Arch. Metall. Mater. **71** (2026), 3, 965-976

DOI: https://doi.org/10.24425/amm.2026.1988

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HEMOCOMPATIBILITY ASSESSMENT OF BLOOD-CONTACTING DEVICES – CASE STUDY BASED ON SELECTED COMPLETED PROJECTS

Heart failure remains a leading cause of mortality worldwide, and advanced stages often require mechanical circulatory support such as ventricular assist devices (VADs). Despite their clinical importance, long-term performance is limited by complications including thrombosis, hemolysis, and infection, which arise from complex blood-material interactions under non-physiological flow conditions. Achieving durable hemocompatibility therefore remains a central challenge in cardiovascular device design.

Recent advances in biomaterials and biomedical engineering have introduced multiple strategies to address these limitations, including additive manufacturing, nanostructured materials, and advanced surface engineering. This review focuses on two complementary approaches: stereolithography (SLA)-based additive manufacturing of photopolymers for fabricating complex blood pump components, and peptide-based self-assembled monolayers (SAMs) for molecular-level control of blood-material interactions. SLA enables precise geometric optimization and tailored mechanical properties, while oligoproline SAMs reduce protein adsorption and platelet adhesion under dynamic flow conditions.

Together, these strategies highlight the importance of integrating bulk material design with surface biofunctionalization to improve hemocompatibility. The review also outlines emerging trends in biomimetic design and intelligent, data-driven approaches for next-generation ventricular assist systems, aiming toward safer, more durable, and patient-specific cardiac support technologies.

Keywords: Ventricular assist devices (VADs); Hemocompatible biomaterials; Additive manufacturing; Surface engineering; self-assembled monolayers

Highlights

- Advanced biomaterials significantly improve hemocompatibility in cardiac assist devices
- Additive manufacturing enables patient-specific and biomimetic VAD geometries
- Surface engineering strategies reduce thrombogenicity and protein adsorption
- Smart materials and embedded sensors allow real-time monitoring of hemodynamics
- Artificial intelligence accelerates design optimization and complication prediction

1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, accounting for nearly one-third of global deaths and imposing a growing burden on healthcare systems. A significant proportion of patients with advanced heart failure require mechanical circulatory support systems such as left ventricular assist devices (LVADs), total artificial hearts, extracorporeal membrane oxygenation (ECMO), and hemodialysis circuits. These devices have transformed clinical management of end-stage cardiovascular disease; however, their long-term success is still fundamentally constrained by blood-material incompatibility [1-3]. Despite decades of progress in biomaterials science, no synthetic surface has yet achieved true hemocompatibility equivalent to the native endothelium. The vascular endothelium maintains a highly regulated, antithrombotic interface through dynamic secretion of nitric oxide, prostacyclin, thrombomodulin, and other anticoagulant

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factors. Once this biological interface is replaced by artificial materials, blood is exposed to non-physiological surfaces that rapidly trigger a cascade of protein adsorption, cellular adhesion, and coagulation activation [4-6]. The initial interaction between blood and biomaterial surfaces occurs within seconds and is dominated by plasma protein adsorption. This event determines the subsequent biological response and is often referred to as the "Vroman effect," where proteins with higher mobility initially adsorb and are later displaced by higher-affinity proteins such as fibrinogen [7]. The adsorbed protein layer acts as a bioactive interface that mediates platelet adhesion, leukocyte activation, and complement cascade initiation [8].

In clinical practice, these molecular-level events manifest as severe complications including pump thrombosis, hemolysis, stroke, and device failure. For LVADs in particular, thromboembolic complications remain one of the most serious adverse outcomes, often requiring device exchange or resulting in mortality [9]. Therefore, improving hemocompatibility is not merely a material design challenge but a critical clinical necessity.

Traditional biomaterials such as titanium alloys, cobalt-chromium steels, and medical-grade polymers (e.g., polyurethane and polyethylene terephthalate) have been widely used due to their mechanical strength and chemical stability. However, even these clinically established materials exhibit significant thrombogenicity when exposed to blood without surface modification [10,11]. Consequently, modern biomaterials research has shifted toward two synergistic strategies:

1. Bulk material innovation, focusing on mechanically robust and manufacturable materials suitable for complex device architectures.
2. Surface engineering strategies, aiming to regulate interfacial biological interactions at the molecular level.

In this context, stereolithography (SLA)-based additive manufacturing has emerged as a powerful tool for fabricating complex blood-contacting geometries with micrometer-scale precision. SLA enables the production of optimized LVAD rotors and flow channels that minimize regions of stagnation and high shear stress, both of which are strongly associated with thrombosis formation [12-14]. However, SLA resins must simultaneously satisfy strict requirements for mechanical stability, chemical resistance, and hemocompatibility.

Parallel to advances in additive manufacturing, molecular-level surface engineering has provided new opportunities for controlling blood-material interactions. Among these, peptide-based self-assembled monolayers (SAMs) represent a particularly promising class of antifouling coatings. These systems mimic biological macromolecular structures and can be engineered to resist protein adsorption and platelet adhesion under physiological flow conditions [15,16].

Recent studies have demonstrated two complementary technological directions:

- The development of SLA-manufactured haemocompatible photopolymers for blood pump applications, combining design flexibility with biological evaluation in vitro and in vivo [17];
- The engineering of oligoproline-based SAM surfaces, which exhibit strong antifouling behavior and reduced thrombogenicity under dynamic blood flow conditions [18].

These two approaches operate at fundamentally different length scales – macro/micro-scale structural engineering versus nano/molecular-scale surface chemistry – yet converge on the same objective: reducing thrombosis and improving long-term device performance.

This review integrates these developments and critically evaluates their implications for next-generation cardiovascular devices. It further explores how additive manufacturing and molecular surface engineering can be combined into a unified design paradigm for hemocompatible biomaterials.

1.1. Blood-Material Interactions

1.1.1. Hierarchical Nature of Blood-Material Interfaces

Blood-material interactions are inherently hierarchical and governed by tightly coupled processes spanning molecular, nanoscale, cellular, and macroscopic (device) levels. This multiscale organization is a defining characteristic of hemocompatibility and explains why even subtle modifications in material chemistry or surface structure can lead to disproportionately large changes in biological response. Importantly, these processes do not occur independently but rather evolve sequentially and synergistically, forming a cascade that ultimately determines clinical outcomes in blood-contacting medical devices such as ventricular assist devices (VADs), vascular grafts, and extracorporeal circulation systems [1,5]. At the molecular level, the interaction between blood and artificial materials is dominated by rapid adsorption of plasma proteins. This event occurs within milliseconds to seconds after blood contact and represents the first and most decisive stage in determining downstream biological responses. The adsorbed protein layer is not static; instead, it undergoes continuous exchange and conformational rearrangement driven by differences in protein mobility, affinity, and surface energetics. This dynamic process leads to the formation of a conditioning film that effectively defines the "biological identity" of the material surface. Even when a material is chemically inert in bulk form, its interfacial behavior is governed by the composition, orientation, and structural state of adsorbed proteins, which can expose cryptic binding sites and alter biological recognition pathways [1,5]. At the nanoscale-to-cellular transition level, the protein-conditioned surface mediates direct interactions with circulating blood cells. Platelets are particularly sensitive to surface-bound fibrinogen and von Willebrand factor, which facilitate adhesion through receptor-mediated binding mechanisms. Once attached, platelets undergo activation characterized by shape change, degranulation, and expression of adhesion molecules, which amplifies recruitment of additional platelets and accelerates thrombus growth. In parallel, leukocytes can be activated through complement-mediated pathways and adhesive interactions with adsorbed proteins, contributing to inflammatory signaling and

further destabilizing hemocompatibility. These early cellular events are highly dependent on the structure and mechanical properties of the adsorbed protein layer, linking molecular-scale phenomena directly to cellular responses [1,5]. At the system level, localized cellular activation evolves into macroscopic coagulation phenomena. Activation of the coagulation cascade leads to thrombin generation, fibrin polymerization, and the formation of stable thrombi that can obstruct device function or embolize into the systemic circulation. In blood-contacting devices, these processes are strongly influenced by hemodynamic conditions, including shear stress gradients, flow stagnation zones, and recirculation regions. These mechanical factors interact with surface-driven biochemical events, amplifying thrombogenic potential in specific regions of the device. Consequently, thrombosis in cardiovascular implants is not solely a material problem or a flow problem, but rather a coupled bio-chemo-mechanical phenomenon [1,5]. The hierarchical coupling across these scales introduces significant complexity into biomaterial design. Modifications at one level – for example, altering surface chemistry to reduce protein adsorption – can unintentionally influence higher-order processes such as platelet adhesion or coagulation kinetics. Similarly, changes in device geometry that improve flow characteristics may alter local shear environments, thereby modifying protein adsorption behavior at the interface. This interdependence makes hemocompatibility fundamentally a systems-level property rather than an intrinsic material attribute. As a result, successful design of blood-contacting medical devices requires a multiscale engineering approach that integrates molecular-level surface control, cellular response modulation, and macroscopic hemodynamic optimization. This hierarchical perspective provides the conceptual foundation for emerging strategies such as peptide-based antifouling coatings and additive-manufactured device architectures, which aim to simultaneously address multiple levels of the blood-material interaction cascade [1,5].

1.1.2. Protein Adsorption and the Vroman Effect

The initial stage of blood-material interaction is governed by rapid adsorption of plasma proteins, which occurs within milliseconds to seconds after blood contact. This extremely fast interfacial event represents the first biological transformation of an artificial surface into a biologically active interface and ultimately determines the trajectory of all subsequent cellular and coagulation responses. The resulting adsorbed protein layer – often referred to as a conditioning film – acts as the true "biological identity" of the material rather than its native chemical composition [7].

In the earliest phase of exposure, highly abundant and mobile plasma proteins such as albumin dominate surface coverage due to their high diffusion rates and concentration in blood plasma. Albumin adsorption is typically rapid but relatively weak and reversible, forming a transient layer that is continuously remodeled as the interface evolves. Although albumin is often considered biologically inert or even passivating, its presence is highly dynamic and strongly influenced by local shear conditions and competitive adsorption effects [7].

As the interfacial system evolves, a time-dependent exchange process occurs in which initially adsorbed proteins are progressively replaced by proteins with higher surface affinity but lower bulk concentration. This phenomenon is known as the Vroman effect and represents a central principle in biomaterial surface science. According to this mechanism, protein adsorption is governed not only by thermodynamic affinity but also by kinetic competition between proteins with different molecular weights, diffusion coefficients, and binding strengths [7,8]. Consequently, the final composition of the adsorbed layer is not determined solely by plasma abundance but by a dynamic balance between adsorption, desorption, and surface rearrangement processes.

Within this exchange cascade, proteins such as fibrinogen, immunoglobulins, and high-molecular-weight kininogen gradually displace early adsorbed species like albumin. Among these, fibrinogen plays a particularly critical role in thrombogenesis due to its direct involvement in platelet adhesion pathways. Fibrinogen contains specific binding domains that interact with platelet glycoprotein receptors, particularly GPIIb/IIIa, enabling platelet attachment and subsequent aggregation [8]. This receptor-mediated interaction forms the molecular basis for thrombus initiation on artificial surfaces.

Importantly, the biological activity of fibrinogen is not determined solely by its presence on the surface but also by its conformational state upon adsorption. Surface-induced denaturation or partial unfolding of fibrinogen molecules can expose previously hidden (cryptic) epitopes that significantly enhance platelet binding affinity and activation potential. This conformational rearrangement transforms fibrinogen from a soluble plasma protein into a highly bioactive pro-thrombotic ligand, amplifying downstream coagulation responses [8,9]. Thus, protein structure at the interface is as important as protein identity in determining hemocompatibility outcomes.

Surface physicochemical properties play a decisive role in governing adsorption behavior and protein conformation. In particular, surface hydrophobicity is one of the most influential parameters controlling protein-surface interactions. Hydrophobic surfaces tend to promote strong, often irreversible protein adsorption accompanied by significant conformational deformation and unfolding. This increases the likelihood of exposing bioactive binding sites that promote platelet adhesion and activation. In contrast, hydrophilic surfaces generally support weaker, more reversible adsorption characterized by reduced structural perturbation of proteins, thereby lowering their biological reactivity [10].

Surface energy also contributes significantly to adsorption thermodynamics. High surface energy materials typically exhibit stronger initial protein binding, while low-energy surfaces may reduce overall adsorption density. However, in physiological conditions, competitive adsorption and dynamic exchange processes often override simple equilibrium predictions, reinforcing the importance of kinetic factors in the Vroman effect.

Overall, protein adsorption and the Vroman effect represent the fundamental molecular gateway through which blood first interacts with biomaterial surfaces. This stage sets the foundation for all subsequent biological responses, including platelet adhesion, coagulation cascade activation, and inflammatory signaling. As such, even minor modifications in surface chemistry, roughness, or energy can significantly alter the composition and structure of the adsorbed protein layer, leading to large-scale differences in hemocompatibility performance [7-10].

1.1.3. Platelet Adhesion and Activation Cascade

Once adsorbed proteins establish a conditioning layer on the biomaterial surface, the interface becomes biologically active and capable of mediating direct cellular interactions. Among circulating blood cells, platelets are the primary responders to foreign surfaces and play a central role in initiating thrombotic events. Platelet adhesion and activation are therefore critical downstream events in the blood-material interaction cascade and represent a key determinant of device hemocompatibility [3,4].

Platelet adhesion is primarily mediated through receptor-ligand interactions between platelet membrane glycoproteins and adsorbed plasma proteins, particularly fibrinogen and von Willebrand factor. These interactions facilitate initial platelet tethering under flow conditions, even in the presence of high shear stress typical of cardiovascular devices. Once adhered, platelets undergo a rapid and irreversible activation process characterized by profound biochemical, morphological, and mechanical changes [3,4].

A hallmark of platelet activation is the morphological transformation from a resting discoid shape into a spherical or irregularly spread morphology. This shape change is driven by cytoskeletal reorganization involving actin polymerization and microtubule disassembly, enabling platelets to increase surface contact area and strengthen adhesion to the substrate. Concurrently, activated platelets extend filopodia and lamellipodia, which further stabilize interactions with the underlying protein layer and neighboring cells [3].

Biochemically, platelet activation is accompanied by the release of intracellular granule contents, including α-granules and dense granules. α-granules contain a variety of pro-coagulant and adhesive proteins such as fibrinogen, factor V, and platelet factor 4, which amplify local coagulation signaling. Dense granules release small molecules such as ADP, calcium ions, and serotonin, which act as potent secondary mediators of platelet recruitment and activation. These released factors establish a positive feedback loop that accelerates thrombus formation at the biomaterial interface.

In addition to granule secretion, activated platelets exhibit upregulation of surface activation markers, most notably P-selectin (CD62P), which plays a key role in platelet-leukocyte interactions and inflammatory signaling. P-selectin expression facilitates binding to leukocytes via PSGL-1 receptors, linking thrombosis and inflammation in a process often referred to as thromboinflammation. This coupling is particularly relevant in long-term blood-contacting implants, where chronic inflammatory responses may exacerbate device-related complications [3,4].

Another critical feature of platelet activation is the de novo synthesis of thromboxane A_2 (TXA_2). TXA_2 is a potent vasoconstrictor and platelet agonist that further enhances platelet aggregation and stabilizes developing thrombi. Its production reinforces the amplification loop of platelet activation, ensuring rapid propagation of the hemostatic response once initiated at the material surface.

Following activation, platelets aggregate through fibrinogen-mediated crosslinking of GPIIb/IIIa receptors, forming multilayered cellular clusters that evolve into stable thrombi. These aggregates serve as nucleation sites for fibrin deposition once the coagulation cascade is activated, ultimately leading to the formation of a structurally reinforced clot [3,4].

A particularly critical challenge in blood-contacting medical devices is the amplification and propagation of platelet activation under continuous flow conditions. Unlike physiological wound healing environments, artificial devices such as ventricular assist systems operate under sustained circulation, where activated platelets are not confined to a localized injury site. Instead, they may detach, circulate downstream, and re-adhere at distant sites, promoting thrombus propagation and embolization.

This flow-mediated dissemination of activated platelets significantly increases the risk of systemic thromboembolic events, including ischemic stroke and organ infarction. Furthermore, regions of disturbed flow – such as recirculation zones, stagnation points, or sudden changes in shear stress – can exacerbate platelet activation and aggregation, even in the absence of surface defects.

Overall, platelet adhesion and activation represent a highly sensitive amplification system that converts molecular-scale protein adsorption events into macroscopic thrombotic complications. Because of this extreme biological responsiveness, even subtle variations in surface chemistry, topography, or hydrodynamic conditions can lead to pronounced differences in device thrombogenicity. Consequently, controlling platelet-surface interactions remains a central objective in the design of hemocompatible cardiovascular biomaterials [3,4].

1.1.4. Coagulation Cascade Activation

The coagulation cascade represents the final biochemical amplification stage of blood-material interactions and is responsible for transforming localized cellular activation into a stable fibrin-based thrombus. It is a tightly regulated enzymatic network involving a series of zymogen activations that proceed through two primary initiation routes: the intrinsic (contact activation) pathway and the extrinsic (tissue factor-mediated) pathway. Despite their distinct initiation mechanisms, both pathways converge at the activation of factor X, marking the central amplification point of the coagulation system [2,6].

Once factor X is activated to factor Xa, it forms a complex with factor Va on phospholipid surfaces, collectively known

as the prothrombinase complex. This complex catalyzes the conversion of prothrombin (factor II) into thrombin (factor IIa), which serves as the key effector enzyme of the coagulation cascade. Thrombin plays a dual role: it acts both as a potent serine protease driving fibrin formation and as an upstream amplifier that further enhances coagulation through feedback activation of factors V, VIII, and XI [2,6].

The primary structural function of thrombin is the enzymatic conversion of soluble fibrinogen into insoluble fibrin monomers. These monomers spontaneously polymerize to form a fibrous network that stabilizes the developing thrombus. Subsequent crosslinking by factor XIIIa strengthens the fibrin mesh, producing a mechanically stable clot capable of withstanding physiological shear forces. This fibrin scaffold also entraps activated platelets and red blood cells, contributing to thrombus growth and consolidation [2,6].

In blood-contacting medical devices, the coagulation cascade can be prematurely or excessively activated through surface-induced contact activation, which is primarily mediated by factor XII (Hageman factor). When blood is exposed to artificial materials, particularly those with negatively charged, hydrophobic, or nanoscale rough surfaces, factor XII can undergo conformational activation to factor XIIa. This initiates the intrinsic pathway and accelerates downstream thrombin generation even in the absence of vascular injury [2].

Surface properties play a critical role in modulating this process. Negatively charged surfaces can promote adsorption and activation of plasma proteins involved in contact activation, while nanoscale roughness increases effective surface area and creates microenvironments that favor protein unfolding and enzymatic activation. These effects collectively enhance the likelihood of initiating coagulation at the biomaterial interface.

Importantly, coagulation activation in artificial devices does not occur in isolation but is strongly coupled with platelet activation and inflammatory signaling. Thrombin itself is a potent platelet activator via protease-activated receptors (PARs), thereby linking the enzymatic coagulation cascade to cellular thrombogenic responses. This creates a self-amplifying loop in which platelet activation enhances coagulation, and coagulation further enhances platelet activation.

In continuous-flow blood-contacting devices such as ventricular assist systems, this amplification loop is particularly problematic. Non-physiological flow conditions, including regions of stasis, recirculation, or elevated shear gradients, can locally concentrate activated coagulation factors and accelerate fibrin deposition. Once initiated, these localized coagulation zones can expand rapidly, leading to device thrombosis or systemic embolization.

Overall, coagulation cascade activation represents the final and most irreversible stage of blood-material interaction. It integrates molecular-level protein activation, platelet-driven amplification, and flow-dependent transport phenomena into a single pathological endpoint: fibrin thrombus formation. As such, controlling contact activation at the material interface remains a critical requirement for achieving long-term hemocompatibility in cardiovascular devices [2,6] (Fig. 1).

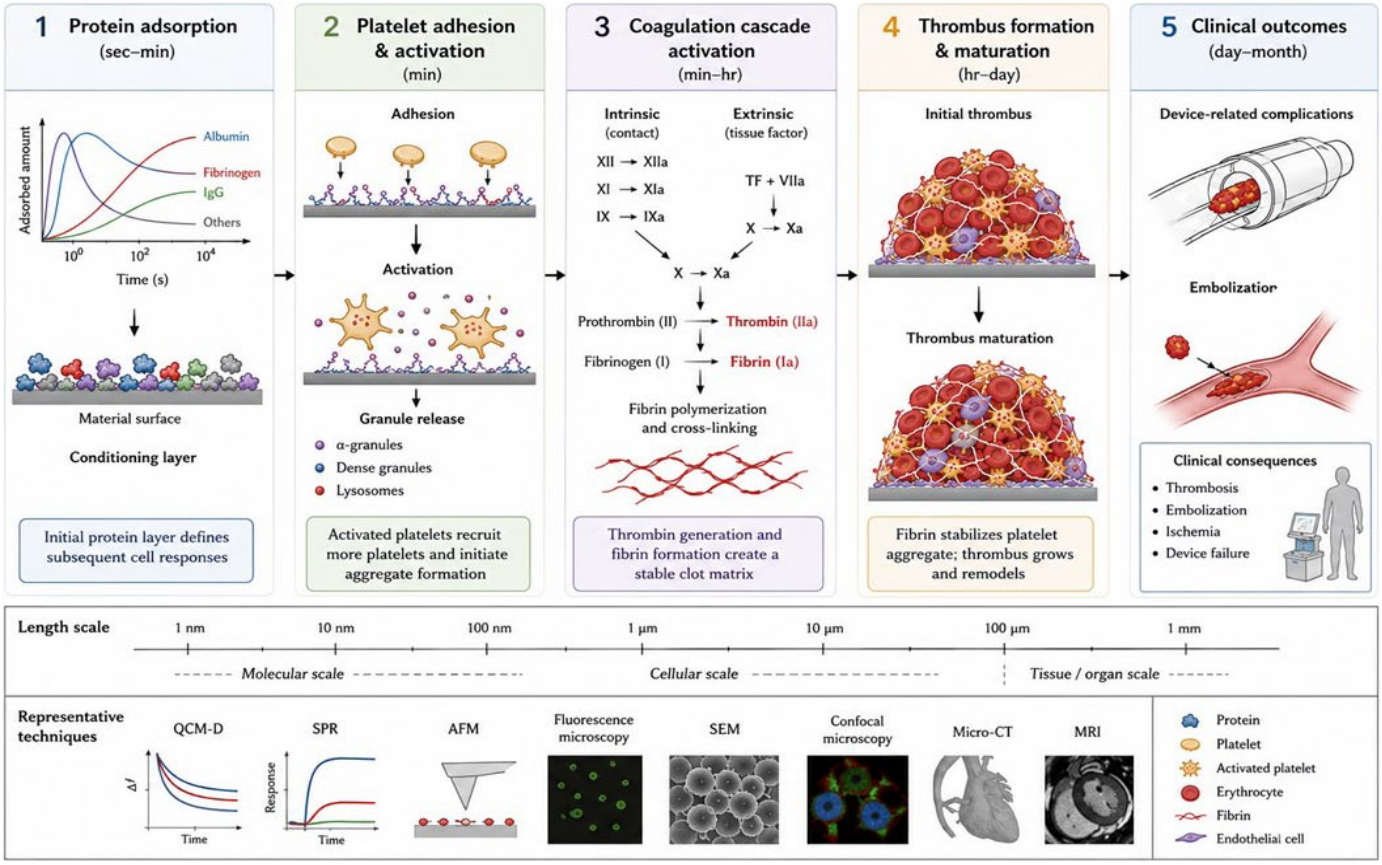

Fig. 1. Hierarchical nature of blood-material interactions leading to thrombosis

1.2. Hemolysis and Mechanical Blood Damage

Beyond biochemical pathways of blood activation, mechanical forces within cardiovascular devices play a critical role in blood trauma. One of the most significant consequences of these forces is hemolysis, the rupture of erythrocytes, which results from exposure to excessive shear stress. When red blood cells are subjected to high mechanical loads, their membranes deform and may ultimately fail, leading to the release of free hemoglobin into the plasma. This process not only reduces oxygen-carrying capacity but also initiates secondary complications, including oxidative stress and potential renal injury due to hemoglobin filtration in the kidneys [11].

The extent of hemolysis is closely linked to both device design and material characteristics. Flow conditions within the device are particularly important: regions of elevated shear stress, turbulent flow patterns, and zones of flow stagnation are all associated with increased risk of mechanical blood damage. Sharp gradients in velocity and recirculation zones can subject erythrocytes to repeated or prolonged stress exposure, exacerbating membrane fatigue and rupture.

Additionally, surface properties of the device, such as roughness and material composition, influence blood-surface interactions. Irregular or poorly finished surfaces can disrupt laminar flow and create localized microenvironments of high stress, further contributing to hemolysis. Therefore, optimizing flow geometry and ensuring smooth, biocompatible surfaces are essential strategies in minimizing mechanical blood damage in cardiovascular devices [12].

1.3. Complement System Activation and Inflammation

The complement system represents a crucial component of the innate immune response and plays a central role in biomaterial-induced inflammation. Its activation can proceed through three primary pathways: classical, alternative, and lectin. Regardless of the initiating mechanism, all pathways converge on a common cascade that leads to the opsonization of foreign surfaces, enhancement of phagocytosis, and recruitment of immune cells to the site of implantation [5].

When biomaterials are introduced into the body, their surfaces can be recognized as foreign, triggering complement activation almost immediately upon contact with blood. This results in the deposition of complement proteins on the material surface, effectively marking it for immune recognition. Subsequently, inflammatory mediators are released, promoting leukocyte adhesion, activation, and migration to the affected area.

Sustained or uncontrolled complement activation is particularly problematic in the context of long-term implants. Persistent stimulation of this pathway can contribute to chronic inflammation, which may impair tissue integration and healing. Over time, this prolonged inflammatory state can lead to complications such as fibrosis, reduced device functionality, or eventual implant failure. Therefore, controlling complement activation through material selection and surface modification remains a key consideration in the design of biocompatible medical devices.

1.4. Influence of Material Properties on hemocompatibility

Material properties play a decisive role in determining the hemocompatibility of cardiovascular devices, as they directly govern the nature and extent of interactions between the biomaterial surface and blood components. These interactions begin immediately upon contact with blood and evolve dynamically over time, influencing protein adsorption, cellular responses, and ultimately the biological performance of the device.

Surface chemistry is one of the most critical determinants of hemocompatibility. The type, density, and distribution of functional groups present on a material's surface dictate its physicochemical interactions with plasma proteins. Hydrophilic groups (e.g., hydroxyl, carboxyl) tend to reduce nonspecific protein adsorption, whereas hydrophobic surfaces often promote stronger and less reversible protein binding. Importantly, it is not only the amount but also the conformation and orientation of adsorbed proteins that matter. For example, adsorption-induced conformational changes in fibrinogen can expose binding sites that promote platelet adhesion and activation. Tailoring surface chemistry through coatings or chemical modification – such as grafting polyethylene glycol (PEG) or zwitterionic groups – can significantly reduce undesirable biointeractions.

Surface energy is closely related to surface chemistry and influences the thermodynamics of protein adsorption. Materials with high surface energy generally exhibit stronger interactions with biomolecules, leading to rapid formation of a protein layer upon blood contact. While this may stabilize the interface, it can also enhance the likelihood of platelet adhesion and activation if the adsorbed proteins adopt pro-thrombotic conformations. Conversely, low surface energy materials may resist protein adsorption but can suffer from poor integration with surrounding tissues. Achieving an optimal balance is therefore essential, often requiring fine-tuning of surface properties to control both the quantity and biological activity of adsorbed proteins.

Topography at the micro- and nanoscale introduces another layer of complexity. Surface roughness and patterning can significantly alter local flow conditions and cellular behavior. Micro-scale roughness may increase turbulence and create localized shear gradients, potentially enhancing platelet activation and hemolysis. On the other hand, nanoscale features can be engineered to modulate protein adsorption and cell adhesion more subtly. For instance, specific nanostructures may reduce platelet adhesion while promoting endothelial cell attachment, which is desirable for vascular healing. The spatial distribution, size, and geometry of these features are all critical parameters that must be carefully controlled during material fabrication.

Mechanical stiffness also plays an important role in the biological response to implanted materials. A mismatch between the mechanical properties of the biomaterial and the surrounding tissue can lead to abnormal stress distributions, influencing cellular signaling pathways and inflammatory responses. For example, excessively stiff materials may promote activation of immune cells and contribute to fibrotic encapsulation, whereas overly compliant materials may lack the structural integrity required for device function. In the vascular context, compliance mismatch can disturb normal hemodynamics, potentially contributing to thrombosis or intimal hyperplasia. Therefore, selecting or engineering materials with appropriate elastic properties is essential for maintaining both mechanical performance and biological compatibility.

In addition to these primary factors, other material characteristics such as degradation behavior, electrical properties, and long-term stability can further influence hemocompatibility. Modern biomaterial design increasingly relies on a synergistic approach, combining optimized chemistry, controlled topography, and tailored mechanical properties to minimize adverse reactions while promoting favorable biological integration.

1.5. An example of the application of materials science in the design of a cardiac assist pump

Understanding blood-material interactions is fundamental to the rational design of blood-contacting cardiovascular devices, particularly left ventricular assist devices (LVADs), where thrombotic complications remain a major clinical limitation [19-21]. In these systems, even modest improvements in local hemodynamics, surface chemistry, or biomaterial composition may substantially reduce platelet activation, protein adsorption, and thrombus formation [19,20]. Current evidence indicates, however, that no single modification strategy is sufficient to achieve durable hemocompatibility. Instead, effective thrombosis mitigation requires an integrated, multi-scale design approach that combines optimized flow geometry with advanced biomaterials engineering and bioinspired surface functionalization [19-23].

Accordingly, contemporary LVAD development increasingly focuses on the synergistic integration of: (i) flow path optimization to minimize regions of flow stagnation, recirculation, and excessive shear stress; (ii) hemocompatible bulk materials with favorable mechanical and physicochemical properties; (iii) antifouling surface coatings that suppress nonspecific protein adsorption and cellular adhesion; and (iv) biomimetic strategies designed to emulate the antithrombotic characteristics of the native endothelium [19,20]. Such a comprehensive framework provides the conceptual basis for both stereolithography (SLA)-based material development and the application of oligoproline self-assembled monolayer (SAM) coatings discussed in this review [22]. Together, these approaches aim to reduce adverse blood-surface interactions while maintaining the structural and functional requirements necessary for long-term LVAD performance [19,23].

2. Case Study: SLA Photopolymers and Oligoproline SAMs – Results of Completed Projects

This section of the review focuses on emerging material and surface engineering strategies aimed at improving the hemocompatibility of next-generation cardiovascular devices, with particular emphasis on ventricular assist devices (VADs) based on own research experiences. It critically addresses the persistent gap between advanced mechanical design and inadequate biological integration observed in current clinical systems.

A central topic is the application of stereolithography (SLA)-manufactured photopolymers, which enable high-resolution fabrication of complex geometries essential for optimizing internal flow fields in blood-contacting devices. These materials offer tunable mechanical properties, and their performance can be further enhanced through controlled resin composition, post-curing processes, and advanced surface modification techniques such as atomic layer deposition (ALD) and plasma-enhanced chemical vapor deposition (PECVD). Experimental evidence indicates that SLA-based materials exhibit favorable cytocompatibility, low cytotoxicity, and acceptable hemolysis levels, making them promising candidates for structural components in LVAD systems. Fig. 2 presents a demonstrator developed within the project.

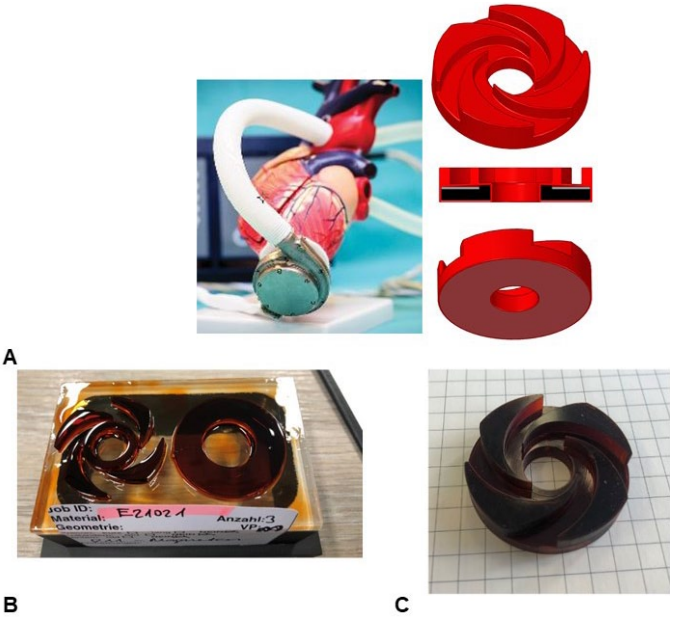

Fig. 2. Demonstrator elaborated within the project The work was financially supported by The Polish National Centre of Research and Development (Grant no. M-ERA.NET/2014/01/2016, "Nonthrombogenic metal-polymer composites with adaptable micro and macro flexibility for the next generation heart valves in artificial heart devices") A. Design of concept; B. The rotor immediately after the printing process; C. Demonstrator of the rotor

Complementing bulk material design, the review highlights the importance of bioinspired surface engineering, which addresses thrombosis initiation at the blood-material interface. Among the most promising approaches are oligoproline self-

assembled monolayers (SAMs), which form stable, well-ordered molecular coatings on gold substrates. These peptide-based interfaces provide antifouling functionality through hydration layer formation, steric repulsion, and the absence of charged binding sites, collectively reducing nonspecific protein adsorption and platelet adhesion. Importantly, their hemocompatibility has been shown to depend on peptide chain length, indicating tunable performance at the molecular level.

A comparative analysis reveals that SLA photopolymers and oligoproline SAMs operate at fundamentally different hierarchical scales – macroscale structural engineering versus nanoscale biointerface control – yet are highly complementary in function. While SLA materials provide mechanical integrity and optimized device geometry, oligoproline coatings regulate the immediate biological response at the blood-contacting surface. The blood-material interaction test was performed following the given protocol; The study was designed to evaluate the performance of an alternative in vitro dynamic assay for hemocompatibility assessment. The proposed test system was based on a cone-and-plate analyzer, rather than the conventional linear flow chamber. The cone-and-plate instrument used in this study is a commercially available device that has previously been validated for clinical applications, particularly in the assessment of thrombotic disorders and the evaluation of antiplatelet therapy efficacy. The rationale for selecting this system was threefold: (1) it requires a smaller volume of donor blood compared with linear flow-based methods, (2) it utilizes a readily available commercial instrument, and (3) it is based on the well-established principle of a rotating cone generating controlled shear stress over a plate surface, a configuration commonly applied in rheological and viscometric measurements. In addition to assessing the suitability of the cone-and-plate system for hemocompatibility testing, the study design included an evaluation of inter-day variability using blood samples obtained from a single donor. This approach was implemented to determine the impact of day-to-day biological variation on the reproducibility of test outcomes.For immunostaining, samples were incubated with fluorochrome-conjugated antibodies in PBS containing bovine serum albumin under dark conditions at room temperature. After incubation, unbound antibodies were removed by washing with PBS. The stained samples were subsequently analyzed using fluorescence microscopy and flow cytometry. Quantitative analysis included the determination of the percentage contribution of CD62P-positive platelets, CD45-positive leukocytes, and vWF-associated structures present on the investigated surfaces.

Additionally, surface morphology and blood element adhesion were examined by laser scanning confocal microscopy (CLSM). Representative CLSM micrographs were acquired for both center and edge regions of each sample. Quantitative image analysis was performed to determine the percentage of surface coverage by blood morphotic elements.

All experiments were performed in triplicate. The results were expressed as mean values ± standard deviation. Statistical analysis was carried out using one-way ANOVA followed by a post hoc test, with statistical significance accepted at $p < 0.05$. The results of the blood-material interaction are presented in Fig. 3. The abbreviations Pro6 and Pro9 (oligoproline peptides) refer to short peptide chains composed of repeating units of the

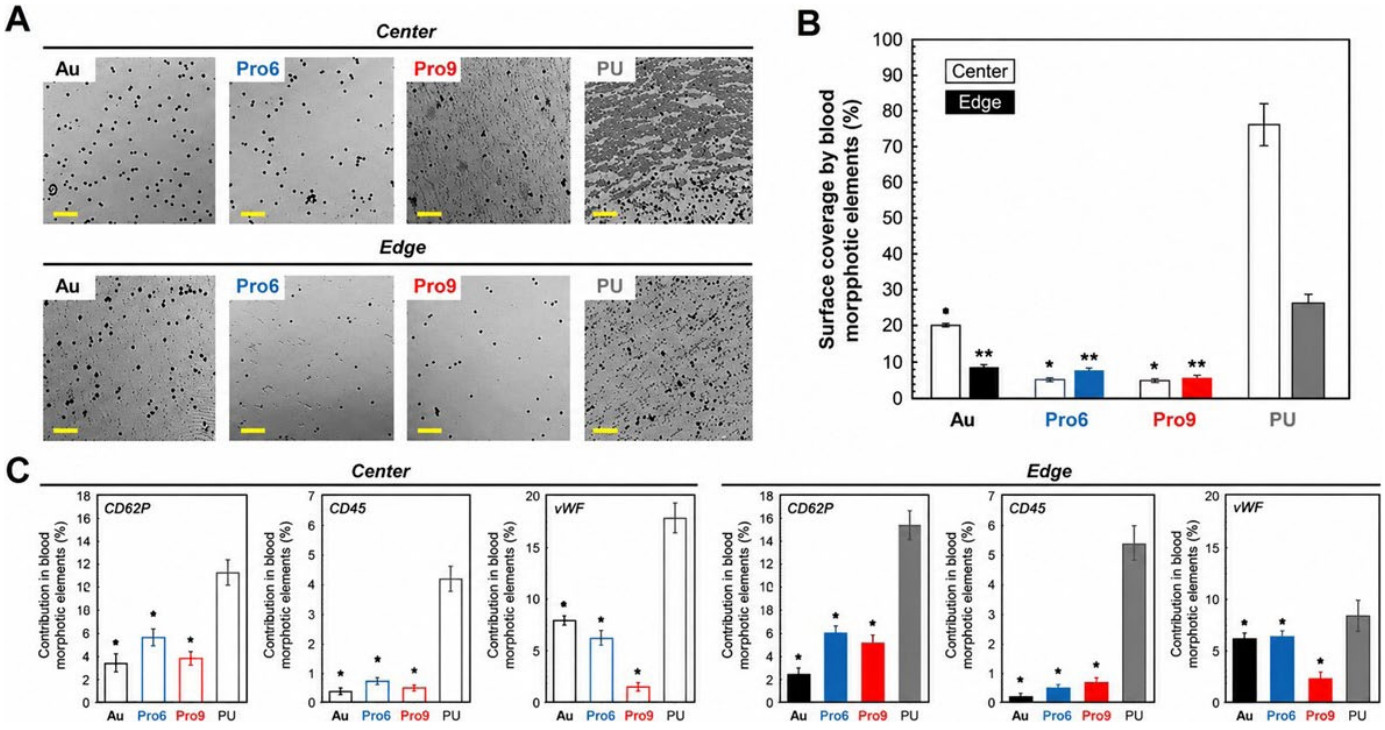

Fig. 3. Blood-material interaction; oligoproline interaction with blood; Au- gold- reference material, PU- clinically used polyurethane- reference material Pro6 = an oligomer (oligopeptide) consisting of 6 consecutive proline residues, i.e., a hexaproline chain. Pro9 = an oligomer consisting of 9 consecutive proline residues A Direct analysis B Surface coverage by blood C Confocal microscopy analysis using the following fluorescent labeled antibodies anti CD62P, anti CD45 and vWF [22]

amino acid proline (Pro). Pro = proline, a cyclic amino acid often represented by the one-letter or three-letter code "Pro" in peptide notation. Pro6 = an oligomer (oligopeptide) consisting of 6 consecutive proline residues, i.e., a hexaproline chain. Pro9 = an oligomer consisting of 9 consecutive proline residues, i.e., a nonaproline chain. In full peptide notation, these are typically written as:

(Pro)_6 or H–(Pro)_6–OH

(Pro)_9 or H–(Pro)_9–OH

Oligoproline coatings are primarily intended for use in the blood-contacting chamber of the pneumatic cardiac assist device (Fig. 4). The image shows a modified chamber developed as part of the project No. M-ERA. NET/2014/01/2016, "Nonthrombogenic metal-polymer composites with adaptable micro and macro flexibility for the next generation heart valves in artificial heart devices").

Fig. 4. The primary purpose of oligoproline coatings. Intended for use on the blood-carrying chamber of a pneumatic cardiac assist device. The image shows a modified chamber developed as part of the project No. M-ERA. NET/2014/01/2016, "Nonthrombogenic metal-polymer composites with adaptable micro and macro flexibility for the next generation heart valves in artificial heart devices"

Based on these findings, the present review proposes an integrated multi-scale design strategy that combines advanced additive manufacturing technologies, antifouling peptide-based surface functionalization, computational fluid dynamics (CFD)-guided flow optimization, and hierarchical surface engineering approaches to improve the hemocompatibility of ventricular assist devices (VADs) and other blood-contacting systems [24-26]. Increasing evidence suggests that thrombotic complications in VADs arise not from a single material-related factor, but rather from the complex interplay between surface chemistry, protein adsorption, local hemodynamics, platelet activation, and inflammatory signaling pathways [27,28]. Consequently, isolated modifications of either device geometry or biomaterial composition are insufficient to prevent adverse blood-material interactions under long-term physiological conditions. Instead, durable hemocompatibility requires the simultaneous optimization of both biological and mechanical determinants across multiple length scales [25,27].

In this context, stereolithography (SLA)-based additive manufacturing offers a particularly attractive platform for next-generation cardiovascular devices because it enables the fabrication of geometrically complex structures with high spatial precision and tunable material properties [29,30]. The ability to locally tailor stiffness, porosity, and surface topography may facilitate the development of flow paths specifically designed to minimize stagnation zones, turbulent recirculation, and excessive shear stresses, all of which are strongly associated with platelet activation and hemolysis [31,32]. CFD-guided optimization has therefore become an increasingly important design tool in contemporary VAD engineering, enabling the prediction and reduction of thrombogenic flow regions prior to device fabrication [32,33]. Such approaches are particularly relevant for rotary blood pumps, where supraphysiological shear stress and non-physiological flow trajectories remain major contributors to thromboembolic complications [28,32].

At the biomaterial level, antifouling and bioinspired surface engineering strategies have emerged as critical components of hemocompatible device development. Among these, peptide-based self-assembled monolayers (SAMs), including oligoproline-functionalized surfaces, represent a promising class of molecular coatings capable of modulating protein adsorption and cellular adhesion at the blood-material interface [18,34]. The work by Mzyk et al. demonstrated that oligoproline SAM coatings significantly reduced platelet adhesion and improved dynamic in vitro hemocompatibility under flow conditions, highlighting the importance of molecular-scale surface organization in regulating thromboinflammatory responses [22]. Importantly, oligoproline architectures exhibit conformational rigidity, hydration-promoting characteristics, and resistance to nonspecific protein adsorption, all of which contribute to their antifouling behavior [22,34]. These findings support the broader concept that precisely engineered molecular interfaces can suppress the initial adsorption of fibrinogen and other plasma proteins that trigger coagulation cascade activation and platelet aggregation [25,35].

Beyond passive antifouling mechanisms, current research increasingly explores hybrid biofunctional coatings that combine non-fouling peptides with biologically active anticoagulant molecules such as heparin, nitric oxide donors, thrombomodulin mimetics, or endothelialization-promoting ligands [36-38]. Such multifunctional systems aim not only to minimize protein adsorption but also to actively regulate coagulation, inflammation, and endothelial cell behavior in a manner that more closely resembles the native vascular endothelium [37]. This biomimetic paradigm reflects a broader shift in cardiovascular biomaterials research from inert "blood-compatible" surfaces toward dynamically interactive interfaces capable of modulating biological responses in real time [24,37].

The review further emphasizes that successful translation of these technologies into clinically viable devices requires

overcoming several major challenges. Long-term coating stability under continuous shear exposure remains insufficiently understood, particularly for peptide-based monolayers subjected to prolonged mechanical and oxidative stress [22,39]. Sterilization processes, including gamma irradiation, ethylene oxide exposure, and autoclaving, may additionally alter surface chemistry, molecular orientation, or bioactivity, potentially compromising hemocompatibility after implantation [39,40]. Furthermore, regulatory approval pathways for biofunctionalized cardiovascular devices remain highly complex due to the difficulty of standardizing biological performance metrics and predicting long-term thrombogenic risk [41]. Scalable manufacturing of bioactive molecules, reproducible surface immobilization methods, and robust quality-control procedures therefore represent essential prerequisites for future commercialization [40,41].

Emerging developments in multi-material SLA printing may further expand the design space for blood-contacting devices by enabling spatially controlled integration of mechanical, biological, and chemical functionalities within a single structure [29,42]. Such systems could allow the fabrication of region-specific interfaces optimized for distinct hemodynamic environments, for example combining rigid structural domains with highly lubricious or endothelialization-promoting surfaces in thrombosis-prone regions [42]. In parallel, advances in machine learning-assisted CFD modeling and digital twin technologies may facilitate patient-specific optimization of VAD geometry and surface properties, thereby improving individualized thrombotic risk prediction and device performance [33,43].

Overall, this section establishes a materials-centered and mechanistically informed framework for understanding cardiovascular device failure and proposes a coherent pathway toward the development of next-generation hemocompatible blood-contacting systems. By integrating additive manufacturing, molecular-scale antifouling coatings, biomimetic biofunctionalization, and hemodynamic optimization, future VAD platforms may achieve substantially improved thromboresistance while preserving long-term mechanical durability and clinical functionality [24,22,27].

3. Discussion and conclusions

The present results demonstrate that hemocompatibility remains one of the principal challenges in the development of cardiovascular devices, particularly for components intended for prolonged blood contact. Although additive manufacturing technologies have substantially expanded the design freedom available for biomedical engineering applications, the intrinsic biological response to polymeric materials continues to limit their direct clinical translation. In this study, SLA-manufactured photopolymers enabled the fabrication of highly complex geometries with excellent dimensional fidelity, confirming the suitability of stereolithography for the production of advanced blood pump components and other cardiovascular device architectures. The ability to accurately reproduce intricate flow channels and miniaturized structural elements is particularly important in cardiovascular systems, where local hemodynamic conditions strongly influence thrombogenicity and device performance.

Despite these structural advantages, the results indicate that the surface properties of SLA-fabricated materials remain a critical determinant of blood compatibility. Photopolymer-based materials are often associated with unfavorable protein adsorption, platelet adhesion, and activation of coagulation pathways, which may contribute to thrombus formation and inflammatory responses during long-term implantation. Consequently, the biological limitations of photopolymeric materials cannot be addressed solely through improvements in manufacturing precision or mechanical performance. Instead, effective surface engineering strategies are required to modulate the initial blood-material interactions that govern subsequent biological responses.

Within this context, oligoproline self-assembled monolayers represent a promising approach for tailoring the interfacial properties of SLA-manufactured substrates. The obtained findings suggest that oligoproline-based surface modification provides molecular-level control over surface chemistry and may reduce the extent of adverse hemocompatibility reactions. The highly ordered structure of self-assembled monolayers enables the generation of more biologically inert interfaces, potentially limiting nonspecific protein adsorption and platelet activation. Such effects are particularly relevant for blood-contacting devices, where even subtle changes in surface physicochemistry may significantly alter thrombotic risk.

An important aspect of the present study is the demonstration that additive manufacturing and molecular surface functionalization should not be considered as independent technological approaches, but rather as complementary strategies. SLA fabrication offers unparalleled flexibility in the production of patient-specific or application-specific cardiovascular components, while oligoproline-based coatings address the biological challenges associated with direct blood exposure. Their integration therefore establishes a multifunctional platform combining structural optimization with improved biological performance. This synergistic concept may be especially advantageous for rotary blood pumps, ventricular assist devices, microfluidic circulatory systems, and other applications requiring both geometric complexity and prolonged hemocompatibility.

The findings also align with previous reports emphasizing that the long-term success of cardiovascular implants depends not only on bulk material properties, but also on the dynamic interactions occurring at the blood-material interface. Surface modifications capable of preserving endothelial-like behavior or minimizing thrombogenic activation are increasingly recognized as essential for next-generation biomaterials. In this regard, oligoproline assemblies may offer advantages over conventional passive coatings due to their molecular organization, tunable chemistry, and compatibility with polymeric substrates fabricated by additive manufacturing methods.

Nevertheless, several limitations should be considered when interpreting the present results. Hemocompatibility is a multi-

factorial phenomenon involving complex interactions between coagulation pathways, complement activation, inflammatory signaling, and flow-induced cellular responses. Therefore, in vitro assessments alone may not fully predict long-term in vivo performance. Additional studies under dynamic flow conditions, as well as extended biological evaluations involving whole blood assays and animal models, will be necessary to confirm the stability and functionality of oligoproline-modified SLA materials during prolonged exposure to physiological environments. Furthermore, the long-term durability of self-assembled monolayers under mechanical stress and continuous shear forces remains an important aspect requiring further investigation.

Overall, the present study demonstrates that the combination of SLA-manufactured photopolymers with oligoproline self-assembled monolayers constitutes a promising strategy for improving the hemocompatibility of cardiovascular devices. The integration of advanced additive manufacturing with molecular-scale surface engineering may contribute to the development of next-generation blood-contacting biomaterials characterized by enhanced safety, reduced thrombogenicity, and improved long-term functional performance. These findings support the growing role of interdisciplinary approaches that combine materials science, surface chemistry, and biomedical engineering in the design of future cardiovascular technologies.

Acknowledgements

The review and some selected research findings were produced as part of the statutory work Z8.

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