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Thrombosis-on-a-chip: Prospective impact of microphysiological models of vascular thrombosis

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Abstract

The most common pathology of the blood-vessel organ system is thrombosis or undesirable clotting of the blood. Thrombosis is life threatening as more than 25% of such cases lead to sudden death from stroke and myocardial infarction. Even though the process of thrombosis has been extensively investigated with animal models, its exact pathobiology in different blood vessels is not yet fully understood and drug assessment remains unpredictable. This is primarily because the cause for thrombus formation is multifactorial and depends on the interplay of flow patterns within the blood vessel, the vessel wall or endothelium, extracellular matrix, parenchymal tissue, and the cellular and plasma components of the blood. Current *in vitro* and animal models do not mimic or dissect this organ-level complexity faithfully. However, microfluidic technology has recently been deployed to effectively recapitulate blood-endothelial–epithelial interactions in the onset of thrombosis in blood vessels. This technology is promising because it permits inclusion of primary human cells and blood obtained from patients, which is currently lacking in other *in vitro* models of thrombosis. In this review, we summarize the current state-of-the-art and practices in microfluidics and expected improvements in this field that will impact basic understanding of thrombosis, drug discovery and personalized medicine.

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Background

Under physiological conditions, the blood remains in a fluid state by maintaining a balance between the procoagulant and the anticoagulant factors present in the blood. When this balance is impaired, a shift towards anticoagulant factors leads to unexpected bleeding and blood loss whereas a shift towards procoagulant factors leads to thrombus formation that occludes blood vessels eventually becoming a cause of stroke [1]. Such undesirable clotting of blood is the most common pathology found in the vasculature. Pathologic clotting of blood, or thrombosis, in the vasculature has been studied extensively since the 18th century. In the earliest studies, the initiation of thrombus formation (thrombogenesis) was related to one of the following factors: hypercoagulability of blood, blood stasis and endothelial damage. However, Rudolf Virchow in 1856 was the first to make a profound observation that all these three factors together are critical to thrombogenesis. These factors that collaboratively contribute to thrombosis are known as the Virchow's triad [2]. Blood can become hypercoagulable due to the activation of blood cells (such as platelets) and release of clotting factors (such as thrombin) into plasma [3]. Stasis of blood flow may occur due to occlusion of the blood vessel resulting from plaque formation in arteries (atherosclerosis) or due to impairment of valves in the deep veins (deep vein thrombosis) [4]. Vascular activation occurs when the endothelium is exposed to circulating stimulants, making it procoagulant and pro-inflammatory [5]. Endothelial cell inflammation increases cell permeability contributing to thrombus formation by the interaction of platelets and clotting factors with the exposed components of the vascular surface [6]. Since the discovery of Virchow's triad, its factors have been extensively investigated independently at molecular and cellular levels, but the mutual interplay of these factors (and others) has not been fully understood

because it requires dissectible organ-level modeling of the physiology of thrombosis. Current methods that are used to investigate the multivariate factors that lead to thrombosis do not permit analysis of the organ-level prothrombotic responses with incremental level of complexity that underlies in several diseases. While several sophisticated animal models of thrombosis exist, and have contributed to our basic understanding of certain specific mechanisms, integrated models that can separate contributions of platelet–endothelial interactions versus tissue-tissue (e.g., epithelial-endothelial) interactions are still underdeveloped and significantly non-predictive. Most current *in vitro* assays of hemostasis and thrombosis on the other hand, do not incorporate vascular function. Several recent studies have enabled microfluidic flow chambers to include endothelial lumen within which whole blood can be perfused and platelet–endothelial interactions can be visualized with high resolution [7–10]. This development is promising as it opens opportunities to include the more complex organ-level interactions in the assessment of thrombosis as well as anticlotting drugs. There are further advantages of using such microphysiological systems (or organs-on-a-chip) due to their micro scale, for e.g. these devices require little amount of blood samples, tight control of dimensions, lower cost per device and easy fabrication and repeatability of large number of experiments [11]. Also, with organ-on-a-chip technology, assessment of thrombosis at a patient-specific level is possible by including specific vessel anatomy, vascular endothelial cells and blood, all derived from the same patient. Here, we succinctly discuss current animal and *in vitro* methods applied in modeling arterial, venous and microvascular thrombosis, followed by an overview of utilization of microphysiological devices in assessing complex features of thrombosis and future directions that could improve status quo.

Current models of thrombosis: the gold standard

Current models used to investigate thrombosis include *in vivo* animal models ranging from zebra fish to nonhuman primate models, and *in vitro* models in the form of parallel plate flow chambers and cone-and-plate viscometers.

Animal models

The most common animal model of thrombosis is the mouse. Numerous murine thrombosis models have been developed to study the arterial, venous, and microvascular thrombosis [12]. In these models, arterial thrombosis is generally induced using injury of the carotid arteries (for example, ferric chloride or Rose Bengal-plus-light), venous thrombosis is induced slowly by stasis or stenosis (both by ligation) or rapidly by an acute injury (using free-radicals) of the inferior vena cava, and microvascular thrombosis is induced by free-radical injury or laser injury of the mesenteric veins. A few other models also exist, like direct electric injury, anastomosis, ultrasound disruption or intraluminal collagen, which are less preferred due to the difficulty in obtaining repeatable results between labs. These diverse mouse models have contributed immensely over the last few decades in decoding several key mechanisms that govern thrombosis [12–16], as well as capturing the thrombus dynamics in human-relevant conditions [17]. They have also been effective in studying the role of genetic variation and different clotting factors in thrombus formation. However, the physiological and genetic differences of these models with respect to humans limits them considerably [18,19]. This is mostly true because several drug trials that succeeded in such animal models have failed in human clinical trials [20], thus contributing to high healthcare costs and stroke remaining to be the biggest cause of patient mortality. While small animal models (zebra fish, mice etc.) are preferred in thrombosis research mostly due to their easy availability and established genetic data [13], the large animal models (dogs, pigs, nonhuman primates etc.) offer increased physiological relevance to humans. However, large animal studies cannot be easily conducted in academic laboratories and impose several ethical restrictions thus making small animals or *in vitro* models the first choice to model thrombotic diseases.

In vitro models

A commonly used *in vitro* thrombosis system, the parallel plate flow chamber is a hollow rectangular space with millimeter or centimeter scale dimensions, through which blood or its components can be transported to induce physiological wall shear stresses over purified proteins (such as, von Willebrand factor (VWF) or tissue factor), extracellular matrix (ECM like collagen, laminin or fibronectin) or cultured vascular endothelial cell monolayers [21]. The flow rates are often controlled using constant-flow pumps, although pressure and gravity are also used to transport blood. While these systems have been useful in studying the effects of shear and recirculating flow [22] on platelet function and coagulation [23], accurate blood vessel anatomy is not replicated in these chambers. For example, these flow chambers have not included the complex vascular features like venous valves where abrupt shear stresses may contribute to the onset of deep vein thrombosis (DVT). The other commonly used *in vitro* system, the cone-and-plate viscometer, works by rotating a cone shaped insert above a stationary plate containing proteins or cultured vascular cells [24]. The rotational speed of the cones in these devices are controlled to generate shear stresses. These devices are bulky and need large amounts of blood, cultured cells and reagents for each experiment, making them low throughput. Also, the experiments in these devices are conducted over 2D monolayers of

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