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An Efficient Method for Establishing a Rabbit Inferior Vena Cava Thrombosis Model

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Abstract

Background: Animal models of deep vein thrombosis (DVT) are crucial for studying its pathogenesis and treatment; however, existing models suffer from issues such as prolonged thrombus formation, inconsistent thrombus size, and a tendency for thrombi to dislodge. This study aims to establish a rapid, size-controllable, and safe rabbit inferior vena cava (IVC) thrombosis model for comparing thrombolytic efficacy.

Methods: The rabbit's IVC was localized and carefully dissected. Then, using haemostats and an appropriate amount of thrombin, the rabbit IVC thrombus model was established. The formation of the IVC thrombus was further verified using ultrasound. **Results:** Ultrasound examination confirmed the successful establishment of the rabbit IVC thrombus model, yielding venous thrombi measuring 1.0–3.0 cm in length and 0.3–0.5 cm in width. The success rate was 96.67%. After thrombin injection, the time required for IVC thrombus formation was 21.93 ± 4.37 minutes.

Conclusion: This model provides a new tool for studying venous thrombosis and interventional therapy. It will aid in the exploration of novel treatment strategies for venous thrombosis.

Keywords: Deep vein thrombosis; Animal models; Inferior vena cava thrombosis

Introduction

Deep vein thrombosis (DVT) is defined as a disorder of venous return caused by abnormal blood clotting within the deep veins. Its pathogenesis is closely associated with a hypercoagulable state, sluggish blood flow, endothelial dysfunction, genetic factors, gene mutations, and secondary risk factors (such as trauma and surgery) [1,2]. The early stages of the disease are often insidious, with subtle symptoms. However, pulmonary embolism may be triggered, and death can be caused in severe cases. A high incidence rate, a tendency to recur, and a significant threat to human health and quality of life are all characteristics of this condition [3,4]. The pathogenesis, diagnosis, and treatment strategies for DVT have been continuously explored. In DVT related research, animal models are considered indispensable tools. By establishing animal models that mimic the pathophysiological processes of human DVT, systematic studies can be conducted on the molecular mechanisms of thrombus formation, the efficacy of anticoagulant or thrombolytic drugs can be evaluated, and interventional treatment approaches can be investigated [5]. The reliability of experimental results and their clinical translational value are directly influenced by the appropriate selection of animal species

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and modeling methods. Currently, numerous methods for establishing animal models of deep vein thrombosis are available, which are primarily based on blood stasis, venous endothelial injury, and a hypercoagulable state. The specific modeling method and animal species to be used need to be determined according to the experimental requirements and conditions. The study of the venous wall and venous thrombi is facilitated by the size of thrombi formed in the inferior vena cava (IVC). Moreover, due to its clear anatomical structure, the IVC is often used as an experimental vessel in DVT research. However, certain limitations are encountered when the IVC is used as a study vessel, including the absence of valves, variable width, many collateral branches, and thin vessel walls. In small animals [6,7], the use of ultrasound and interventional equipment is restricted by the small size of the blood vessels. Traditional methods of model preparation often involve ligation or stenosis of the inferior vena cava, which are time-consuming procedures, and mice or rats are commonly used [8-11]. For studies on therapeutic efficacy (such as interventional treatments commonly used in clinical practice), rabbit models with larger vessel diameters offer distinct advantages [12]. Based on these considerations, rabbits were selected as the experimental subjects in this study, and a modified method for establishing a thrombus model was proposed and validated. This method is aimed at achieving rapid thrombus formation, controllable thrombus size, and effective prevention of pulmonary embolism, thereby providing a more stable and reliable experimental tool for preclinical research, including interventional therapies and drug screening.

Materials and Methods

Considering that interventional procedures require the insertion of devices into blood vessels, which imposes certain demands on the venous diameter of experimental animals, standard-grade male New Zealand White rabbits weighing 2.5–4.0 kg were selected as experimental subjects. The diameter of the inferior vena cava in healthy adult New Zealand White rabbits is approximately 0.1–0.3 cm. A total of 30 rabbits were purchased. The animals were housed at the Animal Experimentation Centre of Peking Union Medical College Hospital. Housing conditions included individual cages, with strict control of environmental temperature, humidity, and light cycles. Standard pellet feed and ample drinking water were provided, and formal experiments began after one week of acclimatization. This study was approved by the Animal Ethics Committee. Throughout the experiment, the 3Rs principle (Replacement, Reduction, Refinement) was followed to minimize the number of animals used and the harm inflicted upon them. At the end of the experiment, all animals were euthanized. The rabbits were fasted for 8 hours before the experiment. Each rabbit was weighed, and the required anaesthetic dose was calculated (20 mg/kg Zoletil 50, administered intramuscularly). After anaesthesia, the rabbit was placed in a supine position on a heated small animal warming pad (covered with a drape), and its limbs and head were secured to the bench with thick ropes. A small artery monitor was then connected. A cannula was inserted into the marginal vein of one ear and flushed with heparin; during the procedure, normal saline or additional anaesthetic could be administered promptly according to condition of rabbit. The fur on the abdomen was shaved with an electric clipper, and the area was disinfected with povidone-iodine and draped. A midline abdominal incision of approximately 6.0 cm was made in the lower abdomen. The intestinal loops were gently pushed aside to fully expose the abdominal aorta and IVC. The exposed intestines were wrapped in gauze and protected with saline-moistened compresses. Along the IVC, the vein was carefully dissected from the abdominal aorta. Because branches on the IVC may interfere with the establishment of a standard thrombus model, an experimental segment with no or as few branches as possible was selected. If branch veins were present within the experimental segment, all such branches were ligated with sutures, taking care to avoid the renal veins. At a point approximately 2.0–3.0 cm distal to the left renal vein (the distance could be adjusted according to the specific anatomy of the IVC), the blood flow was blocked using vascular clamps spaced about 2.0–3.0 cm apart. The clamped segment served as the experimental segment. Using a 1 mL syringe, thrombin (50 U, 0.5 mL) was injected into the selected IVC segment to promote thrombus formation. On the proximal side of the proximal vascular clamp, a semi-ligation of the IVC was performed with sutures to reduce the lumen area to half its original size, thereby preventing acute pulmonary embolism caused by large thrombi detaching and flowing back to the lungs after thrombus formation or during thrombolysis experiments. Heparin (200 U/kg) was administered via the indwelling cannula in the marginal ear vein to prevent the thrombus from extending further. During the wait for thrombus formation, the condition of the IVC was continuously monitored. When thrombosis occurred in the IVC, the color of the experimental segment turned deep purple, and a gelatinous, firm texture could be felt. Ultrasound scanning demonstrated the presence of an IVC thrombus, and the venous lumen could not be compressed by the ultrasound probe. The time required for thrombus formation was recorded. Figure A shows the schematic diagram of modeling.

Results

Among the 30 New Zealand White rabbits, one died from anaesthetic complications. The remaining 29 rabbits all successfully underwent the IVC modelling procedure and survived for at least two hours. Ultrasound examination confirmed successful model establishment in all 29 rabbits.

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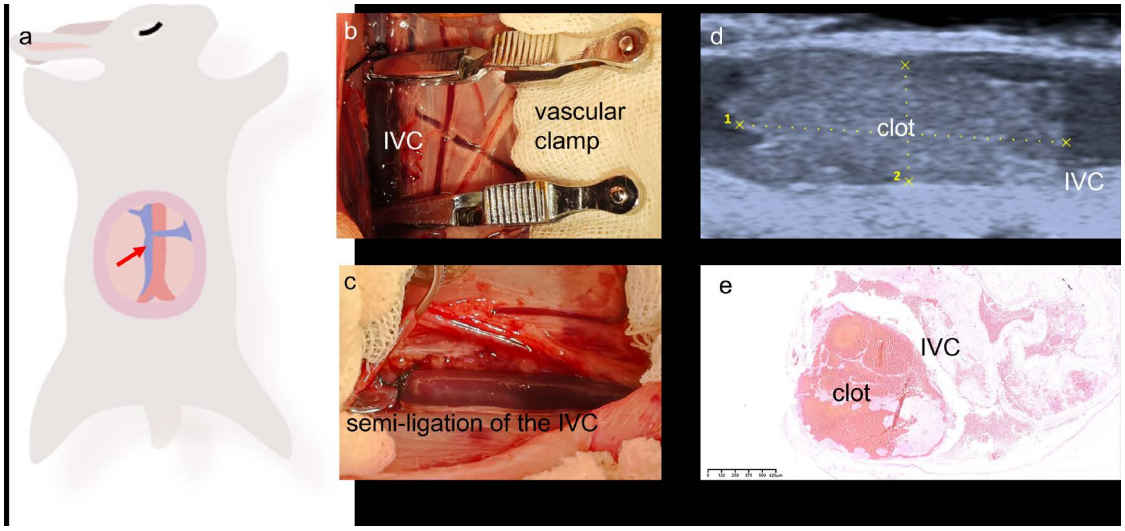

Figure 1: a) Selected blood vessel site. b) Occlusion of the selected vascular segment with a vascular clamp. c) Partial ligation of the proximal inferior vena cava (IVC) before releasing the vascular clamp. d) Ultrasonic image of thrombus formation. e) HE staining of the thrombus.

This method produced acute inferior vena cava thrombi measuring approximately 1.0–3.0 cm in length (adjustable according to the anatomical conditions of the rabbit's IVC and approximately 0.3–0.5 cm in diameter. The modelling success rate was 96.67%. After thrombin injection, the time required for inferior vena cava thrombus formation was 21.93 ± 4.37 minutes.

Discussions

This study aimed to establish a rapid, controllable, infrarenal inferior vena cava thrombosis model in rabbits, to meet the requirements for consistent thrombus size and modelling efficiency in DVT treatment research. Currently, the most commonly used methods for inducing DVT include IVC ligation and IVC stenosis [5, 13]. The ligation method completely blocks venous blood flow, causing local stasis, hypoxia and vascular endothelial injury, which in turn triggers an inflammatory response and activation of the intrinsic coagulation pathway. Although the stasis model is simple to perform and yields a high thrombus formation rate, it often induces severe venous wall reactions, which differ from the pathophysiological state of clinical DVT (typically non-occlusive with residual blood flow). The stenosis method, on the other hand, partially compresses the IVC using external force, reducing local blood flow velocity while maintaining proximal patency, thereby mimicking the human condition in which slowed blood flow leads to thrombosis. Stenosis yields inconsistent thrombosis and variable thrombus size in animals [5, 14]. However, both classical methods usually require 2–6 hours to form a stable thrombus, and the thrombus size, location, and maturity vary considerably [5, 16], making quantitative comparisons of drug efficacy or interventional devices difficult.

Regarding experimental animal selection, mice and rats are widely used due to their abundant genetic tools and lower costs. However, their small body mass, short lifespan and high metabolic rate result in significant differences from humans in coagulation kinetics, venous flow patterns, and spontaneous thrombolysis, which limits the clinical translational value of the results. As medium-sized laboratory animals, rabbits have relatively large deep vein diameters (especially the IVC), which facilitates surgical manipulation. New Zealand White rabbits are also commonly used in thrombosis and haemostasis research [12,17,18]. Nevertheless, traditional rabbit DVT models present two major drawbacks. The animals' high mobility during modelling makes early-formed emboli prone to dislodgement, leading to fatal pulmonary embolism and consequent experimental failure or data loss. The maintenance cost is higher than that of rodents, making large-scale use difficult. Therefore, it is necessary to optimize the modelling method to shorten the thrombus formation time, control thrombus size, and effectively prevent embolism, while preserving the vascular advantages of the rabbit model. In response to the above issues, this study proposed and validated a modified rabbit IVC thrombosis construction method. The target vessel was the infrarenal IVC segment distal to the junction with the left renal vein, and all collateral vessels within this segment were thoroughly ligated to block bypass flow, ensuring exclusive local blood stasis in the model. Blood flow was temporarily occluded using a vascular clamp, and thrombin was injected directly into the experimental segment, rapidly triggering fibrin network formation via the extrinsic coagulation pathway. This reduced the successful modelling time to approximately 22 minutes, a significant improvement over the several hours required

by traditional methods. By semi-ligating the proximal end of the thrombus (incomplete occlusion), thrombus dislodgement into the pulmonary artery was physically prevented, while a certain degree of antegrade flow was maintained to avoid local hypertension caused by complete occlusion. Heparin was administered before flow restoration to prevent further proximal extension or distal embolism of the formed thrombus. This strategy simultaneously achieved rapid thrombus formation, controllable size, and prevention of dislodgement, providing standardized thrombus samples for subsequent efficacy comparisons between treatment and control groups.

No animal model can fully replicate the complex pathophysiology of human DVT. In future studies, the natural evolution of thrombi could be observed under non-anticoagulant conditions, combined with dynamic imaging assessment of thrombus stability. Overall, while retaining the advantage of larger rabbit vessel diameter, this model improves modelling efficiency and thrombus homogeneity with a high success rate. It is suitable for preclinical screening of anticoagulants, thrombolytics, and interventional devices, and serves as a valuable complement to existing DVT animal model systems.

Author Contributions

Yue-Xin Chen: Funding acquisition. Supervision. Methodology. Project administration. Xin-Ran Wu: Writing – original draft. Methodology. Formal analysis. Data curation. Resources. Software. Investigation. Validation. Visualization.

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Conflict of Interest Statement

The authors declare that they have no competing interests.

Ethics Statement

All experiments followed the Guide for the Care and Use of Laboratory Animals (Eighth edition, National Academy of Sciences, United States) and were conducted according to the ethical policies and procedures approved by the Animal Welfare and Ethics Committee of Peking Union Medical College Hospital (NO. XHDW-2024-68).

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