A Systematic Review of Biocompatible Cardiopulmonary Bypass Circuits and Clinical Outcome

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This systematic review and meta-analysis explores the clinical efficacy of biocompatible surfaces for cardiopulmonary bypass in adults. Thirty-six randomized controlled trials were retrieved for a total of 4360 patients. Patients treated with biocompatible circuits had a lower rate of packed red cells transfusions and atrial fibrillation, and shorter durations of stay in the intensive care unit. When the analysis was limited to high-quality studies, only a reduction in atrial fibrillation rate and a shorter stay in the intensive care unit remained significantly associated with the use of biocompatible surfaces. Using biocompatible surfaces without other measures to contain blood activation results in a limited clinical benefit.

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Biocompatible surfaces for cardiopulmonary bypass (CPB) circuits and oxygenators became commercially available in the late 1980s. The first biocompatible treatments were based on heparin bonding, either ionic or covalent. Subsequently, many different kinds of biocompatible treatments became available for clinical use, and currently all major companies manufacturing CPB equipment offer one or more options of biocompatible circuits.

Even taking into account that some biologic differences exist among the different biocompatible treatments, the general philosophy is to mimic the endothelial surface by coating the CPB circuit and oxygenator with different types of molecules (heparin; poly2-methoxyethylacrylate; phosphorylcholine; siloxane/caprolactone; polyethylene oxide chains, sulfate/sulfonate groups).

Many studies exploring biochemical markers of inflammation and activation of the hemostatic system have demonstrated a beneficial effect of these biocompatible treatments in terms of a decrease of the systemic inflammatory reaction to CPB, a lower degree of activation of the hemostatic system, a prevention of platelet adhesion and activation, and a preservation of platelet count.

Despite these beneficial biochemical effects, many clinical studies have offered conflicting results with respect to the real efficacy of this approach in improving patient outcome. For example, the two largest randomized controlled trials (RCTs) published so far either failed to demonstrate any beneficial effect in low-risk patients undergoing coronary revascularization [1] or demonstrated only minor beneficial effects in terms of morbidity in specific subgroups of high-risk patients [2].

Most published studies lack the power for detecting differences in morbidity and mortality: only six RCTs enrolled more than 100 patients in each arm. It is therefore reasonable to conduct a systematic review and meta-analysis focused on the main outcome measurements (morbidity and mortality) to analyze a reasonable number of patients.

In 2007 Mangoush and coworkers [3] conducted a systematic review and meta-analysis of heparin-bonded circuits. Unfortunately, these surfaces have been either withdrawn from the market or replaced by new generations of biocompatible treatments, and as a result, most of the studies analyzed are dated 8 to 20 years ago. Moreover, concerns have been raised with respect to the selection criteria of their meta-analysis that led to the exclusion of some major studies [4].

This article is a systematic review and meta-analysis of the relevant RCTs comparing biocompatible surfaces with conventional systems. The aim of this review is to determine whether biocompatible circuits exert a beneficial effect on the clinical outcome of patients undergoing cardiac operations in terms of reducing morbidity, mortality, and resource utilization.

Methods

The present study was conducted in line with recommendations from the Cochrane Collaboration and the quality of reporting of meta-analyses (QUOROM) guidelines [5, 6].

End Points and Definitions

The following outcome variables have been extracted from the retrieved articles:

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Table 1. Selected Studies

Study (First Author)	Year	Biocompatible Treatment[a]	Jadad Quality Score	Outcome Measurements[b]
Wildevuur [1]	1997	A-ionic	4	1, 2, 3, 5, 6, 7, 8, 9, 10, 15
Ranucci [2]	1999	A-ionic	1	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
de Somer [8]	2002	C	1	1
Kreisler [9]	2005	A-covalent	3	1, 12, 13, 14
Baufreton [10]	1996	A-ionic	2	1, 2, 3, 5, 8, 9, 11, 15
Dickinson [11]	2002	E	2	1, 2, 5, 6, 7, 8, 12, 13, 14, 15
Gunaydin [12]	2005	A	1	12, 13, 14, 15
Gunaydin [13]	2002	B	0	5, 12, 13, 14, 15
Heyer [14]	2002	A-others	1	3, 7, 13, 14, 15
Khosravi [15]	2005	C	1	7, 12, 13, 15
Mahoney [16]	1999	A-covalent	1	1, 2, 3, 8, 9, 14, 15
McCarthy [17]	1999	A-ionic	4	1, 2, 12, 13, 14, 15
Muehrcke [18]	1996	A-ionic	4	1, 3, 6, 7, 8, 11, 15
Ninomiya [19]	2003	B	1	1, 12, 13, 15
Pappalardo [20]	2006	C	3	1, 2
Sudkamp [21]	2002	D	3	2, 3, 6, 7, 12, 13, 15
Vang [22]	2005	B	3	15
Belboul [23]	1997	A-covalent	1	3, 7, 12
Boonstra [24]	1994	A-ionic	1	2
Butler [25]	2002	A-ionic	2	12
de Vroege [26]	2004	A-others	3	2, 12, 13
Jansen [27]	1996	A-ionic	3	1, 2, 3, 5, 7, 8, 15
Jansen [28]	1995	A-ionic	3	12, 15
Oliver [29]	2003	A-ionic	0	1, 2
Parolari [30]	1999	A-ionic	2	1, 3, 7, 12, 13
Svenmarker [31]	1997	A-covalent	4	1, 4, 12, 14
Saenz [32]	1996	A-covalent	1	1, 2, 3, 7, 10, 12, 14, 15
Wan [33]	1999	A-ionic	2	2, 15
Aldea [34]	1996	A–both	3	1, 2, 3, 4, 5, 7, 8, 10, 11, 12, 13, 14, 15
Inui [35]	1999	A-ionic	1	1
Videm [36]	1999	A-ionic	1	2, 8, 9, 10, 11, 15
Belboul [37]	2000	A-ionic	1	5, 12, 13, 14
Collart [38]	2000	A-covalent	1	1, 8, 12, 13, 15
Hamulu [39]	1996	A-ionic	1	15
Wagner [40]	1994	A-covalent	3	1, 2
Borowiec [41]	1992	A-covalent	3	1, 3, 4, 15

[a] Biocompatible treatments: A = heparin-bonded (ionic or covalent or other kind of bonding); B = poly(2-methoxyethylacrylate); C = phosphorylcholine; D = siloxane/caprolactone; E = heparin, polyethylene oxide chains, sulfate/sulfonate groups. [b] Outcome measurements: 1 = packed red cells transfusion; 2 = surgical revision; 3 = perioperative myocardial infarction; 4 = low cardiac output syndrome; 5 = atrial fibrillation; 6 = use of intraaortic balloon pump; 7 = stroke; 8 = lung dysfunction; 9 = acute renal failure; 10 = gastroenteric complications; 11 = sepsis; 12 = mechanical ventilation time; 13 = intensive care unit stay; 14 = hospital stay; 15 = death.

- Packed red cells (PRCs) transfusions (rate of patients receiving at least 1 unit);
- surgical revision due to postoperative bleeding;
- perioperative myocardial infarction, defined per study using author definitions based on electrocardiographic and enzymatic criteria;
- low cardiac output syndrome, defined as the need for major or prolonged inotropic support after the operation;
- use of intraaortic balloon pump after the operation;
- new onset atrial fibrillation (AF);
- stroke, defined as focal neurologic injury documented by computed tomography scan;
- lung dysfunction, defined in each study using author definitions;
- gastroenteric complications, including gastric bleeding, pancreatitis, hepatic failure, and mesenteric infarction;
- sepsis (systemic infection) according to the study definition;
- mechanical ventilation time (hours);
- intensive care unit (ICU) stay and postoperative hospital stay (days); and
- hospital mortality.

Postoperative bleeding was not included within the outcome variables due to the great variation among the

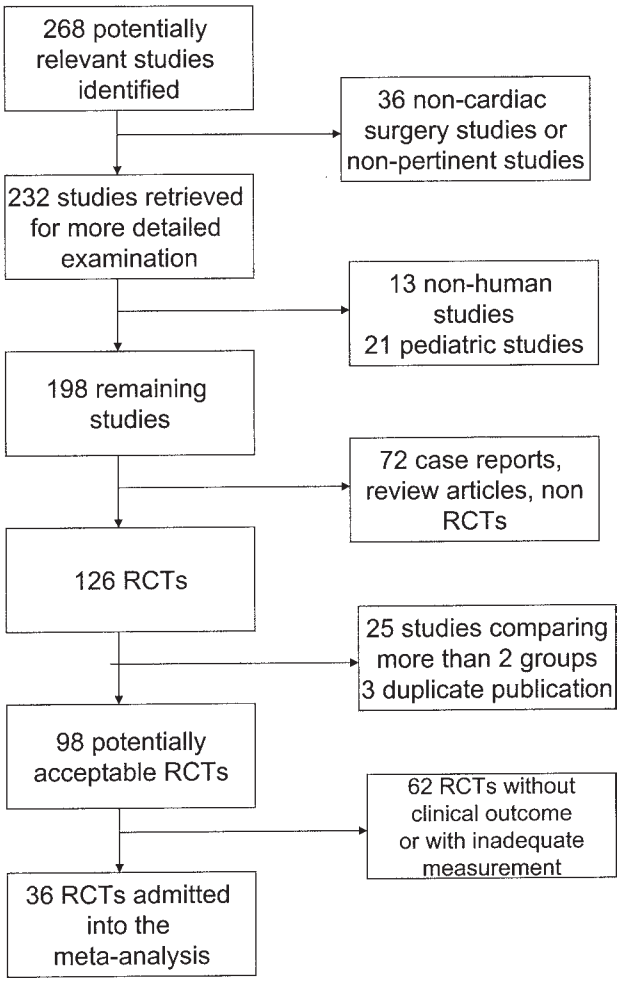


Fig 1. Flow chart of study search and selection. (RCT = randomized controlled trial.)

different institutions with respect to the time frame for its evaluation (6, 12, or 24 postoperative hours).

Categoric binary variables have been considered as the rate of events, and continuous variables (mechanical ventilation time, ICU and hospital length of stay) have been considered as mean ± standard deviation (SD) of the mean. When these variables were expressed as median and range, or other nonparametric measures, they were excluded from the meta-analysis.

The following a priori criteria were established before initiating the article search: (1) only outcome measurements correctly assessed with the preestablished unit of measure in at least eight different studies were to be admitted to the general meta-analysis; and (2) a subgroup analysis for high-quality studies was planned. For this subgroup, only outcome measurements correctly assessed with the preestablished unit of measure in at least three different studies were to be admitted to the meta-analysis.

Search Strategy

Pertinent studies were independently searched by two trained investigators (MR, SB) and one independent researcher (AB) in BioMedCentral, CENTRAL, PubMed, PubMed Central, Scopus, and the Cochrane Library (updated May 1, 2008).

The following key words were used: cardiopulmonary bypass, extracorporeal circulation, biocompatible treatment, heparin coated, heparin bonded, phosphorylcholine, PMEA, siloxane/caprolactone; poly(2-methoxyethylacrylate), polyethylene oxide, sulfate/sulfonate, trillium, X-coating, SMA coating, Duraflo II, and Carmeda.

To conduct the research, we followed the strategy suggested by Biondi-Zoccai and coworkers [7]. Further searches, either manual or computer-assisted, involved the recent (from the year 2002) proceedings and abstracts from congresses of the following scientific associations: American Thoracic Society; Society of Thoracic Surgeons; Society of Cardiovascular Anesthesiologist, European Association of Cardiothoracic Anaesthesiologists; and American College of Chest Physicians. In addition, retrieved articles and pertinent reviews references were scanned, and international experts were contacted and interviewed. No ongoing trials were included.

Study Selection

An initial selection of the references obtained by the search was performed by two independent investigators (MR and AB) on the basis of title and abstract; divergence was resolved by consensus. If considered pertinent, the studies were retrieved as complete articles.

The following inclusion criteria were applied for selecting potentially relevant studies: (1) prospective studies with random allocation to treatment (RCTs), (2) comparison of a biocompatible treatment of any kind vs untreated circuit and oxygenator of the same type, or (3) studies performed in patients undergoing cardiac surgical procedures.

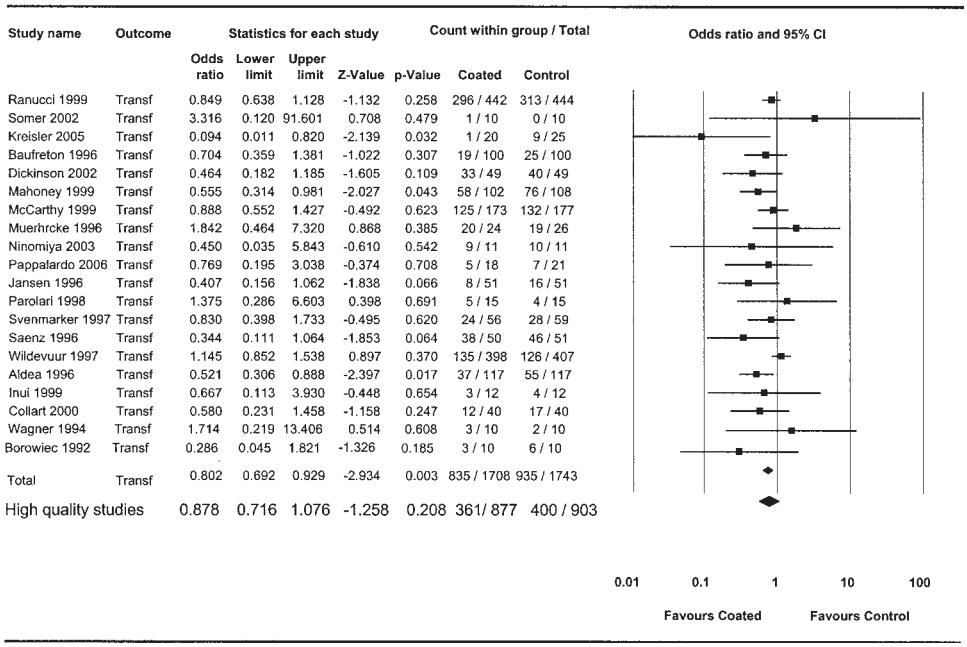
Exclusion criteria were (1) duplicate publications (in this case only the article reporting the larger patient population was considered), (2) pediatric patients (<12 years old), (3) nonhuman experiments, (4) outcome data or outcome data reported with intractable units of measure, or (5) three or more study arms. This last exclusion criterion was decided on due to the impossibility of a homogeneous comparison with respect to the oxygenator type because of the very high risk of selection bias in randomization and performance bias due to the impossible blinding of the study.

The selected studies (Table 1) [1, 2, 8-41] were independently decided on by two investigators (MR and AB), with divergence finally resolved by consensus.

Data Abstraction

The main outcome data in the selected studies were independently abstracted by two investigators (AB and AD), with divergence resolved by consensus. In case of an unclear definition of the outcome, the relative data were removed from further analyses. Units of measurement different from the accepted ones resulted in removing the relative data from further analyses.

Fig 2. Forest plot comparing coated and control group for the outcome of packed red cells transfusions. Vertical line represents no difference between coated and control group. Squares indicate point estimates of treatment (odds ratio). Horizontal bars indicate 95% confidence interval (CI). The diamond represents the summary estimate from the pooled studies with 95% CI.



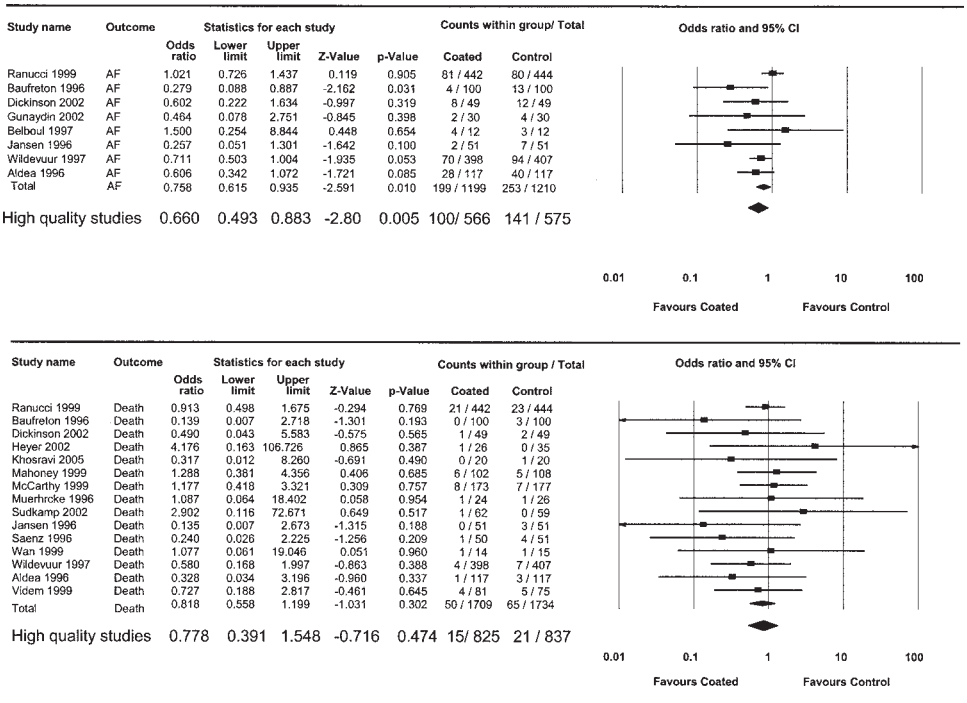
Internal Validity

The internal validity of the selected trials was appraised by three independent researchers (MR, AB, and AlB) according to the Cochrane Collaboration methods by assessing the risk for selection, performance, attrition, detection biases, and allocation concealment. Each study received a quality assessment according to the Jadad score [42].

Data Analysis, Bias, and Heterogeneity Assessment

Each binary outcome variable was analyzed according to the Mantel-Haenszel model to compute an odds ratio (OR) with a pertinent 95% confidence interval (CI) for each selected study. Continuous outcome variables were expressed as standard differences in means with standard error.

Fig 3. Forest plots comparing coated and control group for the outcomes of (upper panel) atrial fibrillation and (lower panel) death. Vertical lines represent no difference between coated and control group. Squares indicate point estimates of treatment (odds ratio). Horizontal bars indicate 95% confidence interval (CI). The diamonds represent the summary estimate from the pooled studies with 95% CI.



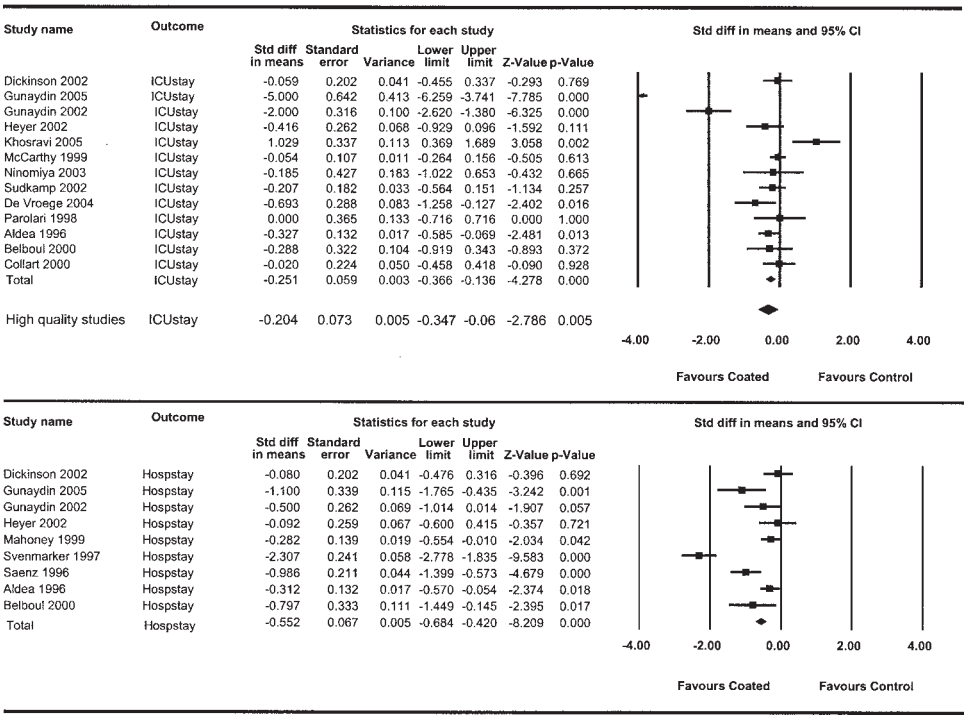


Fig 4. Forest plots comparing coated and control group for the outcomes of (upper panel) intensive care unit and (lower panel) hospital stay. Vertical lines represent no difference between coated and control group. Squares indicate point estimates of treatment (standard difference in means). Horizontal bars indicate 95% confidence interval (CI). The diamonds represent the summary estimate from the pooled studies with 95% CI.

Pooled summary effects were calculated by means of fixed-effects or random-effects models according to the heterogeneity and inconsistency detected using Cochran Q test and I^2, respectively [43, 44]. Publication bias was assessed by visual inspection of funnel plots and by computing the Egger test [45, 46].

Statistical significance was set at the two-tailed $p < 0.05$ level (α) for hypothesis testing and at $p < 0.10$ (β) for heterogeneity testing. I^2 values of 25%, 50%, and 75% were considered representing, respectively, low, moderate, and severe statistical inconsistency [11]. Unadjusted p values are reported throughout the text, tables, and figures. Computations were performed using Comprehensive Meta Analysis 2.2 software (Biostat, Engelwood, NJ).

Results

Database searches and other sources yielded 268 articles (Fig 1). On the basis of title and abstract, 70 studies were excluded (noncardiac surgery studies, nonhuman studies, pediatric studies). The same procedure was used to exclude an additional 72 studies classified as case reports, case series, review articles, and systematic reviews after cross-checking the references to search possible missing articles. The remaining 128 articles were retrieved in complete form and assessed according to the selection criteria. Careful review of these articles led to the exclusion of 25 studies with more than two arms; three studies being duplicate publications; and 64 studies not reporting clinical outcome measurements or using inappropriate reporting systems. The final group of selected studies

Table 2. Heterogeneity Statistics

Outcome variable	Q Value	df	p Value	I^2, %	Heterogeneity	Model Effects
Transfusions	24.0	18	0.19	21	No	Fixed
Surgical revision	7.98	14	0.89	0.1	No	Fixed
POMI	10.0	10	0.44	13	No	Fixed
Atrial fibrillation	9.3	7	0.23	25	No	Fixed
Lung dysfunction	7.4	9	0.59	0	No	Fixed
Stroke	2.6	8	0.95	0	No	Fixed
Death	8.1	14	0.88	0	No	Fixed
Mechanical ventilation	203	18	0.001	91	Yes	Random
ICU stay	108	12	0.001	89	Yes	Random
Hospital stay	76	8	0.001	90	Yes	Random

df = degrees of freedom; ICU = intensive care unit; POMI = perioperative myocardial infarction.

Table 3. Publication Bias Statistics: Test of Asymmetry of the Funnel Plot

Outcome Variable	Egger's Intercept	df	95% CI	*t* Test	*p* Value	Publication Bias
Transfusions	−0.54	17	−1.43 to 0.35	1.27	0.21	No
Surgical revision	−0.48	13	−1.35 to 0.38	1.21	0.25	No
POMI	0.22	9	−0.99 to 1.42	0.41	0.65	No
Atrial fibrillation	−1.06	6	−2.66 to 0.54	1.62	0.16	No
Lung dysfunction	−0.95	8	−2.20 to 0.29	1.76	0.12	No
Stroke	−0.51	7	−1.70 to 0.67	1.02	0.34	No
Death	−0.47	13	−1.25 to 0.31	1.31	0.21	No
Mechanical ventilation	−2.94	17	−5.58 to −0.31	2.35	0.03	Yes
ICU stay	−2.75	11	−6.65 to 1.12	1.54	0.15	No
Hospital stay	−3.95	7	−11.3 to 3.39	1.27	0.24	No

CI = confidence interval; df = degrees of freedom; ICU = intensive care unit; POMI = perioperative myocardial infarction.

comprised 36 RCTs [1, 2, 8-41] that fulfilled the predefined selection criteria.

The 36 selected RCTs randomized 4360 patients, 2197 being placebo-controlled, and 2163 attributed to different types of biocompatible circuits.

Quantitative Results

According to the predefined strategy, only outcome variables reported in at least eight studies were statistically analyzed. The outcome variables fulfilling this criterion were transfusions, resternotomy, perioperative myocardial infarction, atrial fibrillation, pulmonary complications, stroke, hospital mortality (expressed as rate of events), mechanical ventilation, ICU stay, and hospital stay (expressed as time, mean ± SD of the mean).

The effect of biocompatible circuits resulted in a significantly lower incidence of PRCs transfusions (OR, 0.8; 95% CI, 0.69 to 0.93; $p = 0.003$; Fig 2) and AF (OR, 0.76; 95% CI, 0.61 to 0.93; $p = 0.01$; Fig 3), and in significantly shorter times of ICU stay (6 hours, $p = 0.001$) and hospital stay (13 hours, $p = 0.001$; Fig 4). No significant differences were observed for resternotomy, perioperative myocardial infarction, pulmonary complications, and stroke. The OR for hospital mortality (Fig 3) was 0.82 (95% CI, 0.56 to 1.2), not significantly different between groups ($p = 0.302$). In the subgroup of high-quality studies with a Jadad quality score of at least 3 (14 studies including 2114 patients), the PRCs transfusion rate was not significantly different between patients treated with biocompatible circuits and controls (OR, 0.88; 95% CI, 0.72 to 1.08, $p = 0.21$). The AF rate was significantly lower in patients treated with biocompatible circuits (OR, 0.66; 95% CI, 0.49 to 0.88, $p = 0.005$), and the ICU stay was significantly shorter (5 ± 2 hours, $p = 0.005$). All other outcome variables were not significantly different between the two groups or were included in too few studies to be analyzed.

Additional Analyses

Each outcome variable was explored for heterogeneity and risk of publication bias. Table 2 reports the results of the heterogeneity and Table 3 reports publication bias tests. No heterogeneity was detected for the outcome variables of PRCs transfusions, surgical revision, stroke, perioperative myocardial infarction, AF, lung dysfunction, and death. Therefore, these variables were tested with a fixed-effects model. A significant heterogeneity was detected for mechanical ventilation time, ICU stay, and hospital stay, and these variables were entered into a random-effects model. Publication bias was absent for all outcome variables except mechanical ventilation time. This last variable was therefore excluded from subsequent analyses.

Other Outcome Measurements

Additional outcome measurements that were not included in the meta-analysis and non-outcome measurements were:

- Low cardiac output syndrome was reported in only three studies (all in favor of the treated group);
- intraaortic balloon pump use was reported in five studies (one in favor of the treated group, two null, and two in favor of the control group);
- acute renal failure was reported in five studies (two in favor of the treated group, one null, and two in favor of the control group);
- gastroenteric complications were reported in four studies (three in favor of the treated group and one in favor of the control group);
- sepsis was reported in four studies (two in favor of the control group and two null).

In seven studies [10, 12, 21, 22, 25, 26, 39] postoperative chest drain blood loss was significantly less in the treated group vs the control group.

Non-outcome variables recorded in the set of 36 RCTs reported results in favor of the biocompatible group with respect to platelet count preservation [12, 29] and platelet activation markers [11], white blood cells count [23, 36, 41] and leukocyte activation markers [8, 29, 41], cytokine release [27, 36] and markers of hemostatic system activation [27, 30], and complement system activation [8, 29, 35].

Comment

The present meta-analysis demonstrates no effect of biocompatible circuits on death after cardiac operations and a limited effect (lower transfusion needs and AF rate) on morbidity, leading to a shorter ICU and hospital stay. When analyzing only high-quality studies, these benefits remain significant only for AF rate and ICU stay.

PRCs transfusions in patients undergoing cardiac operations depend on a number of factors [47], and not surprisingly, the effect of biocompatible circuits is marginal and absent at all in high-quality studies.

Atrial fibrillation after cardiac procedures may recognize an inflammatory triggering mechanism [48–50], and the reduction in its postoperative rate observed even in the subgroup of high-quality studies may be explained through this mechanism. In our opinion, the lower AF rate is the main determinant of the shorter ICU and hospital stay observed in the biocompatible circuits group.

The present review addresses only clinical outcome data, and a detailed analysis of biochemical outcome is beyond our purposes. We note, however, that many studies could demonstrate a decrease in complement activation, leukocyte activation, and cytokine release in patients treated with biocompatible (especially heparin-coated) surfaces. Conversely, it is quite well established that these materials do not decrease thrombin formation, as demonstrated by studies where the thrombin generation marker PF 1.2 was measured [51].

Possible limitations and sources of bias in the present review and meta-analysis may be:

1. Heterogeneity of the different biocompatible treatments: it has been shown that different kinds of heparin coating (ionic vs covalent) may exert different effects on biochemical markers, even if this difference was not reflected by differences in clinical outcome.
2. Because 78% of the selected articles were based on heparin-bonded surfaces, the results should be considered basically related to this treatment. New generation treatments are presently lacking a large supporting literature, and further RCTs are needed to address their specific effect on postoperative outcome.
3. We could not stratify patients according to their preoperative risk (only one study was dedicated to high-risk patients), and we cannot exclude that selected subpopulations of patients may receive more clinical benefits by the use of biocompatible surfaces.
4. Some studies used a full-dose heparinization, whereas others [34] reduced systemic heparinization. We are not able to clarify whether this strategy is effective; however, considering that thrombin formation is not reduced by the simple use of heparin-coated surfaces, the rationale for this strategy is doubtful.

The present meta-analysis confirms that the biochemical effects of biocompatible circuits do not necessarily translate into clinical effects. As a matter of fact, blood activation and thrombin generation during cardiac operations may be due to both *material-dependent* and *material-independent* factors [51]. By modulating the contact surface between blood and foreign materials, only the first reaction may be controlled. Unfortunately, much evidence suggests that the *material-independent* blood activation during cardiac operations may be even more important than the simple reaction to foreign materials. Actually, patients undergoing off-pump coronary operations experience an increased procoagulant activity in the first 24 hours after the operation [52].

The use of cardiotomy suction during CPB results in a significant increase in thrombin, neutrophil, and platelet activation [53]. Retransfusion of pleuropericardial shed blood could obscure possible improvements in the biocompatibility of extracorporeal circuits [54, 55], and the overall effects of the *material-independent* blood activation (blood–air interface, cardiotomy suction, hemolysis, etc) may finally blunt the total effect of biocompatible surfaces [18].

To overcome this multifactorial pattern of blood activation and to limit the deleterious effects of CPB, comprehensive strategies have recently been proposed in a new approach to CPB that configures the concept of minimally invasive CPB. With certain differences, all the proposed systems share some concepts: closed circuit, separation of the cardiotomy suction, reduced priming volume, centrifugal pumps, and biocompatible surfaces [56–61]. The preliminary clinical experiences with these CPB systems are promising, and biocompatible treatment of the CPB circuit and oxygenator surfaces is one key point within this system.

Certainly, the rationale for this multifactorial approach seems more adequate for addressing the complex reactions that are leading to both inflammatory and coagulation cascade activation during cardiac operations. The key issue, from this point of view, is probably thrombin formation, which is at the same time a marker of coagulation cascade activation and a trigger for endothelial-based reactions, including consumption of antithrombin and protein C; platelet adhesion, aggregation and activation; adhesion molecules expression; and adhesion and activation of leukocytes. Not surprisingly, an intervention limited to the modulation of the blood-foreign surfaces interaction seems largely insufficient to produce an important clinical benefit.

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