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Cardiopulmonary Bypass Circuit Coatings: Recent Advances and Future Perspectives

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ABSTRACT

Introduction: Cardiopulmonary bypass (CPB) circuits expose blood to non-physiological surfaces, leading to platelet activation, coagulation disturbances, complement activation, hemolysis, and systemic inflammation. Early-generation heparin-coated circuits reduced thrombin formation, decreased heparin requirements, and mitigated inflammatory responses, laying the foundation for modern hemocompatible devices.
Objective: This review aims to summarize recent advances in CPB circuit coatings, critically evaluate their hemocompatibility, and highlight emerging strategies that enhance blood compatibility and reduce complications during extracorporeal circulation.
Method: Literature from the past decade was analyzed, focusing on polymer-based, zwitterionic, endothelial-mimetic, and nitric oxide–releasing coatings. Studies evaluating in vitro, preclinical, and clinical outcomes were considered, with emphasis on platelet activation, coagulation, complement activation, hemolysis, and inflammatory markers.
Results: Hydrophilic polymers such as PEG- and PMEA-based coatings reduced protein adsorption and platelet adhesion. Zwitterionic polymers demonstrated non-fouling properties under prolonged blood contact. Endothelial-mimetic coatings replicated vascular surface functions, enhancing hemocompatibility in preclinical models. Nitric oxide–releasing surfaces inhibited platelet activation and fibrin deposition. Improved hemocompatibility assessment using biomarkers including PF4, β-thromboglobulin, P-selectin, complement factors, and hemolysis indices enabled comparative evaluation of coating performance. Miniaturized extracorporeal circuits further decreased systemic inflammation and improved clinical outcomes.
Conclusion: Contemporary CPB circuit coatings substantially improve blood compatibility compared with uncoated circuits. While heparin-coated systems remain widely used, emerging polymeric, zwitterionic, endothelial-mimetic, and nitric oxide–releasing surfaces offer additional benefits. Ongoing research into hybrid multifunctional coatings, long-term durability, and clinical translation is essential to optimize CPB safety and physiological performance.

Keywords: Cardiopulmonary Bypass, Circuit Coatings, Hemocompatibility, Heparin Coating, Zwitterionic Polymers.

INTRODUCTION

CPB provides the surgeon with a bloodless and motionless operative field; however, this advantage also carries significant risks of complications such as platelet activation, dysfunction, and abnormal bleeding (1). CPB is a surgical technique used in the treatment of cardiac diseases, in which a heart lung machine temporarily takes over the functions of the heart and lungs. During CPB, contact between blood and the non-biocompatible surfaces of extracorporeal circulation components may lead to several adverse effects, including coagulation disorders, damage to blood cells and plasma proteins, ischemia–reperfusion injury, inflammation, and oxidative stress (2). Severe manifestations of these complications can result in systemic inflammatory response syndrome (SIRS) and sepsis, ultimately leading to organ failure. Most of these complications originate from platelet activation upon contact with foreign surfaces, such as the coatings of CPB circuits. During bypass, platelets adhere to these artificial surfaces, triggering the release of inflammatory cytokines and activation of the coagulation-fibrinolysis systems (3). Platelet surface markers, such as platelet factor 4 (PF4), β-thromboglobulin (β-TG), glycoprotein IIb/IIIa (GPIIb/IIIa), and soluble P-selectin, are released during the coagulation cascade and are considered reliable biomarkers for platelet activation during CPB (4). Recent advances in bypass technologies have enabled the development of biocompatible surfaces with the potential to reduce platelet activation during CPB, thereby decreasing the incidence of postoperative complications. Heparin-coated circuits are widely employed, as they do not induce excessive platelet activation compared to non-coated circuits. Another commonly used circuit, poly-2-methoxyethyl acrylate

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(PMEA), possesses a protective water layer that maintains protein conformation and minimizes adhesion to foreign surfaces (5). While this has been the focus of research and advancement in cardiothoracic surgery, there is limited scientific and data-driven evidence supporting the biocompatibility of these circuits or their potential benefits in reducing platelet activation during CPB; consequently, a reliable and standardized laboratory protocol that compares these biocompatible circuits in vitro with respect to their effects on platelet function and activation has yet to be established (6). Heparin coated circuits were first introduced in the early 1990s to mitigate coagulation and inflammatory responses during CPB, while PMEA and other polymeric coatings were subsequently developed to provide enhanced hemocompatibility. In addition to platelet activation, contact with foreign surfaces activates the complement system, may induce hemolysis, and triggers systemic inflammation, which can exacerbate postoperative morbidity (7). Recent advances have focused on zwitterionic polymers, endothelial mimetic surfaces, and nitric oxide releasing coatings, which aim to further improve blood compatibility and reduce postoperative complications. Despite promising experimental results, comparative clinical data remain limited, and standardized laboratory protocols for evaluating biocompatible circuits are still lacking. Therefore, this review aims to systematically summarize historical and contemporary CPB circuit coating technologies, critically evaluate available data on their hemocompatibility and clinical effects, and highlight current knowledge gaps and future directions for research and development (8).

Types of CPB Circuit Coatings

Coating technologies used in CPB circuits aim to enhance biocompatibility, mitigate inflammatory responses, and reduce perioperative complications by minimizing the contact between blood and artificial surfaces during extracorporeal circulation. These coatings modify the blood-contacting surfaces of circuit components to limit undesirable processes such as platelet activation, complement system activation, coagulation cascade stimulation, and the loss of endothelial-like functionality. Currently, coating strategies employed in CPB circuits are generally classified into three major categories: heparin coatings, polymer-based coatings (e.g., PMEA), and next-generation functional coatings (9).

Heparin-coated circuits have been one of the most widely used biocompatibility strategies since the 1980s. Through the covalent binding of negatively charged heparin molecules to the surface, the anticoagulant effect becomes localized, thrombin generation is reduced, and a significant decrease in complement activation is achieved. Clinical studies have demonstrated that heparin-coated circuits reduce platelet consumption, lower inflammatory mediators, and may decrease transfusion requirements (10). The second major group of coatings consists of polymer-based materials, with PMEA (poly-2-methoxyethyl acrylate) being the most prominent example. PMEA exhibits hydrophilic properties and forms a surface that provides “low protein adsorption.” This characteristic minimizes the contact between blood cells and the artificial surface, resulting in a substantial reduction in platelet activation. A key advantage of PMEA coatings is that they do not carry the risk of heparin-related allergic reactions or HIT (heparin-induced thrombocytopenia). For these reasons, PMEA-based surface technologies have become widely preferred in modern heart–lung machines. With advances in material science, a third group of next-generation coatings has emerged. These include zwitterionic polymers, coatings designed to mimic endothelial surface architecture, and nitric oxide (NO)-releasing surfaces (11). Table 1 summarizes the main types of next-generation coatings, along with their mechanisms, advantages, and limitations.

Zwitterionic surfaces provide a superhydrophilic structure that minimizes protein adsorption; endothelial-mimetic coatings confer antithrombotic and anti-inflammatory functions; and NO-releasing coatings mimic physiological antiplatelet effects, thereby inhibiting platelet activation and aggregation. The common goal of these next-generation technologies is to render the circuit blood-contacting surfaces “non-reactive” and as close as possible to a natural endothelial surface. However, this field is still rapidly evolving, and comparative data on the clinical translation and long-term performance of new materials remain limited; therefore, standardized laboratory evaluation protocols and well-designed clinical studies are required (12).

Table 1. Main types of next-generation coatings, their mechanisms, advantages, and limitations

Coating Type	Mechanism / Feature	Advantages	Limitations
Heparin	Binding of negatively charged heparin molecules to surface, anticoagulant effect	Local anticoagulation, reduced thrombin generation, reduced platelet loss	HIT risk, limited long-term stability in some types, production variability
PMEA (Poly-2-methoxyethyl acrylate)	Hydrophilic surface formation, low protein adsorption	Reduced platelet and protein adhesion, no HIT risk	Mixed clinical outcomes, less platelet protection than heparin
Phosphorylcholine (PC/MPC)	Phosphatidylcholine-like head groups, zwitterionic	Reduced protein adsorption, good antithrombotic performance	Limited long-term durability
Zwitterionic Polymers	Contain positive and negative groups, superhydrophilic	Antifouling, antithrombotic, potential antibacterial	Long-term durability and homogeneity challenges
Endothelial-Mimetic (Biomimetic)	Endothelium and glycocalyx mimicry, heparin immobilization	Antithrombotic, anti-inflammatory, supports re-endothelialization	Production difficulty, sterilization effects, limited clinical data
NO-Releasing Coatings	Release of nitric oxide to inhibit platelet activation	Reduced platelet adhesion and thrombus, less systemic anticoagulation needed	Controlled long-term release, requires toxicity monitoring

Heparin-Coated Circuits

Two primary strategies exist for heparin surface coatings: covalent binding and ionic/adsorptive binding. Covalent binding techniques chemically immobilize heparin onto the surface, minimizing drug elution and thereby maintaining long-lasting and stable anticoagulant activity. In contrast, ionic/adsorptive approaches are more practical to apply but may lead to faster loss of the coating (through elution or desorption) under mechanical stress or prolonged blood exposure (13).

The significance of the binding type becomes evident in the effectiveness of heparin-coated circuits on hemostatic function. Heparin-coated surfaces create a localized anticoagulant effect, reducing thrombin generation and thereby limiting coagulation cascade activation. Clinical studies have reported that heparin-coated circuits allow for reduced systemic heparin doses (targeting lower ACT levels) while maintaining similar or even lower bleeding and transfusion requirements, and some studies have additionally observed reductions in thrombin generation markers. The efficacy of these hemostatic effects is closely linked to the type of covalent or ionic binding described above, as more stable immobilization prolongs anticoagulant activity and enhances thrombin inhibition. However, the effects vary depending on the heparin binding method, surface density, and operative protocols; consequently, some randomized trials have reported mixed or inconclusive clinical benefits (14).

Heparin coatings can modulate blood surface interactions and thereby suppress complement activation; the literature has shown that heparin-coated surfaces reduce levels of C3a, C5a, and the terminal complement complex (sC5b-9). These anti-complement effects may result both from direct heparin complement interactions and from decreased protein adsorption on the surface. However, recent studies particularly in minimally invasive or mini-CPB models have reported that the effect of heparin coatings on complement activation is sometimes small or not statistically significant; thus, the magnitude of complement inhibition depends on the experimental or clinical conditions (15).

Complement inhibition becomes particularly relevant when considered together with the platelet-preserving capacity of heparin coatings. One of the main claims of heparin-coated circuits is the reduction of platelet loss and activation. Both in vitro studies and some clinical comparisons have demonstrated that covalently bound heparin surfaces better preserve platelet survival and function. Nevertheless, some large clinical trials have reported minimal or no differences in platelet count or activation markers. Therefore, platelet preservation depends on the type of heparin coating, the duration of surgery, and hemodynamic/flow conditions (16).

These mechanistic effects have been evaluated in the context of clinical outcomes. Results from clinical studies are heterogeneous; many reports indicate that heparin-coated circuits can improve inflammatory markers, postoperative drainage/bleeding, intensive care unit stay, and transfusion requirements. For example, some series observed reductions in postoperative drainage and transfusion needs in patients

managed with heparin-coated circuits. On the other hand, some randomized controlled trials reported neutral outcomes rather than significant clinical benefits; therefore, careful consideration of systematic application, clinical protocols, and patient selection is warranted.

Finally, heparin coatings have several inherent limitations. The risk of heparin-induced thrombocytopenia (HIT) persists, as immobilized heparin can theoretically form heparin–PF4 complexes and elicit antibody production; although clinically significant cases are rare, immunologic adverse events should be closely monitored during both intraoperative and postoperative periods. With respect to durability and long-term performance, covalent binding generally provides greater stability, whereas certain surfaces may lose anticoagulant activity under mechanical stress or during prolonged ECMO-like support. Moreover, variations in manufacturing techniques, surface chemistry, and heparin density across different products lead to inconsistencies in clinical performance and hemostatic outcomes, underscoring the need for standardized testing protocols and direct comparative studies (17). Over the past decade, research has consistently shown that heparin-coated CPB circuits confer mechanistic and biochemical benefits, including reduced thrombin generation, diminished complement activation, and improved platelet preservation. However, the overall clinical advantage remains variable and is influenced by study design, procedural protocols, and the specific type of coating employed.

Polymeric Coatings

Polymeric coatings have been developed primarily to enhance biocompatibility and reduce thrombogenicity on blood-contacting surfaces.

PMEA Coatings

PMEA (poly-2-methoxyethyl acrylate) is a polymer with both hydrophilic and hydrophobic properties; this dual nature allows the surface to adhere to the material while creating a “blood-compatible / non-fouling” interface on the blood-contacting side. Consequently, protein adsorption and denaturation are reduced, and platelet and coagulation factor adhesion to the surface is minimized. In vitro studies using PMEA-coated circuits in a 6-hour whole blood circulation model reported markedly reduced fibrin deposition and thrombus formation on the surface, while antithrombin capacity and antithrombogenic properties were preserved. Protein and fibrinogen adsorption were found to be lower compared with both heparin-coated and uncoated circuits (18). In animal (porcine) models, PMEA-coated circuits demonstrated similar or sometimes superior hemocompatibility compared with heparin-coated circuits; notably, fibrinogen adsorption was significantly decreased, and thrombin–antithrombin complexes and bradykinin levels remained lower in the PMEA group. These findings suggest that PMEA may represent a reasonable alternative for clinical circuit applications. Clinical data, however, are partially promising and partially inconsistent: in pediatric cardiac surgery using PMEA-coated oxygenators, no significant reduction was observed in thrombin/fibrinolytic activation markers during surgery, although postoperative chest drainage volume and transfusion requirements were significantly reduced. Another study reported that PMEA-coated circuits were less effective than heparin-coated circuits in preserving platelet counts; no advantage was observed in inflammatory markers or oxidative stress parameters. Taken together, these data indicate that PMEA coatings provide strong biomechanical and biochemical advantages; however, their clinical benefits may not always be as consistent as those of heparin coatings. Therefore, before advocating a transition to or routine use of PMEA, further studies especially randomized “heparin vs. PMEA” clinical trials are required (19).

Phosphorylcholine (PC/MPC) –Based Coatings

Phosphorylcholine (PC)-based coatings are synthetic polymers designed to mimic the phosphatidylcholine head groups found in the outer leaflet of cell membranes. Their zwitterionic, electrically neutral structure minimizes nonspecific protein adsorption and reduces platelet adhesion under both static and dynamic conditions. PC-coated CPB circuits have historically been one of the most widely used non-heparin alternatives and have demonstrated improvements in hemocompatibility, including decreased complement activation, lower thrombin generation, and reduced inflammatory response during bypass. Comparative studies report that PC coatings provide similar antithrombogenic performance to heparin-based systems, although often with shorter durability under prolonged

perfusion. Despite declining commercial availability in recent years, PC/MPC technology remains an important reference standard in the development of next-generation biomimetic CPB circuit coatings (20).

PEG-Based and Other Hydrophilic Polymer Coatings

In recent years, hydrophilic and "anti-fouling / non-fouling" polymers particularly PEG and its derivatives have been investigated as promising alternatives for blood-contacting surfaces. A 2022 study demonstrated that heparin-loaded PEG-based hydrogel coatings could create an antithrombogenic surface for ECMO circuits, provide prolonged heparin release, and significantly reduce platelet adhesion (23). These findings indicate that PEG-based coatings may offer potential advantages for long-term extracorporeal circuits, such as ECMO or prolonged CPB. The primary mechanism of PEG and similar hydrophilic polymers involves the formation of a dense hydration layer on the surface, which prevents protein and cellular adhesion, thereby reducing thrombosis, platelet adhesion, protein adsorption, and inflammation risk. Recent reviews have further emphasized the "non-fouling" potential of PEG/PEO and other hydrophilic polymer coatings, highlighting their capacity to significantly reduce platelet, protein, and complement activation. Despite these promising mechanistic data, several critical challenges remain before PEG-based coatings can be widely implemented clinically. These include oxidative stress, exposure to high shear conditions, fluctuations in pH and blood chemistry, long-term coating stability, heparin loading efficiency, and controlled release capabilities. Currently, there is insufficient long-term clinical evidence supporting the safe routine use of these coatings in CPB or ECMO circuits (21).

Therefore, PEG-based and other hydrophilic polymer coatings are considered promising alternatives; however, in the context of reviews or clinical guidelines, it is more appropriate to classify them as "emerging / experimental" technologies pending further validation.

Next-Generation Functional Coatings:

Zwitterionic and Composite Polymer Strategies

One of the emerging strategies in polymeric surface modifications in recent years is zwitterionic coatings. These coatings contain both positive and negative charge groups within the same molecule, forming a dense hydration layer on the surface; this significantly reduces protein and cell adhesion, providing advantages in terms of thromboresistance and cell attachment. For example, a study published in 2024 reported that high-density zwitterionic polymer "brushes" exhibited strong antifouling and antithrombotic effects on blood-contacting surfaces, significantly reducing platelet and fibrinogen adhesion (22). Further advancements in 2023–2024 have led to zwitterionic hydrogel coatings that demonstrate both antithrombogenic and antimicrobial properties. In particular, a super-hydrophilic carboxymethyl-chitosan-based zwitterionic coating largely prevented thrombus formation and showed resistance to bacterial/biofilm formation in both in vitro and in vivo tests (23).

In addition, efforts have been made to develop zwitterionic coatings not only as single-function but also as multifunctional surfaces. A 2025 study described a heparin/zwitterion composite coating that provided anticoagulant (heparin immobilization), antifouling (zwitterionic), and antibiotic/antimicrobial properties on the surface; this coating reduced thrombus weight by 98.7% compared to bare PVC after 6 hours of whole blood exposure. However, significant challenges and uncertainties remain in translating zwitterionic and composite coatings to clinical application. Issues such as mechanical stability, long-term durability, manufacturing standardization, coating thickness, surface homogeneity, and reproducibility are actively discussed in the literature (24).

In conclusion, zwitterionic and new polymer-based coatings have the potential to reduce thrombogenicity, protein/platelet adhesion, and infection risk compared to conventional heparin or simple polymer coatings; however, wider clinical use of these technologies requires additional preclinical and clinical studies, surface standardization, and long-term data.

Endothelial-Mimetic Coatings

Endothelial-mimetic coatings have emerged as a significant direction in polymeric and biomimetic surface modification strategies, aiming to replicate key physiological functions of the native vascular endothelium and its glycocalyx layer. This approach integrates both biopassive elements (to reduce protein and cellular adhesion) and bioactive components (to support anticoagulation and modulate inflammatory responses), thereby creating surfaces that are more stable, thromboresistant, and biocompatible during blood contact in extracorporeal devices. A notable example was reported in 2024, in which a super-hydrophilic endothelial-mimetic coating (SEMMC) was applied to the surface of polypropylene (PP) hollow-fiber membrane (HFM) oxygenators. This design combines heparin immobilization to provide anticoagulant bioactivity with a zwitterionic PMPCC interface to achieve strong antifouling properties and markedly reduced protein adsorption. The study demonstrated that total protein adsorption could be reduced to below 30 ng/cm², and in an animal ECMO model performed without systemic anticoagulation, the SEMMC-treated membranes maintained stable oxygenation for 15 hours. In contrast, uncoated and conventional heparin-coated membranes exhibited thrombosis or plasma leakage within 4–8 hours (25). These findings highlight that endothelial-mimetic surface designs have substantial potential to improve hemocompatibility in long-term extracorporeal support systems (including ECMO) by reducing thrombosis, protein accumulation, and membrane failure marking an important step toward future clinical translation.

A similar study demonstrated that endothelial-mimetic surface modification applied to vascular grafts significantly enhanced both antithrombogenic performance and graft patency, with these effects validated in both rat and porcine models. These coatings were reported not only to markedly suppress thrombus formation but also to promote endothelial cell adhesion and surface re-endothelialization; thus, they were shown to provide a microenvironment that is simultaneously anticoagulant and supportive of endothelial regeneration (26).

Moreover, a comprehensive review reported that biomimetic coatings mimicking extracellular matrix (ECM) and glycocalyx components reduce platelet and leukocyte adhesion, complement activation, and inflammatory responses, thereby lowering inflammation and infection risk and improving overall biocompatibility. Notably, combined surface strategies such as integrating polydopamine-PEG interfaces with NO-releasing coatings have been described as having the potential to create a functional “biomimetic endothelial surface” by simultaneously offering antifouling, anticoagulant, and antimicrobial properties. However, significant technical challenges still limit the clinical translation of endothelial-mimetic coatings. The literature highlights several limitations, including coating stability, long-term mechanical durability, uniform and sufficient coverage of the entire circuit or oxygenator surface, lack of standardization during manufacturing, potential deterioration of coating functionality during sterilization, and time-dependent inactivation of biologically active molecules (27). Therefore, endothelial-mimetic surface technologies are still regarded in the current literature as a “promising yet experimental” approach.

Nitric Oxide–Releasing Coatings

NO releasing (or NO generating) coatings aim to mimic the natural antithrombogenic signaling of the vascular endothelium, thereby locally suppressing thrombus formation and platelet activation on artificial blood contacting surfaces. In these coatings, NO donors or catalytic components are embedded within a polymer matrix to provide sustained NO release from the surface; consequently, platelet adhesion, aggregation, and thrombus formation are markedly reduced.

Preclinical studies using various models have demonstrated that NO releasing coatings confer significant protective effects against both thrombosis and platelet activation. For instance, in a four hour rabbit extracorporeal circulation model, a combination of copper nanoparticle containing polyurethane coating with systemic RSNO infusion (NOGen/SNAP) significantly reduced thrombus formation compared to control surfaces, while preserving platelet count and fibrinogen levels. Similarly, in polymer-coated oxygenator fibers treated with a biomimetic microgel coating (leveraging an endogenous RSNO reservoir), clot formation was largely inhibited in human blood under flow conditions, with reduced β thromboglobulin release and decreased platelet loss. More recently, in a six

hour full blood porcine circulation model using a “slippery liquid infused + NO releasing (LINO)” circuit, platelet loss was delayed, the proportion of P selectin–positive activated platelets was significantly lower compared to controls, and surface thrombus accumulation was markedly reduced. Importantly, NO flux did not induce observable toxic effects such as methemoglobin formation (28).

Taken together, these findings suggest that NO releasing coatings offer multiple hemocompatibility benefits: they inhibit platelet adhesion and activation, reduce thrombus formation, and potentially decrease the requirement for systemic anticoagulation. In particular, for long-duration extracorporeal circuits (e.g., CPB or ECMO), such coatings may provide a more “endothelium mimetic,” physiologic surface environment, thereby lowering both thrombotic and inflammatory risks.

Hemocompatibility Assessment Methods for Blood-Contacting Surfaces in CPB and ECMO Circuits

A properly engineered CPB/ECMO circuit surface must be capable of maintaining safe and prolonged contact with blood, and this capability is determined not only by the surface chemistry itself but also by how surface blood interactions are evaluated. Therefore, hemocompatibility assessments must be multidimensional, reproducible, and compliant with standardized protocols.

Platelet Adhesion / Activation and Protein Adsorption

The adhesive and activation potential of platelets on coated materials is commonly evaluated using static incubation assays with platelet-rich plasma (PRP) or whole blood. After incubation, the number of platelets adhering to the surface can be quantified using immunostaining, fluorescence microscopy, or scanning electron microscopy. In parallel, plasma proteins adsorbed onto the material particularly fibrinogen, albumin, and immunoglobulins should be examined through protein adsorption assays. Low protein adsorption generally correlates with enhanced hemocompatibility (29).

Dynamic Flow / Whole-Blood Circulation Tests

While static models provide useful information about surface blood interactions, they fail to replicate actual CPB/ECMO conditions, where continuous circulation, flow dynamics, and shear stress are present. Therefore, dynamic systems such as flow-loop setups (e.g., Chandler loop), rotary pump models, or rotating circuits should be employed. In these models, coated surfaces are exposed to prolonged whole-blood circulation, during which platelet activation, hemolysis, protein adsorption, and surface thrombus formation are systematically evaluated. For example, in ex vivo systems using slippery or liquid-infused surfaces, fibrinogen adsorption and platelet adhesion were markedly reduced after 6 hours of circulation, and no visible thrombus formation was detected (30).

Hemolysis and Red Blood Cell Integrity

During prolonged exposure to extracorporeal circuits, not only platelets but also red blood cells (RBCs) are subjected to mechanical stress and surface interactions. Therefore, hemolysis assays such as measurements of plasma free hemoglobin, lactate dehydrogenase (LDH) levels, RBC membrane integrity, and erythrocyte morphology are essential. These parameters indicate whether a surface coating preserves RBC structural integrity or contributes to mechanical or biochemical injury (31).

Coagulation and Complement Activation Marker Analysis

Coated surfaces may also influence the coagulation cascade and immune–complement pathways. Thus, coagulation-related markers, including thrombin–antithrombin complexes (TAT), D-dimer levels, and fibrinogen consumption, should be monitored. Complement activation can be assessed through markers such as C3a, C5a, and the terminal complement complex (sC5b-9). Together, these analyses reveal the extent to which a surface remains immunologically “silent” or triggers pro-inflammatory or pro-thrombotic responses (32).

Standardization, Protocol Consistency, and Compliance

The reliability of hemocompatibility testing depends heavily on standardized protocols and adherence to international guidelines for biomaterial safety. To ensure comparability across laboratories, key

parameters including incubation duration, flow rate, blood source (human vs. animal), temperature, and the surface-to-blood volume ratio must be controlled consistently. Lack of standardization remains one of the major challenges in interpreting hemocompatibility data across studies (33).

Evaluating only a single parameter for example, platelet adhesion can be misleading, as overall hemocompatibility reflects the integrated response of multiple systems, including platelets, erythrocytes, plasma proteins, coagulation pathways, and the complement system. Therefore, a comprehensive assessment should combine biochemical markers, microscopy-based surface analyses, and dynamic whole-blood circulation tests to provide a complete understanding of coating performance under clinically relevant conditions.

Future Perspectives and Research Gaps;

Modern polymeric, zwitterionic, and biomimetic coatings offer significant improvements in biocompatibility and hemocompatibility compared to older-generation heparin or PMEA-based coatings. Nevertheless, substantial research gaps remain in this field, and further development is needed. In the following section, the current literature is synthesized to highlight emerging future directions and existing limitations.

Clinical Potential of Hybrid / Multifunctional Coatings

Recent years have seen the development of heparin/zwitterionic composite coatings that not only provide anticoagulation but also exhibit antifouling and antimicrobial properties. For instance, one study reported that a heparin/zwitterion composite coating reduced thrombus weight on PVC surfaces by 98.7% over 6 hours, highlighting the potential of multifunctional coatings to simultaneously mitigate thrombosis and biofilm formation. Moreover, a “universal zwitterion coating” strategy applicable to devices with complex geometries and long structures, such as catheters, has demonstrated near-zero protein fouling across a wide pH range, high mechanical stability, and sustained anticoagulant performance (34). In light of these findings, it is crucial to systematically evaluate hybrid coatings in CPB circuits particularly in multi-component systems such as oxygenator membranes, pump surfaces, and tubing. Such assessments can enable the development of surface designs that optimize antithrombotic, antifouling, and antimicrobial properties concurrently, thereby facilitating safer translation into clinical practice.

Endothelial Mimetic (Biomimetic) Surface Designs

A study published in 2024 reported the modification of an artificial oxygenator membrane using an endothelial membrane-mimetic coating (SEMMC), which reduced protein adsorption on the surface to less than 30 ng/cm². Notably, the coating enabled 15 hours of continuous oxygenation in an anticoagulant-free animal model.

In addition, PMPCC/Hep-based coatings have been shown to reduce protein adsorption and platelet adhesion by approximately 50% and 90%, respectively, compared to conventional heparin coatings (35).

These findings underscore the potential of endothelial-mimetic coatings to enhance hemocompatibility in CPB circuits. Therefore, it is essential to implement such biomimetic surface modifications across all blood-contacting components and systematically evaluate their impact, particularly in long-duration surgeries or cases requiring circuit re-use. This approach would clarify whether these coatings can effectively reduce thrombosis, inflammation, and plasma leakage risks, thereby supporting safer and more reliable clinical applications.

Zwitterionic / Anti-fouling Coatings

Zwitterionic polymers have emerged as one of the most promising candidates for creating ultra-low protein adsorption and non-fouling surfaces. These coatings have the potential to reduce both thrombus formation and bacterial or biofilm accumulation, which is particularly critical in patients undergoing long-term ECMO, dialysis, or CPB where infection risk is high.

However, uncertainties remain regarding the long-term mechanical and chemical stability of zwitterionic coatings, maintenance of surface integrity after sterilization, and durability under high shear stress. Additionally, achieving homogeneous coating across entire circuit components remains a challenge (36). Therefore, zwitterionic coatings should be systematically evaluated in vitro and in preclinical models under long-term circulation, post-sterilization conditions, and physiologic flow/shear scenarios. Such studies are essential to determine their true potential for safe and effective clinical application.

Clinical Translation of Nitric Oxide-Releasing (NO-Releasing) Surfaces

A phosphorylcholine coating grafted with organic selenium has been developed, and this surface has been shown to release nitric oxide (NO). This coating significantly reduces thrombus formation and inflammatory responses in both in vitro and in vivo models.

This strategy aims to transfer the antithrombotic and anti-inflammatory NO production of the native endothelium to artificial circuits, and if successful, it could represent a substantial advancement by reducing systemic heparin requirements, lowering thrombosis risk, and mitigating inflammation. In this context, pilot preclinical and Phase I clinical studies should be initiated to evaluate the potential of NO-releasing coatings in CPB and ECMO circuits. In particular, in circuits operated with no or low-dose heparin, parameters such as thrombus formation, thrombosis, hemolysis, and inflammation should be systematically monitored, and the clinical benefits of the coating should be directly assessed (37).

Hemocompatibility Assessment Methods;

Evaluating the hemocompatibility of blood-contacting surfaces is critical for determining whether a coating induces thrombosis, complement activation, hemolysis, or inflammatory responses. A comprehensive hemocompatibility assessment requires the combined use of biochemical marker measurements, cell-level activation assays, dynamic whole-blood circulation models, and surface characterization techniques. Although international standards (ISO 10993-4 and relevant ASTM guidelines) provide a foundational framework for test selection, the literature increasingly emphasizes the need for device-specific and physiologically realistic in vitro models (38).

Platelet Activation and Adhesion Assays

Platelet response is one of the most fundamental indicators of hemocompatibility. The most commonly used soluble and cellular markers include platelet factor-4 (PF4), β-thromboglobulin (β-TG), and P-selectin (CD62P), all of which reflect platelet degranulation and activation. Detection of activated GPIIb/IIIa receptors using PAC-1 binding by flow cytometry provides additional information on functional activation status. Quantitative and morphological analysis of platelets adhering to the surface is performed using fluorescence microscopy and scanning electron microscopy (SEM). The combined use of soluble activation markers and adhesion assays substantially enhances the discriminatory power between different coating strategies (39).

Coagulation Markers (Thrombin Generation)

Activation of the coagulation system is typically assessed by measuring thrombin–antithrombin complexes (TAT), one of the most sensitive indicators of surface-induced coagulation and a widely used parameter in extracorporeal circuit studies. D-dimer levels and the detection of fibrin deposition on circuit surfaces provide complementary information regarding downstream clot formation and fibrinolytic activity (40).

Complement Activation

Contact between blood and artificial surfaces frequently triggers complement activation. Therefore, soluble anaphylatoxins (C3a, C5a) and the terminal complement complex (sC5b-9) are essential parameters in hemocompatibility testing. Increases in these markers have been associated with inflammatory responses and organ dysfunction, representing important indicators of surface-driven complement activation during CPB and ECMO (41).

Leukocyte Activation and Inflammatory Cytokines

Innate immune activation is assessed through leukocyte surface markers (e.g., neutrophil and monocyte CD11b expression), oxidative stress enzymes such as myeloperoxidase (MPO), and circulating cytokines including IL-6 and TNF-α. These parameters are critical for determining whether the surface has the potential to trigger SIRS-like inflammatory responses (42).

Hemolysis and Red Blood Cell Integrity

Hemolysis is a critical safety parameter for extracorporeal devices. In both static and dynamic hemolysis assays, plasma-free hemoglobin and lactate dehydrogenase (LDH) levels serve as primary indicators. Microscopic evaluation of erythrocyte morphology complements these biochemical measurements. When assessing hemolysis in blood pumps and extracorporeal circuits, adherence to ASTM F1841, ASTM F756, and related guidelines is essential to ensure comparability and reproducibility across studies (43).

Surface Characterization and Physicochemical Analysis

To interpret the biological behavior of a coated surface, multiple physicochemical analyses are required. Surface morphology is assessed by scanning electron microscopy (SEM), surface roughness by atomic force microscopy (AFM), chemical composition by X-ray photoelectron spectroscopy (XPS), and hydrophilicity/hydrophobicity by contact angle measurements. Because changes in these parameters directly influence protein adsorption and cellular interactions, they play a key mechanistic role in interpreting hemocompatibility data (44).

CONCLUSION

Advances in surface coating technologies for cardiopulmonary bypass (CPB) circuits have significantly reduced key complications arising from blood–material interactions, including thrombosis, inflammation, and hemolysis. Conventional coatings such as heparin, phosphorylcholine, albumin, and various hydrophilic surfaces, as well as newer nitric oxide–releasing and endothelial-mimetic strategies, have demonstrated meaningful reductions in platelet activation, coagulation pathway engagement, and systemic inflammatory responses. Nevertheless, none of these approaches fully replicate the complex and multifactorial biological functions of the native endothelium. Current evidence indicates that while many coatings provide notable benefits during short-term use, their long-term stability, surface integrity, and performance under high shear stress conditions remain variable. Although heparin coatings are well-established in clinical practice, anticoagulant effectiveness differs among patients, and platelet activation cannot be entirely suppressed. More physiologically inspired NO-releasing and endothelial-mimetic coatings show considerable promise, yet widespread clinical adoption is still limited due to challenges related to manufacturing, stability, and regulatory approval. Overall, the available data suggest that an ideal hemocompatible surface for CPB circuits has not yet been achieved; however, current technologies have substantially improved the safety and biocompatibility of extracorporeal circulation.

Future Perspectives

Future developments in CPB circuit coatings are expected to move beyond single-mechanism approaches toward more comprehensive strategies capable of modulating multiple biological pathways simultaneously, including coagulation, inflammation, complement activation, and oxidative stress. Biomimetic designs that more closely replicate endothelial function such as glycocalyx-like polymer architectures, endothelial-derived peptides, or surfaces engineered to promote the adhesion of circulating endothelial progenitor cells may offer more physiologically relevant protection against thrombosis and inflammation. In parallel, the creation of more stable and controllable nitric oxide–releasing systems capable of sustaining physiological NO fluxes could further enhance hemocompatibility. The use of nanoscale surface topographies that regulate protein adsorption and cellular activation also represents a promising direction for next-generation coatings. Moreover, standardization of hemocompatibility assessment methods in accordance with ISO 10993-4 will be essential to improve comparability across studies and accelerate the translation of emerging technologies

into clinical practice. Ultimately, larger, multicenter, and long-term clinical investigations will be necessary to determine whether new coating strategies meaningfully improve patient outcomes. Overall, the future direction of the field points toward durable, biologically active, multifunctional, and clinically feasible surface technologies.

DESCRIPTIONS

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