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Device thrombosis and pre-clinical blood flow models for assessing antithrombogenic efficacy of drug-device combinations☆

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ABSTRACT

Thrombosis associated with blood-contacting devices is a complex process involving several component interactions that have eluded precise definition. Extensive investigations of individual biological modules such as protein adsorption, coagulation cascade activation and platelet activation/adhesion/aggregation have provided an initial foundation for developing biomaterials for blood-contacting devices, but a material that is intrinsically non-thrombogenic is yet to be developed. The well-recognized association between fluid dynamics parameters such as shear stress, vortices, stagnation and thrombotic processes such as platelet aggregation and coagulation aggravate thrombosis on most device geometries that elicit these flow disturbances. Thus, antithrombotic drugs that were developed to treat thrombosis associated with vascular diseases such as atherosclerosis have also been adapted to mitigate the risk of device thrombosis. However, balancing the risk of bleeding with the antithrombotic efficacy of these drugs continues to be a challenge, and surface modification of devices with these drug molecules to mitigate device thrombosis locally has been explored. Pre-clinical blood flow models to test the effectiveness of these drug-device combinations have also evolved and several in-vitro, ex-vivo, and in-vivo test configurations are available with their attendant merits and limitations. Despite considerable efforts toward iterative design and testing of blood contacting devices and antithrombogenic surface modifications, device thrombosis remains an unsolved problem.

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1. Introduction

An adverse consequence of using biomaterials in blood-contacting devices is the adsorption and adhesion of certain blood components such as platelets and plasma proteins onto the biomaterial interface which may potentiate thrombus formation [1]. In the case of vascular

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implants (e.g. stents), this thrombus on the device may directly occlude the blood vessel in which the device is deployed [2,3]. In addition, the thrombus on a device may also be torn off by the forces of flowing blood, resulting in thromboemboli that can block micro-vasculature in distal organs. This may lead to impaired organ function (e.g. cerebral stroke) as noted in patients with left ventricular assist devices (LVADs) [4] and synthetic heart valves [5]. Further, even in cases where patients do not physiologically exhibit clinically significant symptoms of device thrombosis or thromboembolism, device dysfunction may result from this pathology (e.g. occlusion of hemodialysis catheters [6]).

Device thrombosis is a multicomponent pathology that can progress via diverse pathways and is influenced by several factors. Fibrinogen, von Willebrand factor, clotting factors, platelets, white blood cells, complement system, etc. may all participate in thrombus formation on a device [7]. Several different platelet aggregation pathways may be triggered and the intrinsic and extrinsic coagulation pathways may be involved in device thrombosis [1,7]. Biomaterial surface properties [8], fluid dynamics around the device [9], and the patient's hemostatic and homeostatic conditions are some of the major factors that may influence device thrombosis.

While many of the aforementioned components, pathways, and factors have been studied extensively as individual modules, the complexity of the combined process of device thrombosis has eluded precise understanding [1]. As a result, strategies aimed at mitigating device thrombosis by targeting one or a few individual components or modules have met with limited success [6]. Further, simplistic modular tests and test models used to ascertain the efficacy of thromboresistant and antithrombogenic device treatments have not consistently predicted the performance of these treatments in the more complex and comprehensive physiological environment [10,11]. Thus, the need for more sophisticated antithrombogenic device treatments has been recognized along with the need to evaluate candidate technologies in pre-clinical test models that feature a more expansive array of relevant components and factors [11]. This review will provide an overview of the factors influencing device thrombosis and pre-clinical blood flow models that are useful for the assessment of antithrombogenic technologies in drug-device combinations.

2. Device thrombosis process

Platelets, clotting factors, and certain plasma proteins are central components of device thrombosis. As shown in Fig. 1, platelets adhere to the biomaterial surface through plasma proteins such as fibrinogen and von Willebrand factor that are adsorbed onto the biomaterial surface and bound to the platelet on glycoprotein receptors [12–14]. Platelet aggregation is triggered by multiple pathways such as the cyclooxygenase pathway and the adenosine di-phosphate pathway and occurs when a fibrinogen molecule binds to glycoprotein IIb/IIIa receptors on two platelets, thereby linking them [15]. Coagulation is mediated by the intrinsic and extrinsic pathways which eventually lead to the formation of fibrin, and a biomaterial may initiate the coagulation cascade directly and indirectly [1,16]. The interplay between platelets and the clotting cascade has also been identified wherein activated platelets release pro-coagulant proteins (e.g. Factor V) [17] and intermediate clotting factors generated in the coagulation cascade are potent platelet activators (e.g. thrombin) [18]. The biochemistry and molecular biology of these major processes have been studied extensively for decades and antagonists to specific pathways have been developed: anticoagulants such as heparin, rivaroxaban, and dabigatran, and antiplatelet agents such as aspirin, thienopyridines, and glycoprotein IIb/IIIa inhibitors are widely used drugs for the prevention of thrombosis in many clinical situations [19–21], including those involving devices. Some of these pharmacological agents are used in surface modification of biomaterials to render them antithrombogenic and will be discussed later.

Considering these components and pathways, the process of device thrombosis is envisioned to progress as follows [22]: (1) the proteins in blood are adsorbed onto the surface of the biomaterial; (2) the platelets are activated (especially by high shear stress) and adhere to the protein layer; (3) the coagulation cascade may be initiated by the adsorbed

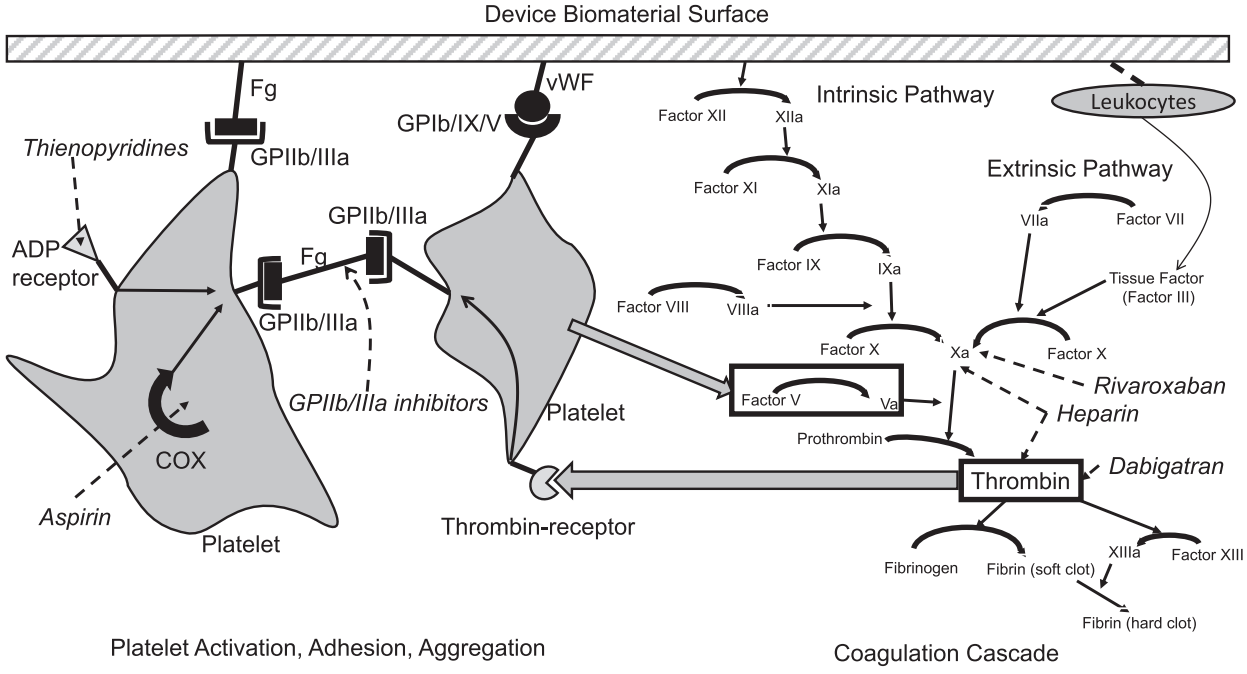

Fig. 1. Simplified schematic of some of the major platelet adhesion, aggregation, and coagulation pathways, and their interactions. Commonly used anticoagulants and antiplatelet agents are also shown (in italics) along with the primary pathways that they inhibit (dashed lines). Numerous other independent, complementary, and compensatory pathways have been identified beyond those shown here which underscores the multicomponent biochemistry and molecular biology of the complex device thrombosis process. Abbreviations: COX (Cyclooxygenase), Fg (Fibrinogen), vWF (von Willebrand Factor), ADP (Adenosine di-phosphate), GP (Glycoprotein).