Chapter 6
Blood–material Interactions

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6.1 Introduction

The importance of understanding mechanisms of blood-material interactions is emphasized by the increasingly widespread use of cardiovascular devices; hence, this field has been the subject of intense inquiry as described in several excellent reviews [1–4]. Unfortunately, it is still not possible to simply rank or classify materials with respect to their suitability for particular blood-contacting applications. Nor is it possible to predict in any general way, based on the properties of devices and of their blood-contacting surfaces, the behavior of blood in contact with materials or the propensity of devices to produce clinically adverse events. Despite many attempts to correlate biologic responses to physicochemical property measurements, our success in understanding blood-material interactions, and the clinical application of many blood-contacting devices, has been largely empirical. It is not appropriate to discuss in detail this large and controversial literature, which has been reviewed elsewhere [1, 2]. Rather, this section will focus on the available experimental data in humans, or results which may likely be extrapolated to humans from relevant animal studies, that may guide in the development of new designs for blood-contacting devices. Cardiovascular device applications in humans have also been the subject of an excellent review [5].

6.2 Experimental Difficulties

Before summarizing relevant experimental findings, it is appropriate to review briefly the theoretical and practical limitations to our understanding of blood–material interactions.

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There are several factors which have precluded the rational engineering design of devices based on first principles. While thousands of materials have been put forward as 'biocompatible' or non-thrombogenic, based on *in vitro* studies and animal testing, the relevance of these tests for outcomes in humans remains uncertain. Device responses *in vivo* depend upon actual device configuration and resulting flow geometry as well as upon intrinsic materials' properties. In many applications, mechanical and physical property requirements may dominate materials' selection. For example, membranes used in dialyzers and oxygenators must be both solute and gas permeable; chronic vascular grafts and heart valves must be mechanically durable and chemically stable for years; heart assist devices require flexible pumping chambers. Thus, the use of *in vitro* assays or simplified *in vivo* flow geometries, as in many animal models, has not proven adequate to predict actual device performance in patients. Furthermore, most animals and humans, as individuals, differ markedly from one another in both blood chemistry and in blood response to foreign materials [6]. It is deemed unethical to perform screening tests in humans, hence relatively few materials have undergone clinical evaluation and only limited human comparative data are available. In the case of chronic implants, devices removed at autopsy provide only a single set of observations which cannot be related to dynamic blood–material interactions prior to explantation.

Another limitation is our recognition that all blood–material interactions of clinical consequence are preceded by complex interactions between the biomaterial surface and circulating blood proteins. Plasma contains more that 100 identified proteins with specific functions and varying biologic properties [7]. These proteins interact with surfaces in a complex, interdependent and time-dependent fashion that remains poorly understood, except in low dilution, simplified model systems [8]. These reactions may vary from individual to individual depending upon coagulation status, the use antithrombotic or other drug therapies, or the administration of contrast media for fluoroscopic imaging. A partial listing of variables which may affect device outcomes following blood exposure is given in Table 6.1.

Despite these limitations, the design engineer may be guided by previous successful applications of materials in a variety of device configurations, and by certain generalizations which have resulted from these studies. Devices which are commonly used include catheters, cannulae, guide wires, stents, shunts, vascular grafts, heart valves, heart and ventricular assist devices, oxygenators, and dialyzers. With respect to these devices it is important to consider those events which can lead to serious clinical complications. These complications include: (1) thrombosis, (2) thromboembolism, (3) consumption (ongoing destruction) or activation of circulating hemostatic blood elements, and (4) activation of inflammatory and immunologic pathways. An appreciation for the biologic mechanisms of these events is essential for understanding the blood-compatibility of devices, and may be briefly described as follows. Thrombus forms as the localized accumulation of blood elements on, within, or associated with a device, and thrombus which is actively deposited can accumulate to the extent of producing device dysfunction or blood vessel occlusion. Interruption of normal blood flow may produce ischemia (relative lack of oxygen) and infarction (tissue death due to total oxygen deprivation) in distal circulatory beds leading to heart attacks and strokes. Thrombus structure may be complex, and is

Table 6.1. Variables influencing blood interactions with cardiovascular devices

Device Properties
Size and shape
Surface composition
Texture or roughness
Mechanical properties
blood Flow Phenomena
Shear forces
Convection and diffusion of reactants, products, cofactors and inhibitors
Disturbed flow and turbulence
blood Chemistry-related Effects
Coagulation status
Antithrombotic and other therapies
Contrast media
Other Variables
Duration of device blood exposure
Tissue injury
Infection

distinguished from that of whole blood clots which are often formed under static flow conditions. Thus, clots are relatively homogeneous structures containing red blood cells and platelets trapped in a mesh of polymerized protein (fibrin), while thrombus formed under arterial flow conditions and high fluid shear rates ('white thrombus') may be composed primarily of layers of fibrin and platelets (small procoagulant cells occupying only about 0.3% of the total blood volume). Under conditions of low fluid shear, as found in veins, thrombus may more closely resemble the structure of whole blood clots ('red thrombus'). Thromboembolism is the dislodgement by blood flow of a thrombus which is then transported downstream, ultimately blocking vessels which are too small for the thrombus to traverse. Thromboembolism is a common cause of stroke (cerebrovascular infarction) and peripheral limb ischemia. Often the balance between dynamic processes of thrombus deposition and its removal by embolic and lytic mechanisms will produce platelet consumption (ongoing destruction) and a net reduction in circulating platelet levels. Other clotting factors may be consumed as well [9]. Finally, certain devices, particularly those having large surface areas, may activate enzyme systems (e.g., complement) leading to inflammatory or immunologic responses [10]. With these issues in mind we will now review the performance of various classes of biomaterials in actual device configurations.

6.3 Conventional Polymers

Conventional polymers, such as polyethylene (Intramedic™), poly (vinyl chloride) (Tygon™), polytetrafluoroethylene (Teflon™), and poly (dimethyl siloxane) (Silastic™), and certain polyurethanes, have been used for many decades in short-term applications including catheters, cannulas, arteriovenous shunts for

hemodialysis, and tubing components of extracorporeal circuits. When used for periods of only a few hours, and most often in patients receiving systemic anticoagulation agents, the performance of such materials has usually been clinically acceptable. For example, although thrombus on angiographic catheters can be demonstrated in about half of all cases, most thromboembolic or occlusive events are clinically silent and significant complications occur in less than 1% of procedures [5]. Even total occlusion of small peripheral veins, by short term catheters used for venous sampling or drug administration, is usually inconsequential. However, longer-term indwelling catheters in a variety of configurations and polymer compositions, particularly in infants and children, are now recognized to produce a significant risk of thrombosis which can ultimately lead to organ or limb damage, and even death [11]. Comparative, quantitative studies with different polymer formulations remain to be performed in humans.

Polyurethanes, due in part to their flexibility and toughness, are perhaps the polymer of choice for ventricular assist devices and blood pumps. Consequently, they have received considerable interest as blood-contacting materials. In nonhuman primates, those polyurethanes, such as Pellethane™, which exhibit the most hydrophobic surface chemistry produce the least platelet consumption [12]. In dogs, early platelet interactions with polyurethanes vary considerably although relationships to polymer surface chemistry remain unclear [13]. Thus while polyurethanes are chemically versatile and possess many desirable mechanical properties, it is generally not possible to predict their biologic responses in humans.

6.4 Hydrophilic Polymers

These materials, which preferentially adsorb or absorb water (hydrogels), were initially postulated to be blood compatible based on the view that many naturally occuring phospholipids, comprising the cell membranes of blood contacting tissues, are also hydrophilic. Thus, water, as a biomaterial, was expected to show minimal interaction with blood proteins and cells [14, 15]. Interestingly, in animal studies highly hydrophilic polymers based on acrylic and methacrylic polymers and copolymers, as well as poly(vinyl alcohol) are all found to consume platelets excessively although they accumulate little deposited thrombus [12, 16]. The materials have variable thrombogenicity, but little capacity to retain adherent thrombus, i.e., they shed deposited platelets as microemboli. Thus, while surface-grafted hydrogels (which are mechanically weak) are currently used to improve catheter lubricity and as reservoirs for drug delivery, they have not received widespread application for improving blood-compatibility.

Another hydrophilic polymer that has received considerable attention is poly(ethylene oxide) [17, 18]. While poly(ethylene oxide) surfaces have been shown (like hydrogels) to have relatively low interactions with blood proteins and cells in *in vitro* studies and in some animal models, the suitability of such poly-

mers for actual device applications and long-term implants has not been established.

6.5 Metals

Metals, as a class, tend to be thrombogenic, and are most commonly applied in situations requiring considerable mechanical strength, such as in the struts of mechanical heart valves and as endovascular stents [3, 19] or electrical conductivity, as in pacing electrodes. Stents are metallic mesh devices placed within blood vessels to preserve vessel patency after procedures to expand the vessel lumen diameter (e.g., after balloon angioplasty). Metals most commonly employed are stainless steel (316L type) and tantalum; however, both are thrombogenic [19, 20]. Catheter guide wire thrombogenicity, although readily documented, has been less of a clinical problem because of the usually short period of blood exposure involved in most procedures.

In early canine implant studies, the thrombogenicity of a wide series of metallic implants was seen to be related to the resting electrical potential of the metal which was generated upon blood contact [21]. Metals with negative potentials tend to be antithrombogenic, while stainless steel tends to be neutral. Copper, silver, and platinum are positive and extremely thrombogenic. Indeed, the use of copper coils inserted into canine arteries continues to be a widely used model for inducing a thrombotic response [22].

Theoretically, reduced thrombogenicity of metallic stents and heart valve components might be achieved by thin film polymer coatings, although the clinical effectiveness of this strategy has not been demonstrated. Thus, chronic systemic anticoagulation is generally employed in patients with prosthetic heart valves (with metallic components) and stents.

6.6 Carbons

Cardiac valves with components fabricated from low temperature isotropic carbons (pyrolytic carbon) are successfully used clinically [23]. These materials are appropriate for such applications as mechanical valves which require long-term chemical inertness, smoothness, and wear-resistance. The reasons for the marked improvement in the performance (reduced thrombosis and thromboembolic stroke rates) of these newer vs. older style heart valves are not entirely understood, but are undoubtedly multifactorial and related to improved patient management and valve design, as well as to the nature of the carbon surface. The specific benefits conferred by pyrolytic carbons with respect to blood cell and protein interactions, resulting in a very low frequency of clinical complications, remain to be defined. The use of carbon coatings has been proposed for other devices, i.e., vascular grafts, although such devices have not yet been used clinically.

6.7 Ultra-thin Film Coatings

Polymeric thin films of widely varying chemical composition may be deposited onto polymers, metals, and other surfaces using the method of plasma polymerization (also called 'glow-discharge' polymerization) [24]. This method is advantageous since very thin films (e.g., 100 nm) may selectively modify the surface chemistry of devices, but not their overall mechanical properties or surface texture. Plasma polymers form highly cross-linked, covalent, inert barrier layers which may resist the adsorption of proteins, lipids, and other blood elements. Plasma reacted coatings, based on hydrocarbon monomers such as methane, may produce durable diamond like coatings. Plasma polymer coatings have been proposed for vascular grafts and stents, based on promising animal studies [25], but are not used clinically at the present time.

6.8 Membranes

Blood contacting membranes are used for gas exchange (e.g., blood oxygenators) or solute exchange (e.g., dialyzers). The large membrane surface area, which may exceed 2 $m^{2,}$ and the complexity of cardiopulmonary bypass circuits can produce consumption and dysfunction of circulating blood elements such as platelets, leading to an increased risk of bleeding as well as thromboembolism [26]. The activation of inflammatory and immune response pathways (complement system) by dialysis and oxygenator membranes may also produce significant complications [27]. Complement activation by dialysis membranes may be related in part to the availability of surface hydroxyl groups, particularly on cellulosic membranes. Complement activation may be greatly attenuated by the use of other membrane materials such as polysulfone and polycarbonate. Complement activation by biomaterial membranes has been reviewed [27].

6.9 Biological Surfaces

The use of biological and bioactive molecules as device surface coatings may confer thromboresistance. Such coating materials include phospholipids and heparin. Phospholipids such as phosphorylcholine, a normal constituent of cell membranes, may orient polar head groups towards the aqueous phase and locally organize water molecules, much like hydrogel surfaces. These surfaces may minimize protein and complement interactions [28]. In preliminary animal studies, phosphorylcholine coated stents, guide wires, and vascular grafts have shown improved thromboresistance. This approach is being actively developed for clinical applications.

Heparin, a naturally occuring anticoagulant glycosaminoglycan, has been considered an attractive surface coating based on its ability to directly catalyze the inactivation of procoagulant enzymes, and thus suppress thrombus development. Recently, the reduced thrombogenicity and improved biocompatibility of heparinized metallic stents has been demonstrated in animals [29]. In these studies, heparin was covalently attached to a polymer surface coating. This method has also been used clinically for the heparin coating of catheters and other devices, although it remains unclear whether the improved biocompatibility is a function of heparin's anticoagulant activity, nonspecific physicochemical properties, or both.

With biomolecule modified surfaces, there may also be important questions regarding the possible deleterious effects of sterilization procedures required before implantation.

6.10 Surface Texture

Surface 'smoothness' is a generally desirable feature of blood contacting surfaces. In this context, a smooth surface is one with irregularities with typical dimensions less than those of cells (< 1 μm). However, in certain applications, device incorporation by tissue is desirable, or the texturing of polymers may increase mechanical flexibility and durability. Thus, the sewing ring of mechanical heart valves is typically composed of poly(ethylene terephthalate) (Dacron™) fabric to permit tissue in growth and healing, which is associated with a reduction in thromboembolic events. Vascular grafts used to replace diseased blood vessels are most commonly fabricated from woven or knitted DacronTM or textured (expanded) polytetrafluoroethylene (ePTFE) (Goretex™). In tubular form, these textured polymers remain flexible and stable for many years following implantation. Smooth-walled vascular grafts have generally not been considered attractive for long-term applications since smooth surfaces may not permit tissue ingrowth or flow surface healing. Textured flow surfaces are initially thrombogenic upon blood contact, although ePTFE appears less thrombogenic and thromboembolic than fabric Dacron™ prostheses [30]. These grafts perform acceptably in man when the graft diameter exceeds about 6 mm since the layer of thrombus that forms does not significantly restrict blood flow. Interestingly, both smoothwalled and textured ventricular assist devices have also performed successfully in clinical trials [31, 32].

6.11 Conclusion

Because the variables affecting cardiovascular device responses are sufficiently numerous and complex, those properties of blood-contacting surfaces which would be desirable to minimize adverse reactions cannot, in most instances, be predicted with confidence. The choice of material is usually constrained by mechanical property considerations and by variable requirements for material durability and chemical stability. Cardiovascular device engineering must therefore be guided by previous experience in successful clinical applications.

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Additional Reading

Colman, R.W., Hirsch, J., Marder, V.J. and Salzman, E.W. (eds)(1994) *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*, 3rd edn, J.B. Lippincott, Philadelphia.

This book is highly recommended. This state-of-the-art text covers in detail essentially all important hematological aspects of cardiovascular device blood compatibility. In particular, Chapter 76, Interaction of blood with artificial surfaces, which considers many theoretical, experimental, and animal studies, and Chapter 77, Artificial devices in clinical practice, which describes clinical device thromboembolic complications, are of great practical value.

Harker, L.A., Ratner, B.D. and Didisheim, P. (eds)(1993) Cardiovascular Biomaterials and Biocompatibility, *Cardiovascular Pathology*, **2**(3) (suppl.), 1S–224S.

In this volume, 20 chapters by expert authors treat all aspects of biomaterials and blood compatibility including pathologic mechanisms, material characterization, blood-material interactions and device performance. This volume updates an excellent earlier book *Guidelines for blood-Material Interactions*, National Institutes of Health, Washington, DC, Publication No. 85–2185 (1985).

Szycher, M. (ed.) (1983) *Biocompatible Polymers, Metals, and Composites*, Technomic Publishing Co., Lancaster, Pennsylvania.

Many of the same issues of blood–material interactions are broadly covered while selected polymer and device applications are described in additional detail. of particular interest are Section I (Fundamental Concepts in blood/Material Interactions) and Section II (Strategies for Hemocompatibility).

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