Selected Papers from the Heart Valve Summit

Is Prosthetic Valve Thrombogenicity Related to Design or Material?

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In 1952, Charles Hufnagel[1] inserted a prosthetic heart valve into the descending thoracic aortas of patients with aortic insufficiency. The ball-valve prosthesis was made of polished methyl methacrylate and was inserted into the divided aorta during brief periods of occlusion through the use of innovative multiple-point fixation rings at either end. Hufnagel's valve was the 1st "machine" (a device with moving parts) inserted into a human being and was the 1st prosthesis inserted into the circulation. Thrombosis and thromboembolism occurred in some of these patients, but Hufnagel's valve and the simultaneous development of the heart-lung machine by John and Mary Gibbon[2] established the feasibility of replacing diseased heart valves. The race began.

Over the next few years, surgeons developed a myriad of homemade prosthetic heart valves that often "copied" the design of the native valve in a variety of synthetic materials.[3] In December of 1958, Muller successfully replaced a single aortic cusp, and by April 1960 he had replaced the entire aortic valve in 9 patients with a trileaflet valve made of Dacron (there were 4 hospital survivors).[3] Nina Braunwald copied the mitral valve in Dacron and polyurethane and successfully replaced the diseased valve in 1 of 5 patients.[3] Dwight Harken developed an aortic ball-valve prosthesis, but only 2 of 7 patients survived by April 1960. The 1st successful series (6 of 8 hospital survivors), reported by Starr and Edwards,[4] used the ball-valve design: a Silastic ball, a highly polished stainless steel cage, and a well fitted sewing ring of knitted Teflon cloth. These collaborators chose function over form and introduced state-of-the-art workmanship and manufacturing techniques to achieve the 1st long-term success with a prosthetic heart valve. But once patients survived operation, the problem of prosthetic valve thromboembolism emerged. Within 5 years, approximately 35% of patients with Starr-Edwards aortic valves and over 70% of patients with Starr-Edwards mitral valves had experienced a thromboembolic event.[5]

Key words: *Biocompatible materials; heart valve prosthesis; history of medicine, 20th cent.; thromboembolism*

Presented at the International Heart Valve Summit, 12-14 July 1994, Lyon, France. The meeting was sponsored by the Fondation Léa et Napoléon Bullukian.

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Pathogenesis of Prosthetic Valve Thromboembolism

The endothelial cell is the only surface known to be nonthrombogenic. This remarkable cell lines the entire circulatory system and, in adults, has a surface area estimated to be between 1000 and 5000 m^2. The endothelial cell maintains both the fluidity of blood and the integrity of the vascular system. To accomplish these tasks, endothelial cells actively metabolize both procoagulants and anticoagulants to establish a balance between blood fluidity and vascular integrity. A biochemical "tug-of-war" is created between these groups of procoagulants and anticoagulants, and a preponderance of one or the other tips the balance toward either bleeding or clotting. Table I lists some of the anticoagulant mechanisms attributed to endothelial cells.

Despite intensive research for over 40 years, no material or cell other than the endothelial cell has been found to be nonthrombogenic. Yet a large number of biomaterials that are nontoxic, noncarcinogenic, nonmutagenic, and nonantigenic have been developed since Smith-Peterson 1st introduced prosthetic material into the human body, in the form of a stainless-steel hip nail in the late 1930s. Some of these biomaterials are "thromboresistant," which means that they induce clotting somewhat more slowly than other biomaterials. However, none is nonthrombogenic.

TABLE I. Anticoagulants Produced by Endothelial Cells:

Produce heparan sulfate
Produce dermatan sulfate
Produce PGI_2, nitric oxide
Inactivate platelet secreted ADP, ATP
Produce protein S (catalyzes protein C)
Produce thrombomodulin (binds thrombin)
Produce tissue factor inhibitor protein
Produce protease nexin-1 (inhibits thrombin)
Produce tissue plasminogen activator (t-PA)

ADP = adenosine diphosphate; ATP = adenosine triphosphate; PGI_2 = prostaglandin I_2

When blood first contacts a biomaterial, plasma proteins are instantly adsorbed onto the surface to form a protein mosaic between 100 and 200 angstroms thick (Fig. 1)[6]. Proteins are not adsorbed in proportion to their bulk concentrations in plasma.[7] The amounts of adsorbed proteins vary according to the physical and chemical composition of the surface, but little is known of the forces that determine the topography and composition of the resulting protein layer.[8] This ignorance is partially due to the fact that surfaces contain reactive groups and differ chemically and physically from the bulk material. Each material quickly establishes a dynamic equilibrium between circulating and adsorbed surface proteins. Fibrinogen is selectively adsorbed. Over time, surface-adsorbed proteins desorb, degrade, or are replaced by other proteins; little is known about surface protein flux over time. Despite many years of intensive research by excellent scientists, all we really know is that fibrinogen is selectively adsorbed, and in greater amounts by hydrophobic surfaces than by hydrophilic surfaces; that rough surfaces are more thrombogenic than smooth surfaces; and that some materials are more "thromboresistant" than others.

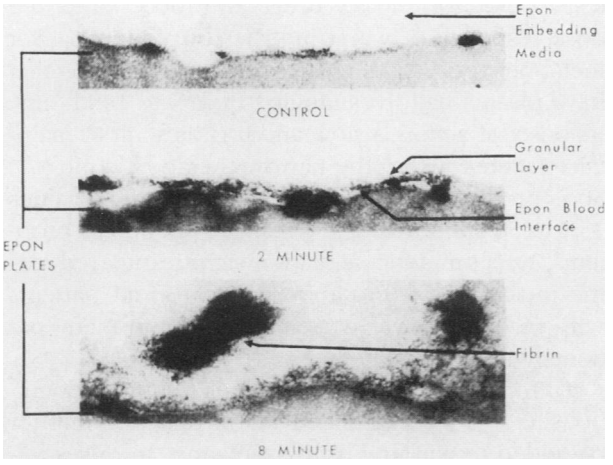

Fig. 1 *Electron micrographs (orig. ×135,000) of an Epon plate not exposed to blood, an Epon plate exposed to blood for 2 min, and an Epon plate exposed to blood for 8 min. (From: Dutton RC, Webber AJ, Johnson SA, Baier RE.[6] Copyright 1969. Reprinted by permission of the Journal of Biomedical Materials Research.)*

Following protein adsorption, platelets are activated to expose their surface GPIIb/IIIa (fibrinogen) receptors.[9] The mechanism that activates platelets is not known, but thrombin generated through the contact system of plasma proteins is suspected. Platelets attach to binding sites located on the alpha chain and C terminal domain of the gamma chain of surface-adsorbed fibrinogen. The number of adherent platelets varies between biomaterials; autografts, homografts, heterografts, and certain man-made biomaterials such as pyrolytic carbons and polyurethanes attract fewer platelets than silicones. However, in patients with either mechanical or bioprosthetic heart valves, platelets are constantly activated.[10] Platelet survival is reduced,[11] thromboxane A_2 is synthesized and released, and plasma beta thromboglobulin from platelet alpha granules is increased.[10]

Contact between blood and biomaterials also activates the contact system of plasma proteins. The contact system consists of 4 plasma proteins: factor XII, factor XI, prekallikrein, and high-molecular-weight kininogen (HK).[12] On a nonendothelial cell surface containing negative charges and in the presence of prekallikrein and HK, factor XII is cleaved into the active serine proteases, FXIIa and FXIIf. FXIIa cleaves prekallikrein to form kallikrein, which amplifies and accelerates the cleavage of factor XII. FXIIa also cleaves factor XI to start the intrinsic coagulation pathway that eventually produces thrombin. Thrombin is a powerful enzyme that directly activates platelets and cleaves fibrinogen to make fibrin. Thus, any biomaterial in contact with blood tilts the balance toward clotting by producing thrombin and by activating platelets.

Rheologic factors also activate blood constituents and help to localize thrombi on or near disturbed sites within the vascular system. Normally, intravascular thrombosis does not occur except at sites of vascular injury or disease. Under normal laminar flow conditions, the deformability of red cells and their propensity to form rouleaux largely determine the position of cellular elements within the blood-flow profile.[13] These properties cause red cells to mainstream and platelets and white cells to marginate.[13] Stenoses, expansions, branches, plaques, in-

jury sites, etc. in the vascular system cause flow separation and areas of high and low shear stress, turbulence, cavitation, secondary flows, vortices, and stagnation.[14] Variations in local shear stress activate platelets, endothelial cells, and some coagulation proteins.[14] Very high shear stresses destroy blood elements. At sites where flow is disturbed, changes in rheologic forces facilitate thrombus formation by affecting the ratio between local wall shear rate and the Brownian coefficient of diffusion within the boundary layer (closest to the vascular wall). High wall shear rates in the presence of low flow velocities allow Brownian forces to bring platelets and other procoagulants near the disturbed vascular wall by diffusion.[14] Except for autografts or unmounted homografts that are sewn directly into the aortic root, all prosthetic valves disturb blood flow. The sewing ring, a priori, creates a collar stenosis on the inflow side and an expansion zone on the outflow side in all mechanical valves and in mounted bioprosthetic valves.

Choices of biomaterials, valve design features, and anticoagulant agents and regimens are the only available means to counteract the procoagulants induced by platelet activation, thrombin formation, and disturbed blood flow. Successful heart valves must restore the balance between procoagulants and anticoagulants to allow endothelial cells to maintain the fluidity of blood and the integrity of the vascular system. Although restoration of this balance is the major factor that influences the thrombogenicity of prosthetic heart valves, it is only one of many factors that must be considered in the design and construction of a successful valve prosthesis. Other factors include hemodynamic pressure and flow characteristics, closing volumes, cavitation sites, leachable chemicals, healing responses, the potential for fabricating materials, and the durability and wear characteristics of materials (Fig. 2). Some of the biomaterials suitable for use in prosthetic heart valves are listed in Table II.[15] So far, no surface coating (e.g., covalently bound heparin) has been found to reduce the thrombogenicity of prosthetic heart valves.

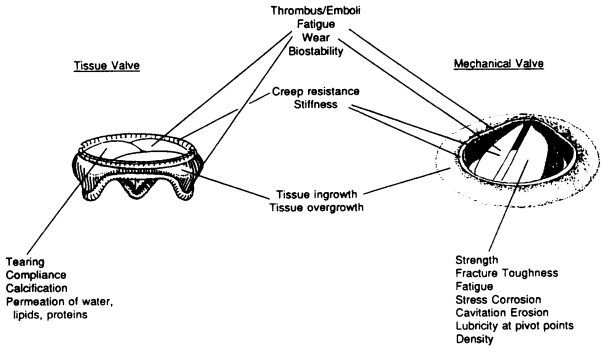

Fig. 2 *Design considerations pertinent to construction and use of prosthetic heart valves. (From: Helmus MN, Hubbell JA.[15] Copyright 1993. Reprinted by permission of Elsevier Science, Inc.)*

TABLE II. Materials Used in Prosthetic Heart Valves

Nondegradable Synthetics
Epoxies
Polyacetals
Polyetherketones
Polyimides
Polysulfones
Silicones
Metals and Alloys
Titanium and titanium alloys
Tantalum, cobalt chrome alloys
Nickel chrome alloys
Stainless steels
Carbons
Pyrolytic carbon
Ultra-low-temperature isotropic carbon
Biologic Materials
Porcine valves
Bovine pericardium
Cryopreserved allografts
Nutrient-preserved allografts

Oral anticoagulants are another means to tip the balance away from thromboembolism. Unfortunately, warfarin and its derivatives are the only oral anticoagulants available. Warfarin is a clumsy drug that has a narrow therapeutic range and a mean half-life in plasma of 42 hours; moreover, it requires a blood test to monitor.[16] Many drugs and foods affect the dose response of warfarin. The drug inhibits liver metabolism of 4 different coagulation proteins that have plasma half-lives ranging from 5 to 100 hours. Its onset of action is slow and it is difficult to maintain patients within the narrow therapeutic range.[16] Spot prothrombin times are outside target values 33% to 50% of the time.[17] Irrespective of these problems, warfarin anticoagulation significantly reduces the incidence of thromboembolism in all patients with mechanical valve prostheses and in many patients with bioprostheses.[16]

To further reduce prosthesis-related thromboembolism, it is recommended that a platelet inhibitor be added to warfarin anticoagulation. In doses tolerated by patients, dipyridamole is ineffective.[18] Aspirin is effective, but increases the risk of bleeding. Fortunately, this risk is directly proportional to the dose, and low-dose aspirin (100 mg) taken every 2 or 3 days inhibits platelets just as effectively.[19] In a recent prospective, randomized study of patients

with prosthetic heart valves, the combination of 100 mg per day of aspirin with warfarin was found to reduce the incidence of all thromboembolic events by 77% and to increase the rate of bleeding complications (nearly all gastrointestinal) by only 55%.[20]

To conclude, let us return to our title: Is valve thrombogenicity related to design or material? Clearly, the answer is both.

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