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Heparin coatings for improving blood compatibility of medical devices☆

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ABSTRACT

Blood contact with biomaterials triggers activation of multiple reactive mechanisms that can impair the performance of implantable medical devices and potentially cause serious adverse clinical events. This includes thrombosis and thromboembolic complications due to activation of platelets and the coagulation cascade, activation of the complement system, and inflammation. Numerous surface coatings have been developed to improve blood compatibility of biomaterials. For more than thirty years, the anticoagulant drug heparin has been employed as a covalently immobilized surface coating on a variety of medical devices. This review describes the fundamental principles of non-eluting heparin coatings, mechanisms of action, and clinical applications with focus on those technologies which have been commercialized. Because of its extensive publication history, there is emphasis on the CARMEDA® BioActive Surface (CBAS® Heparin Surface), a widely used commercialized technology for the covalent bonding of heparin.

Contents

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1. Introduction

The activation of blood defense mechanisms upon exposure to biomaterials poses a challenge to the design and performance of blood contacting medical devices. Activation of the coagulation cascade, complement system, cellular inflammatory mechanisms, and platelets are among the key adverse reactions of blood that may compromise the performance of medical devices [1,2]. This may manifest clinically as thrombotic occlusion and embolization across a spectrum of cardiovascular medical devices, including vascular stents, grafts, and catheters, as well as cardiopulmonary bypass and oxygenation equipment, prosthetic valves, and ventricular assist devices. In some cases, for example in patients with coronary stents, mechanical heart valves, and left ventricular assist devices, chronic pharmacological inhibition with antiplatelet or anticoagulant drugs is required to protect against thrombotic complications.

Modification of medical device surfaces to improve blood compatibility has been sought to reduce device-related thrombus formation and inflammatory reactions. Surface modification technologies can be assigned into two broad categories: passivation of material surfaces and bioactive surface treatments and coatings [3]. Passive approaches are aimed at reducing the inherent thrombogenicity of the material surface through modification of surface chemistry (*e.g.* hydrophilicity) or material physical structure (*e.g.* topography). Bioactive strategies employ direct pharmacologic inhibition of the coagulation response by local drug delivery or permanent immobilization of an active agent.

A precipitating event in the modern field of blood compatible surface modifications was the serendipitous discovery of the thromboresistant properties of a heparin coated surface by Gott and colleagues in 1963 [4]. It was observed that by temporarily immobilizing the anticoagulant drug heparin at the device surface, there was marked reduction in thrombus formation on materials implanted into the vena cava. Numerous approaches to hemocompatible surface modifications have been described since [1–3], including a number of heparin-based surface modifications [5–8].

The focus of this review is on a specific subset of commercialized non-eluting heparin coating technologies which were developed for use in the medical device industry. Of the various heparin-based technologies, the CARMEDA® BioActive Surface (CBAS® Heparin Surface; Carmeda AB, Upplands Väsby, Sweden), has the most extensive publication history describing both basic biochemical mechanisms and clinical applications. Hence, this review will focus on the immobilization of the anticoagulant drug heparin with emphasis on the CBAS Heparin Surface.

2. Coagulation and heparin mechanism of action

Thrombus formation is the result of two interdependent mechanisms, platelets and circulating protein clotting factors. Platelets, small anuclear cells that circulate in blood in ranges from 150×10^6/mL to 400×10^6/mL are a critical component of hemostasis. Activation of platelets by a variety of stimuli triggers complex pathways that result in platelet aggregation and the release of potent pro-thrombotic molecules. It is well known that blood contact with artificial surfaces can elicit platelet activation by a variety of mechanisms [1], including device related alteration in blood flow that trigger shear-related platelet activation [9], and due to direct platelet adherence to the deposited protein layer on synthetic surfaces of the device, an event largely attributed to adsorption of fibrinogen [1,2]. Activated platelets undergo dramatic shape changes which promote aggregation with other platelets, and release platelet and pro-coagulant agonists (such as thromboxane A2, ADP, and FVa) [10]. The phospholipids of the platelet membrane also serve as the substrate for activated clotting factors, resulting in local amplification of the coagulation cascade. Aggregation of platelets, together with explosive activation of protein clotting factors, may result in significant thrombus accumulation on the device surface, embolization of thrombus particles into the bloodstream, and may cause detectable reductions in circulating platelet count (consumption of platelets).

The protein clotting factors are a set of structurally similar serine proteases that circulate in the plasma as inactive proenzymes. After vascular injury, or through the introduction of foreign materials into the circulatory system, clotting factors are triggered and undergo activation in a sequential cascade-like fashion that culminates in the formation of a fibrin clot. This cascade consists of two pathways, the intrinsic and extrinsic, each of which is triggered by different mechanisms. Tissue factor that is released due to vascular injury is the primary initiator of the extrinsic pathway [11]. The intrinsic pathway is considered the more critical pathway in biomaterial-associated thrombosis [1]. Contact activation of FXII, together with kallikrein and high molecular weight kininogen (HMWK), initiates the intrinsic pathway leading to activation of FX, and consequently conversion of prothrombin into thrombin. Thrombin converts soluble fibrinogen into insoluble fibrin, which polymerizes into an insoluble fibrous network. Clotting factor activation is typically accompanied by and promoted by platelet activation, and the resultant thrombus often contains both platelets, fibrin, and other entrapped cells (Fig. 1). A key inhibitor of the clotting factors is the plasma serine protease inhibitor antithrombin (AT). AT binds and irreversibly inhibits the active forms of several clotting factors, including thrombin, FXa, FIXa, FXIa, and FXIIa [12]. AT-mediated inhibition of the clotting factors occurs at relatively slow rate, but is accelerated by binding to the polysaccharides heparan sulfate and heparin [13].

Heparin is a naturally occurring linear polysaccharide that shares chemical and structural similarity to heparan sulfate, a cell surface proteoglycan that provides the natural anticoagulant surface activity of the vascular endothelium [14]. Unlike heparan sulfate, heparin is largely intracellular, within the granules of mast cells. Heparin consists primarily of two highly sulfated sugar monomers, which occur as repeating disaccharide units. The anticoagulant function of heparin is dependent on a specific sequence of five sugars (the so-called pentasaccharide sequence), which are required for efficient binding of antithrombin (AT) [15]. This sequence is only found in approximately one-third of the molecules in a commercial heparin preparation [16–18]. Binding of AT to the heparin pentasaccharide sequence causes a conformational change in the AT molecule and greatly accelerates the rate of AT-mediated inhibition of the various serine protease clotting factors by a factor of 100–1000. Importantly, heparin is not consumed in the reaction and is capable of continuously catalyzing inhibition of activated clotting factors. However, heparin in the blood stream is quickly cleared from circulation through a combination of saturable cell-based binding and non-saturable renal clearance [19–23], with an average half-life of approximately 60 min for unfractionated heparin (UFH) and longer a longer half-life for low molecular weight heparins (LMWH).