterial filter to create larger ones (a term called "coalescence") (27), we cannot definitely prove that the smaller the filter's pores, the better the GME removal (and consequently the better the outcome).

Furthermore, despite the fact that GME can be generated at any time of CPB conductance, we can assume that the two groups at least start with a similar "microembolic" load, given the similar preoperative debubbling time. Certainly, we can only speculate at the moment on this issue, given the fact that a major limitation in the interpretation of our results is related to the lack of postarterial filter GME count, which is indeed the objective of an ongoing study at our institution.

Finally, the efficacy of hs-CRP, as a marker of the systemic inflammatory response to CPB after cardiac surgery, and its prognostic role for cardiovascular mortality and morbidity, have been well documented (31). As mentioned above, both the better biocompatibility of the phosphorylcholine coating and the potential better GME removal—with a lower multiorgan ischemia/reperfusion injury—may help to explain the lower inflammation found in Group-S (4,14,15,28). Furthermore, the lower hs-CRP leakage in the Sorin group may help to explain its better hemocoagulative profile, given the direct link between inflammatory and coagulative/fibrinolytic cascades (32).

From a scientific point of view, it has to be considered that the involvement of two or more perfusionists might have impacted the analyzed outcome variables. However, the strict adherence to the standardized CPB protocol was considered mandatory for the enrollment of any patient in this study. Furthermore, an "ideal" comparison would have involved another two groups of treatment, with the same circuits but opposite surface coatings; however, the availability of the only two reported types of oxygenators, with the only two corresponding coating materials, avoided this ideal comparison.

CONCLUSION

The result of our study demonstrated that despite comparable gas exchange, hemodilution, and pressure gradients, a significant attenuation of the inflammatory response to CPB was evidenced in patients belonging to Group-S, possibly related to a higher biocompatibility of the Sorin system in terms of coating, and to a lower degree of systemic GME related to the specific characteristics of the investigated device. The direct relationship among systemic inflammation, coagulation, and fibrinolysis (32) anticipates also the lower hemocoagulative dysfunction (with consequent lower perioperative bleeding and need for transfusions) experienced by Group-S. However, the reported biochemical differences did not translate into a better clinical outcome in any of the two groups. Further studies enrolling patients at a higher risk profile might help to find out the potential clinical benefits of these new generation integrated oxygenators.

AUTHOR'S CONTRIBUTION

Francesco Onorati: concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article, statistics, data collection.

Francesco Santini: concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article.

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Maria Stella Graziani: concept/design, data analysis/interpretation, drafting article.

Bartolomeo Chiominto: concept/design, critical revision of article, approval of article.
Aldo Milano: concept/design, critical revision of article, approval of article.
Giuseppe Faggian: concept/design, data analysis/interpretation, critical revision of article, funding secured by, approval of article.
Alessandro Mazzucco: concept/design, data analysis/interpretation, drafting article.

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