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# Study and simulation of thrombus properties

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**Abstract.** Thrombosis is a common pathological symptom that endangers cardiovascular and cerebrovascular health, and its essence is that blood clots in the vascular wall cause serious problems in the body. In vitro simulation of thrombosis can help us understand the composition and nature of thrombosis, and provide basis and convenience for better thrombus removal technology. This paper will discuss the existing thrombosis simulation methods and their development, and propose a new in vitro simulation of thrombosis preparation.

**Keywords:** thrombus, thrombus properties, simulated thrombus

## 1. Introduction

In recent years, disability rates and deaths due to blood clots have increased year-on-year. The blockage of blood vessels by thrombus will cause local blood flow [1] obstacles and cause serious injury to the body, which is one of the main causes of cardiovascular and cerebrovascular diseases. Thrombocytopenia itself is the primary target of treatment, either by drug thrombolysis or mechanical thrombolysis. A better understanding of the composition, physical properties, behavior of blood clots, and how these blood clots interact with their environment will contribute to future therapeutic advances and hopefully improve clinical outcomes [1]. As a result, researchers have studied the mechanism of thrombosis in various ways. A large number of studies [2] have shown that blood velocity, flow, concentration and temperature can affect thrombosis formation, and the texture and histological morphology of thrombus have a certain impact on the evaluation of thrombus removal devices. However, it is not easy to obtain blood clots directly from patients and conduct studies. Therefore, the

thrombotic research approach based on in vitro simulations provides a scientific basis and convenience for the study of thrombotic diseases. It is capable of simulating various types and conditions of thrombosis and can safely perform a large number of simulations under controlled and reproducible conditions, providing opportunities to study thrombectomy and evaluate its effects under a variety of conditions. This could be a valuable tool for evaluating the effectiveness of different manipulation techniques under different conditions.

## 2. Classification of thrombus

Human thrombosis types are highly variable, and quantifying the properties of human thromboses could accelerate the development of thrombotic analogs for studying thrombotic outcomes, which are often inconsistent across patients. Blood clots can be classified by location, size, and composition. Large blood clots can be understood as a mixture between small blood clots and platelets, while small blood clots can descend to other locations and may appear in twisted and broken blood vessels. In this paper, we focus on the classification of thrombosis based on location and composition.

### *2.1 Classification by composition*

The composition of a typical thrombus consists of different proportions of fibrin, platelets, red blood cells, white blood cells and other small components, since small components are not common, they are not described too much in this paper.[3]. Often classified in qualitative terms "soft/red", "hard/white", or "aged/calcified" [4], "soft/red" clots are also defined as blood clots that are rich in red blood cells and platelets, while "hard/white" clots are often rich in fibrin and platelets. Generally speaking, in the pathology classification, the simple classification of thrombus based on main components is mainly white thrombus, red thrombus, mixed thrombus, and transparent thrombus [5]. Transparent thrombus is only common under the microscope, so there will not be much of it. When it comes to removing blood clots, the type of clot will partly determine the performance of a device. It has been pointed out that [1] the part of thrombus dominated by red blood cells is generally easy to recover, while the part dominated by fibrin is difficult to recover. Yuki et al. [6] treated two different types of experimental thrombus-blocked pig blood vessels with MT device, and the angiographic analysis showed that compared with the occlusive blood vessels rich in red blood cells, the occlusive blood vessels rich in fibrin showed a lower recirculation rate and a longer average recirculation time. It has also been suggested [7] that blood clots rich in red blood cells tend to break up, whereas fibrin-rich clots are harder and may block the aspiration catheter because the suction does not break the clot, and the applied tension causes downstream emboli or residual occlusion.

### *2.2 Classification by the source*

Arterial thrombosis: Arterial thrombosis is caused by vascular wall lesions and high shear force [8], and most frequently occurs in coronary artery, cerebrovascular artery and pulmonary artery. Therefore, the frequent diseases of arterial thrombosis are acute myocardial infarction, acute ischemic stroke and pulmonary embolism [9]. In terms of the formation mechanism, a large amount of evidence shows [10] that arterial thrombosis is an acute attack of chronic vascular disease, and the inflammatory changes of unstable plaques lead to plaque rupture or fissure, which further stimulates thrombosis. At the cellular level, arterial thrombosis is mainly caused by platelet activation and then the aggregation of other

components, which are usually with atherosclerotic lesions [11]. In terms of treatment, anti-platelet drugs are used to treat arterial thrombosis in a broad sense [12], which can be used not only for the treatment of arterial thrombosis, but also for prevention. The main function is to target platelet activation and aggregation. Histological results of fresh thrombus obtained during mechanical thrombectomy showed [13] that the thrombus obtained from myocardial infarction was mainly fibrin and platelets., while the thrombus obtained from patients with acute ischemic stroke was mainly red blood cells and platelets.

Venous thrombosis: The formation of venous thrombosis is different from that of arterial thrombosis, which mainly consists of red blood cells and fibrin. As venous thrombosis contains a large amount of fibrin, venous thrombosis occurring under low shear stress is mainly driven by coagulation imbalance, so anticoagulants are used for treatment [13]. A clot that forms in a vein can either lock into its own vessel or float away as a small blood clot, most commonly blocking an artery.

## 3.Properties of thrombus

Thrombosis is a kind of coagulation formed in blood vessels, which accumulates in the blood vessel wall and is mainly composed of hemoglobin, fibrin, lipids, coagulation factors and cells [1]. Thrombosis is a complex phenomenon, but it has long been thought that it depends mainly on the interaction of three components: blood composition, blood flow, and surface properties [14]. The nature of blood clots is affected by blood flow status, and a better understanding of the type and nature of blood clots and how they change over time will help assess the optimal combination of timing, imaging techniques, device type, and treatment strategies based on patient occlusion characteristics, allowing clinicians to anticipate thrombotic behavior before treatment and adjust treatment strategies.

### *3.1 Viscosity*

Viscosity is a powerful tool in medical diagnosis of thrombosis, reflecting the pressure on the clot and determining whether the clot has a tendency to block or rupture. At present, only a small number of thrombus extracts from humans have produced quantitative data, and no exact thrombus viscosity range is available. Chueh et al. [15] studied the elastic and stiffness characteristics of the extracted thrombus and prepared thrombus analogues. Karpiouk et al. [16] used the instantaneous force method based on solid spheres to evaluate the viscoelasticity of thrombi with gelatin, and the results showed that although the accuracy of the current method to measure viscosity was not clear, it was reasonable to measure viscosity in the range of 0.16-0.32 Pa·s for blood clots. Chen et al. [17] used shear wave dispersive ultrasonic vibration measurement (SDUV) technology to measure two kinds of blood clots with different hematocrit (hematocrit concentration 20% and 40%). The viscosity of 20% hematocrit blood clots was $0.37 \pm 0.02$ Pa·s. The viscosity of 40% hematocrit clot was $0.27 \pm 0.02$ Pa·s. Huang et al. [18] also used SDUV to measure the elasticity and viscosity of blood clots at the same time, and conducted thrombosis experiments by measuring different concentrations of gelatinized bodies and porcine whole blood (hematocrit ranges from 3% to 40%). The results showed that although SDUV and other rheological measurement methods could not provide accurate viscosity estimation for blood clots, the viscosity measured in this study in the range of 0.29-0.42 Pa·s is reasonable.

*3.2 Hardness and elasticity*

Kim et al. computational work examined the correlation between the structural features of blood clots and their behavior, and their computational model was validated with the experimental work of Ryan et al., showing that the average hardness of fibrin-rich blood clot analogs is about 2.6 times that of RBC-rich blood clot analogs [18]. As the fibrin content in the clot increases over time, the clot also hardens [19]. In animal models of DVT (Deep venous thrombosis), the elastic properties of soft tissues were evaluated noninvasively using ultrasound elastography. Human blood clots grow at different rates, but the clot formation process has the same stages. As the clot progresses, the elasticity of the clot with respect to the vessel wall increases from about 0.25 to 2.0[20][21]. In order to accurately measure the elastic properties of thrombus, Xie et al. developed a benchmark electronic device, Micro Elastometer. Based on the establishment of a good DVT rat model, mechanical measurements were carried out on the two groups of animals in vitro, and the results showed that the deformed thrombus in vivo did not significantly change their elastic modulus [20].

## 4.Thrombus simulation

Thrombosis simulations can help us better understand the mechanisms of thrombosis and develop techniques for thrombosis extraction. Most of the existing simulation methods for thrombosis are animal models of in vivo thrombosis, different types of donors, and synthetic thrombus materials.

*4.1 Thrombosis model in animal*

Studies on thrombosis in vivo involve microvascular and macrovascular animal models [5]. The characteristics of microvascular thrombosis studies tend to be more similar to those of major arteries, such as coronary and cerebral arteries, and can provide more relevant parameters for clinical thrombosis types. The most common method of inducing thromboembolic ischemia is to inject autologous blood clot into the extracranial arteries to reach the more distant intracranial arteries. Busch et al. [6] successively injected multiple fibrin-rich autologous blood clot into the external carotid artery. After 3 h of embolism, cerebral blood flow continues to decrease in the arterial blood supply region and histological damage persists without spontaneous re-calculation, which can be used as a model. Kan et al. [7] reported the development of a new thrombus preparation technique for evaluating a pig model of thrombus extraction device. Experimental thrombosis was prepared by ordinary sedimentation and, due to its fibrin-rich solid component, demonstrated mechanical stability and histological similarity to thrombosis typically recovered from stroke patients.

*4.2 In vitro thrombosis of different donor types*

Simulated thrombosis detection in vitro is an effective method to study thrombosis formation. Lab-produced clot analogues are commonly used to evaluate the performance of MT devices in vitro. Such clot analogues must be representative of human blood clots. Thrombin is one of the most effective activators of platelets and can promote thrombosis under all shear conditions [24]. However, it remains unclear whether it is primarily involved in promoting initial thrombotic growth or whether it is more important for stabilizing already formed thromboses, with in vitro perfusion studies suggesting that the latter function may be more important. The traditional in vitro thrombus model uses a simple flow chamber coated with fibrous type I or Type III collagen from horses or cattle [25] to achieve the effect of simulating real blood vessel walls.

Chueh et al. [26] studied the elastic and hardness characteristics of human thrombi extracted by them, created thrombi analogs by changing the blood donor species (human, pig and cow), thrombin concentration and the presence of barium sulfate, and tested their hardness and elasticity. The results showed that the recombinant porcine thrombocytopenia and thrombocytopenia analogs were similar in hardness and elasticity to those in patients with AIS. The addition of barium sulfate to the thrombus simulation significantly reduced the elasticity. Krasokha et al. [27] conducted a compression test on the blood clot of 12-day-old pigs prepared by adding 25 IU thrombin and 1 g barium sulfate, which showed that barium sulfate particles had a significant hardening effect on thrombus materials. Pig blood has been used to form fibrin clots [28], made with or without thrombin and barium sulfate, while bovine clots (thrombin-induced) mimic aging blood clots in vitro and are hard and brittle [29].

Duffy et al. [30] noted that sheep blood has been found to be a suitable substitute for human blood, and its clot samples are histologically similar to human clots. Weafer et al. [20] also proved that sheep blood was the most suitable clot analogue for coagulation research. Venous blood was obtained by veterinarians from specimens of male and female sheep between the ages of 1 and 7 years, weighing 70 to 120 kg, for research purposes. Soize et al. [31] used three different types of blood clots rich in red blood cells, rich in fibrin and mixed clots in order to explore the impact of different thrombectomy. The RBC-rich clot was spontaneously coagulated from whole sheep blood. Fibrin-rich clots are created by first unspinning a blood sample in a centrifuge and then recombining 5% of the RBC with 95% of the plasma. Mixed clots are prepared by cutting self-forming clots (rich in RBCS) into cubes of 1-1.5 mm. The results showed that the fibrin-rich clot was not easily broken up.

Human blood has also been used to form many in vitro thrombus models, and thrombin-induced human clot simulates soft and elastic fresh thrombi in vitro [29]. Kim et al. [32] prepared fibrin clots by combining human citrate PPP with CaCl2 and human thrombin technologies. The mechanical response of human clot analogues may differ from that of animal clot analogues, and the comparison of tensile and compressive load responses of human clot analogues from the same donor is unknown [33]. Thrombus analogues from pig, sheep, or cow whole blood are routinely used to test thrombus removal devices, but may not produce reliable results and are much weaker than human thrombus analogues [34].

*4.3 Synthetic materials simulate thrombus*

The formation of blood clots is a complex process, and an increasing amount of research has been devoted to improving experimental methods for simulating blood clots. Among them, the simulation of thrombosis with organic materials is an emerging research method that can achieve realistic and reliable simulation results, better simulate thrombosis in human blood vessels, and study the effects of thrombosis. Better provides a new idea for thrombotic suction techniques. In vitro clot materials with a variety of compositions and mechanical properties have been developed to mimic as closely as possible the clot properties found in vivo [35]

In some simulated environments, the use of clot analogues based on blood products is not practical, and to address this limitation, polymer materials have emerged as another option for the production of clot analogues [12]. Merritt et al. [4] studied and developed a new adjustable synthetic polymer (related to samples rich only in RBC), which used hydrogel and polymer structure as synthetic thrombi for study, and the synthetic material had similar shear force and elastic modulus characteristics. Tests on PVA and PVA-hydrogel composites show that hydrogels have high viscosity and minimal elasticity. The results

show that the initial RBC-rich thrombus analogs prepared in this study have a good similarity with respect to the human thrombolysis samples reported in the literature.

Guerreiro et al. [10] described the first completely synthetic blood clot replacement model consisting mainly of agarose or silica gel, and analyzed the suitability of this clot in the evaluation of mechanical thrombolysis models and devices in vitro. In order to explore the effectiveness of pulsating and constant aspiration in cerebral thrombectomy models, Simon et al. [11] cut synthetic polyrethane clot to a specific clot size with a cylindrical template and placed it directly near the catheter tip for aspiration. The polyurethane clotting material used was taken from the training course of the TREVO device and clinical experience was used as a reference. Qualitative evaluation revealed that its volumetric mechanical properties were similar to those of clots successfully removed in thrombectomy cases.

## 5.Discussion

From the point of view of the difficulty of thrombosis, in vitro thrombus simulations and artificial thrombus simulations with different donor types are easier to prepare than animal model thromboses, with low cost and strong reproducibility. There have also been studies suggesting that analogue of thrombus derived from real human or animal blood is superior to synthetic alternatives, but there are no specific studies to support this idea. Through a comprehensive study of the thrombus retrieved from clinical cases, all prepared analogues of thrombus need to be continuously refined because none of them fully reproduce the complex structure and large number of different components in clinical specimens. More importantly, there is no specific demonstration of comparative studies with the real thrombosis, and the preparation method is not easy to replicate. But thrombus and thrombectomy studies can be formulated in an in vitro model and validated against the properties of real thrombi to conduct research. In vitro analogues of thrombus prepared from different donor types are mostly used to test thrombectomy devices, and whether they produce reliable results requires the development of validation techniques. However, artificial material prepared thrombosis can be regulated both in the hardness and viscosity preparation processes. Therefore, we used a pea starch and a stiffening agent to tune the thrombus analogues by different ratios and determined their viscosity density and elasticity, fully demonstrating the strong controllability and reproducibility of the in vitro simulation of the thrombus analogs. This method of in vitro simulation of blood clot analogues is widely used. More conducive to thrombosis research. Overall, synthetic alternatives indicate future research directions for artificial thrombosis, and future directions can be studied on this basis.

## 6. Conclusion

The formation of thrombus is dangerous to human health, so it is very important to further study the mechanism of thrombosis, and thrombosis simulation study is an important means to carry out thrombosis research, which can help to quickly and effectively understand the factors of thrombosis formation and the influence of different drugs on thrombotic lesions, so as to guide the treatment of related diseases. This paper summarizes the existing methods of thrombosis simulation, compares the properties and applications of thrombosis in animal model, in vitro thrombosis simulation of different donor types and synthetic substitute thrombosis, analyzes the research cost and feasibility of different preparation methods, and puts forward a new method of thrombosis analogue preparation. It was concluded that the synthetic substitute prepared thrombus was more worthy of being the best choice for the study of thrombus.

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