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The Catastrophe Revisited:

Blood Compatibility in the 21st Century¹

Buddy D. Ratner

University of Washington Engineered Biomaterials (UWEB) University of Washington Seattle, WA 98195 USA

Abstract

The biomaterials community has been unable to accurately assign the term “blood compatible” to a biomaterial in spite of 50 years of intensive research on the subject. There is no clear consensus as to which materials are “blood compatible.” There are no standardized methods to assess blood compatibility. Since we use millions of devices in contact with blood each year, it is imperative we give serious thought to this intellectual catastrophe. In this perspective, I consider five hypotheses as to why progress has been slow in evolving a clear understanding of blood compatibility:

Hypothesis 1 -- It is impossible to make a blood compatible material. Hypothesis 2 -- We do not understand the biology behind blood compatibility. Hypothesis 3 -- We do not understand how to test for or evaluate blood compatibility. Hypothesis 4 -- Certain materials of natural origin seem to show better blood compatibility but we do not know how to exploit this concept. Hypothesis 5 -- We now have better blood compatible materials but the regulatory and economic climate prevent adoption in clinical practice.

Introduction

In 1993 I wrote an article, “The Blood Compatibility Catastrophe¹.” The title derived from an incident in the history of physics. Toward the end of the 19th century, the physics community was confronted with data and ideas that could not be reconciled by the classical physics that propelled the physicists to what they (somewhat arrogantly) thought of as an intellectual pinnacle. The crowning achievement of classical physics was probably the Maxwell equations of electromagnetic energy along with the laws of thermodynamics and motion. But, the equations stemming from these intellectual triumphs were unable to describe the energy output of a heated black body - this was referred to as “the ultraviolet catastrophe” that soon forced a rethinking and led to a quantum mechanical view of the universe. The blood compatibility catastrophe, in analogy, referred to our inability to accurately assign the term “blood compatible” to a biomaterial in spite of 50 years of intensive research on the subject. There is no clear consensus as to which materials are “blood compatible.” There are no standardized methods to assess blood compatibility. Since we use millions of devices in contact with blood each year, this is indeed a catastrophe.

Has the catastrophe been resolved since my 1993 article? “No” is the answer. The article has been cited 74 times - the “call to action” was noted but not heeded. For example, almost all

¹This Leading Opinion article is submitted in honor of 40 years of accomplishment and service by Dr. David Williams to the biomaterials community. David Williams has made contributions to every area of biomaterials science with his prodigious scientific output and his incisive perspectives. True advances in the field come with a critical assessment of the state-of-the-art. David Williams has assisted us all, to paraphrase Marcel Proust, in seeing with new eyes.

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cardiovascular device procedures, both short term and long term, require significant anticoagulation, at high cost and with considerable risk to the patient. For cardiac stents, when drug eluting systems were developed that inhibited endothelial cell proliferation, these stents were found to be thrombogenic. To this day, we have no synthetic small diameter vascular grafts and the problem is largely early thrombotic occlusion of these devices. Extensive blood damage is associated extracorporeal membrane oxygenation. Many additional examples can be cited. Table 1 estimates the number of devices contacting the blood stream used in humans. All these devices have thrombosis problems.

So, why after 60 years of serious study of blood compatibility and development of blood compatible surfaces do we not have truly blood compatible surfaces? Here are some hypotheses: (1) The task is impossible. (2) We do not understand the biology behind blood compatibility. (3) We do not understand how to test for or evaluate blood compatibility. (4) Certain materials of natural origin seem to show better blood compatibility but we do not know how to exploit this concept. (5) We do have better blood compatible materials but the regulatory and economic climate prevent adoption in clinical practice. Each of these hypotheses will be discussed.

1. It is impossible to develop a blood compatible material

There is merit in this simple hypothesis - that it may be impossible to achieve a blood compatible surface. The surface that we try to emulate is the living lining of human vasculature. A healthy endothelial layer achieves anticoagulation in at least two ways - first, it is a biological factory continuously synthesizing and secreting potent antithrombotic agents such as prostacyclin. The magnitude and nature of this secretion are in direct response to the condition of the blood. Second, the surface molecules comprising the glycocalyx that envelops the blood contacting face of the vascular endothelial cells are themselves “non-fouling” and non-activating, and possibly even actively anti-thrombotic. The superb functionality of the endothelial surface, though dauntingly challenging for emulation by biomaterials scientists, suggests biomimetic design ideas. How perfect a non-fouling layer can we create? Can we decorate the surface with temporally stable but biologically active anticoagulant molecules? Can we evolve a controlled release system to continuously provide antithrombotic agents that are highly localized at the blood contacting wall of the prosthesis?

Numerous examples of each of these strategies have been explored. Though a comprehensive literature citation in this short perspective is impossible, a few promising approaches will be mentioned. Poly(ethylene glycol) surfaces and zwitterionic surfaces both show promising interactions with blood²⁻⁴. Active anticoagulant immobilization to surfaces dates to the early days of modern biomaterials development and continues as a fertile field of exploration to this day^{5,6}. Finally surfaces that very slowly release potent anticoagulants or even catalyze the breakdown of blood elements to make such molecules have been reported⁷⁻⁹. Possibly, real advances will be seen when a material is created that demonstrates the best of all three approaches.

(2) Our understanding of the biology behind blood compatibility

The cell and molecular biology of blood activation and coagulation are immensely complex. Platelet membranes are decorated with numerous (probably hundreds) of protein and oligosaccharide receptor groups. Activation of the intrinsic clotting system, through reasonably well understood, still offers surprises. Less is known about the roles of white cells in coagulation.

There has been much study focused on the role of surface adsorbed proteins in activating blood coagulation. A consideration of such surface-adsorbed proteins is logical because soluble

proteins are always present, but do not activate the coagulation cascade except in rare, pathological conditions. Fibrinogen on surfaces seems to be a major activator of platelets, much more so than other “adhesive” plasma proteins such as fibronectin that have at times been implicated in this process¹⁰. Generally, the amount of fibrinogen on a surface has correlated with blood reaction. However, there are unusual “outlier” materials in the correlation between amount of adsorbed fibrinogen and platelet adhesion that show high levels of fibrinogen adsorbed, but little platelet reaction¹¹. This could suggest that certain polymeric surfaces strongly alter the conformation or orientation of fibrinogen so its functional domains are not accessible to platelets. Related to this, Skarja, et al showed that platelet deposition varied in the order: adsorbed fibrinogen > cross-linked fibrin > thermally denatured fibrinogen = polyethylene¹².

The low reactivity of polyethylene to blood platelets observed in the Skarja study has also been noted in other studies¹³. In fact, many hydrophobic polymers (Teflon, silicones, polyurethanes with octadecyl chains, plasticized poly(vinyl chloride)) seem to exhibit this low platelet reactivity¹³. In clinical practice, blood handling tubing is typically fabricated from a hydrophobic material. The interaction between hydrophobic polymers and adsorbed fibrinogen may explain their reasonable success in clinical medicine.

Other surface-bound proteins that have been implicated as important for blood activation include von Willebrand factor (vWF), a surface protein that may be activated only by high fluid shear such as is found in the arterial stream¹⁴, and serum amyloid P protein¹⁵. Serum amyloid P on surfaces may lead to an enhanced understanding of the role of leucocytes in blood compatibility.

(3) Evaluation of blood compatibility

The issues and complexities of assessing the blood compatibility of a biomaterial have been reviewed^{16,17}. Largely blood compatibility assessment addresses activation of blood elements, adhesion of blood elements, damage to blood, thrombus formation and/or emboli release. Different reactions occur in blood under venous-like flows and at high wall shear rate (arterial) flows¹⁸. If certain blood reactions are ignored, or if the material is not assessed under appropriate flow conditions, the material will not be well characterized as to its interaction with blood.

Many papers in the literature purport to assess blood compatibility by counting adherent platelets on the surfaces of materials. At least two important considerations are ignored in such studies. First, the platelets may not stick (a non-thromboadherent surface), but they may be activated by the surface and aggregate into emboli that travel downstream from the device, potentially occluding blood vessels in the lungs, brain, heart or kidneys. Second, the surface may activate the intrinsic clotting system, but in high shear (arterial) flow, activated clotting factors might be diluted before they reach a concentration that can lead to clot. These considerations have been explored in published studies¹⁹⁻²¹.

An important advance in the assessment of blood interactions with materials was made by observing that microparticle formation in blood correlated with blood reaction²². This measurement, typically made with fluorescence-activated cell sorter (FACS), might be an important parameter to measure in understanding blood reaction to materials.

An article that presented a thorough, “multi-parameter” assessment of blood interaction with materials has recently been published². The surface that suggested good blood compatibility in all tests employed in this study was a non-fouling, poly(ethylene glycol)-like surface prepared by RF-plasma deposition. Another detailed, multi-method study on blood

compatibility looked at ventricular assist device interaction with blood and measured changes in blood chemistry.²³

(4) Certain materials of natural origin show better blood compatibility

The fact that processed natural tissue in the blood stream seems to almost always function better than synthetics may provide the Rosetta stone of blood compatibility-if we can read the message, we may learn to make a new generation of blood compatible biomaterials. Improved blood compatibility compared to synthetics has been seen with tissue heart valves and umbilical cord vascular prostheses. Though such systems are non-living and heavily processed (crosslinked), they still exhibit remarkable blood compatibility.

(5) We have better blood compatible materials but the regulatory and economic climate inhibit adoption

Have we indeed succeeded in this elusive goal of developing a truly blood compatible material? There are hundreds of optimistic papers and patents on this subject, with new ones coming out every day. I personally believe that some of these innovative materials described in this literature are more blood compatible than materials in use clinically today. Regulatory agency approval is an issue, especially when novel materials are used in a device. Such device approval can be obtained, but often at high cost. If the regulatory agency sees a material that is not generally recognized mentioned in an application for device approval, they will demand additional documentation associated with manufacture, quality control, durability and safety. Can the additional cost (both in cash and in delays) be recouped with sales profits that can be traced to superior performance compared to other competing devices? Possibly, it can. A recent case came to my attention where a company put \$40,000,000 into developing a new stent design. After FDA approval was granted, they made this money back in the first 9 months of sales.

Perhaps when the total cost of healthcare is entered into the equation, we might be able to further justify these high costs of regulatory clearance - failed devices can lead to huge, additional hospitalization and treatment expenses that most often are passed on to the healthcare system or the patient. An improved device made of a more blood compatible material might have a low failure rate. A more holistic approach to medical device costs will ask not just about the expenses of device development, approval and manufacture, or about profits, but will address additional costs to the total healthcare system due to device failure. The manufacturer, the patient and the Government are all partners in the cost of healthcare.

Conclusion

The observation that coating a glass tube with paraffin will lengthen blood coagulation time compared to the untreated tube extends back more than 100 years. Modern blood compatibility research can be traced back some 60 years. The absence of generally accepted blood compatible materials, the fact that we still predominantly use the same materials we used in 1960 in the clinic, the slow development of a theory of blood compatibility and the lack of standardization in blood compatibility assessment constitute the catastrophe in this field. In analogy to the ultraviolet catastrophe of the late 19th century, will an "Einstein" come along whose dazzling insight will shift our perception of the whole problem? Possibly, but more likely, through growing understanding of the basic biology of blood interaction and through refined engineering application of this basic science, we will gradually achieve a clear consensus on blood compatibility, and with that consensus will come improved blood contacting biomaterials.

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Table 1
Common Blood Contacting Medical Devices (estimated usage worldwide)

Blood contacting device	Blood contacting material	No. per year
Catheters	silicone, polyurethane, PVC, Teflon	200,000,000
Guidewires	stainless steel, Nitinol	(probably millions)
Pacemaker	silicone, polyurethane, platinum	300,000
Vascular Graft	Dacron, Teflon	200,000
Heart Valve	pyrolytic carbon, Dacron, fixed natural tissue	200,000
Stents	stainless steel, styrene-isobutylene polymer	4,000,000
Extracorporeal Oxygenation	silicone rubber	20,000
Artificial Kidney	polyacrylonitrile, polysulfone, cellulose	1,200,000
Left Ventricular Assist Device (LVAD)	polyurethane	1,000
Glucose or lactate sensors (experimental devices)	hydrogels	No data