

Review Article

Pathophysiology of Venous Thromboembolism with Respect to the Anatomical Features of the Deep Veins of Lower Limbs: A Review

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Here the pathophysiology of venous thromboembolism is reviewed with respect to the anatomical features of the deep veins of lower limbs. A thrombus is less likely to form in the thigh veins compared with that in the calf veins; however, clinical symptoms are more likely to appear in the thigh veins owing to vascular occlusion. When a patient is bedridden, thrombosis is more likely to occur in the intramuscular vein, which mainly depends on muscular pumping and the venous valve, rather than in the three crural branches, which mainly depends on the pulsation of the accompanying artery. Thrombi are prone to be generated in the soleal vein compared with those in the gastrocnemius vein because of the vein and muscle structures. A soleal vein thrombosis grows toward the proximal veins along the drainage veins. To prevent a sudden pulmonary thromboembolism-related death in bedridden patients, preventing soleal vein thrombus formation and observing the thrombus proximal propagation via the drainage veins are clinically important. When deep vein thrombosis occurs, avoiding embolization and sequela caused by the thrombus organization is necessary.

Keywords: pulmonary thromboembolism, deep vein thrombosis, soleal vein, calf vein, pathophysiology

Introduction

The vascular system comprises arteries, veins, and lymph vessels. The structure, function, and diseases vary among the different types of vascular systems. In this study, we explain the pathophysiology of deep vein thrombosis (DVT) of lower limbs with regard to the anatomical features.

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Received: April 5, 2017; Accepted: April 15, 2017
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Differences in the Characteristics of the Venous Perfusion System between the Thigh and Calf Veins

The deep veins of lower limbs are divided into the thigh and calf veins. The calf veins comprise three crural veins (posterior tibial, anterior tibial, and peroneal veins) that receive blood flow from the foot sole and the intramuscular veins (soleal and gastrocnemius veins) and their joint vein (popliteal vein). The thigh veins (iliac and femoral veins) run from the calf veins toward the center. The calf and thigh veins have different anatomical features.

In the thigh veins, one thick blood vessel runs along the artery, with scarce venous valves. Because of the thick structure of the thigh vein, stagnation of blood flow is unlikely to occur, with a thrombus less likely to form in a thigh vein compared with in a calf vein. Once a thrombus is formed in a thigh vein, the single-vein obstruction induces vascular insufficiency on the distal side of the vein, resulting in clinical symptoms such as redness and pain.

In contrast, the calf veins run alongside the artery as paired veins and have several branches and anastomoses with each other. The calf veins have multiple venous valves to maintain the blood flow in a given direction, even when an anastomosis is present. Because of these contralateral veins and anastomoses of the calf veins, symptoms caused by vascular insufficiency are unlikely to occur even when a thrombus is present. If the venous valve is destroyed following the healing process of the thrombus, blood stagnation continues, and post-thrombosis syndromes tend to develop.

Types of DVT with Regard to the Onset Pattern

Lower extremity DVT can be divided into three types on the basis of the onset pattern: iliac, femoral, and calf types (Fig. 1).

The iliac and femoral types are associated with femoral vein thrombosis and are mainly formed by iliac compression and vascular injury by a catheter, respectively.



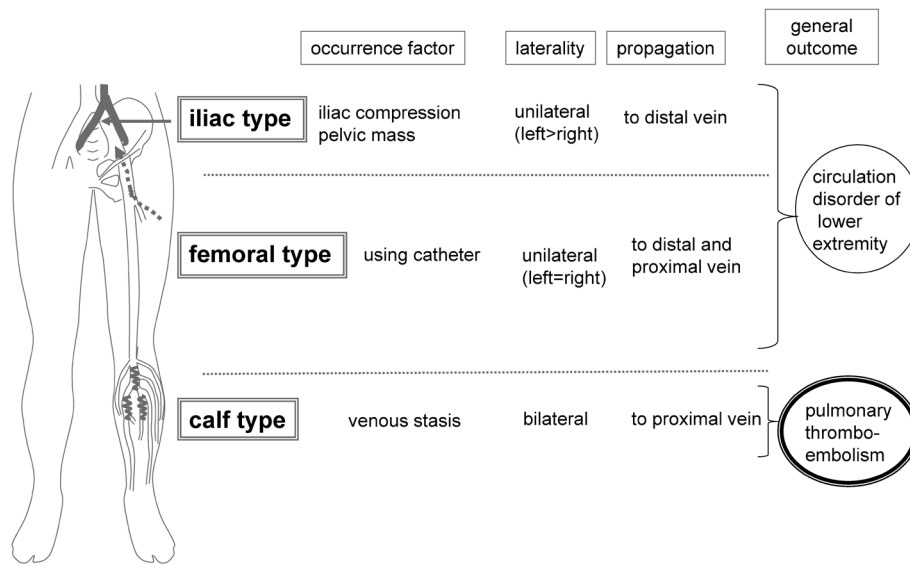


Fig. 1 Clinical characteristics and classification of deep vein thrombosis (from ref. 6, Fig. 11).

A thrombus formation in the thigh veins tends to grow toward the peripheral side because of the proximal obstruction by the thrombus itself. In addition, iliac and femoral vein thrombosis causes clinical symptoms because of proximal vein occlusion. Diagnosis is simple based on the manifestation of symptoms, and such thrombi rarely embolize to the lungs.

In contrast, the main factor involved in the formation of calf-type thrombosis is venous stasis because of lack of limb movement. A calf-type thrombus asymptotically develops along the venous return to the proximal side and can become a large embolic source. Even when the thrombus forms in the calf vein, the clinical symptoms caused by thrombus occlusion are less likely to occur because of the presence of venous anastomoses. If the thrombus propagates to the thigh vein, it usually manifests as a free-floating thrombus without specific clinical symptoms. Therefore, calf-type thrombosis is the most important type for preventing massive pulmonary thromboembolism.

The Perfusion System of the Calf Vein with Respect to Thrombus Formation

Perfusion of the calf vein occurs by muscle pumping and pulsation of the accompanying artery. Functioning venous valves are required for perfusion by pulsation of the accompanying artery. The calf vein is divided into two types: veins that receive blood flow from the foot sole and the intramuscular veins.

The former type of calf vein are accompany veins of three crural branches of the popliteal artery, i.e., the posterior tibial, peroneal, and anterior tibial veins (Fig. 2). These three crural branches run in pairs along the artery, which runs vertically from the foot sole. Their venous

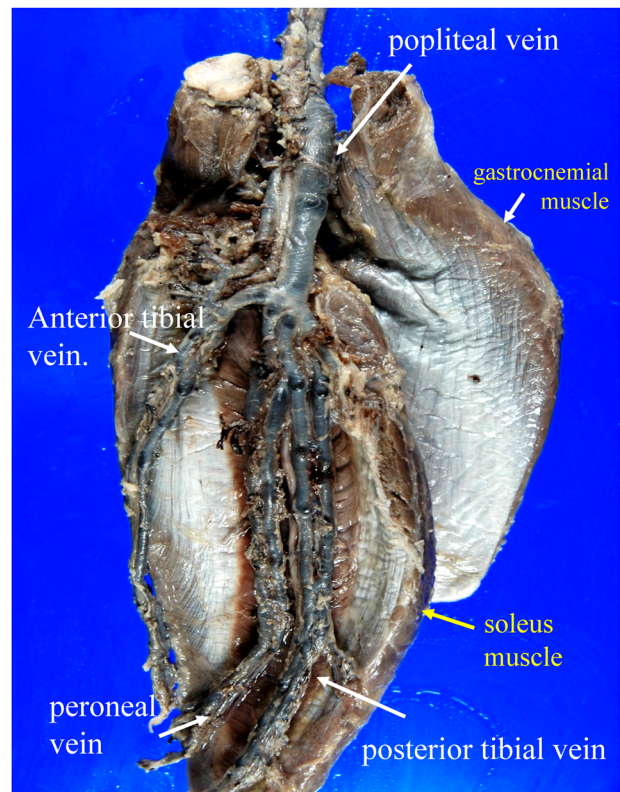


Fig. 2 A representative autopsy case of calf deep vein thrombosis. The popliteal vein and three crural branches are present. The vein is full of thrombus, and the valves are easily observed. The soleal and gastrocnemius veins run inside their respective muscles.

return is mainly owing to the pulsation of the accompanying artery. The pulse movement of the thick artery causes physical pressure directly to the adjacent paired vein and produces an ejection in the same manner as muscle pump-

ing. Hence, the presence or absence of lower limb muscle contraction is not substantially involved in the venous return.

In contrast, the intramuscular vein has many anastomoses that do not necessarily run with the artery. Therefore, the perfusion of the intramuscular vein depends on muscle pumping and adequate venous valve function. If calf muscles do not contract because of prolonged bed rest or similar conditions, the intramuscular vein, which mainly depends on muscle pumping, becomes perfusion insufficiency and a thrombus is likely to form owing to venous stasis.

Close attention must be paid to the intramuscular veins for preventing venous thrombosis of patients without adequate leg movements.

Anatomical Features of Intramuscular Veins (Gastrocnemius and Soleal Veins)

The calf muscle comprises multiple muscles, and the gastrocnemius and soleus muscles are the ones most linked to DVT. We herein explain the characteristics of these two muscles and their accompanying veins.

The gastrocnemius muscle is located on the upper side of the dorsal surface of the calf, whereas the soleus muscle is located in the deep part of the gastrocnemius muscle. Two intramuscular veins, namely the gastrocnemius and soleal veins, run through their respective muscles (Figs. 2 and 3). These two muscles and veins have anatomical differences, which are related to thrombus formation (Fig. 4).

Muscle type and function

The gastrocnemius muscle connects the femur and calcaneus and is involved in knee joint and foot sole movements. It is a unipennate muscle that lacks an aponeurosis. The soleus muscle connects the tibia and fibula to the calcaneus, is involved in foot sole movement, and is a multipennate muscle with many aponeuroses. While the gastrocnemius muscle contracts by active knee joint movement, the soleus muscle is involved in the antigravity actions of standing. Because of these anatomical differences, knee bending and stretching exercises cannot effectively act for contracting the soleal muscle to enhance muscle pumping in a bedridden patient.

Differences in hemodynamics during muscle contraction

The blood flow of the gastrocnemius vein is pushed and ejected to the center by a pumping action secondary to muscle contraction. In the soleal vein, blood is ejected toward the center by muscle contraction, which is similar to squeezing a lemon (Fig. 5). Therefore, persistent soleus muscle contraction is necessary for the perfusion of the soleal vein.

Venous structure and running of the vein

The proximal part of the gastrocnemius vein runs in the center of the gastrocnemius muscle along its accompanying artery. In contrast, those of the soleal vein runs as a pair along the aponeurosis or merges to become one vein. Unlike other lower deep veins, the soleal vein on the distal

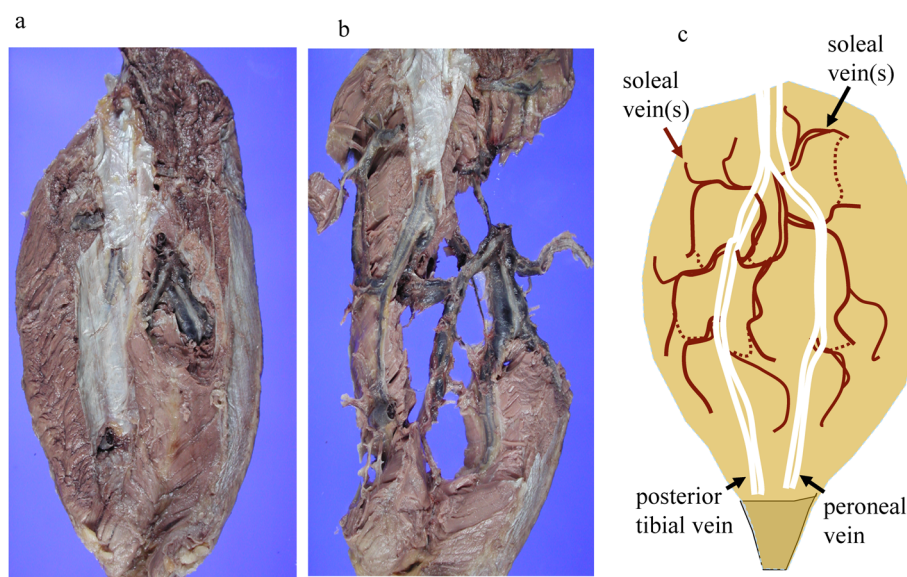


Fig. 3 A representative autopsy case of soleal vein thrombosis. (a) After narrow removal of the surrounding soleal muscle. The dilated soleal vein with thrombi is present. (b) After broad removal of the surrounding muscle of (a). The complicated running course of the soleal vein can be observed. (c) Schema of the running of the soleal vein (indicated by brown).

Muscle type and function

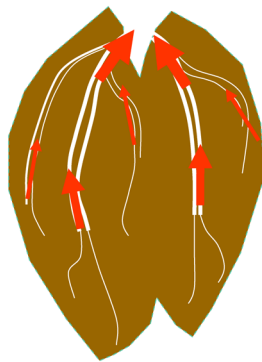
	Gastrocnemial muscle	Soleus muscle
Type of muscle fiber	Fast twitch	Slow twitch
Function	Lower limb movement	Antigravity action
Origin and insertion	Femur and calcaneus	Sole and tibia/fibula
Motion site (joint)	Knee and ankle	Ankle

Venous structure and running of vein

	Gastrocnemius vein	Soleal vein
Form of venous valve	Bifurcated firm	Few and incomplete
Location of valve	Main trunk and vein junction	Gathering site of a thin vein
Running of vein	Runs with a pair	Repeat anastomosis
Hemodynamics during muscle contraction	Ejected to the central side by the muscle pumping	Ejected to the central side while diffusing

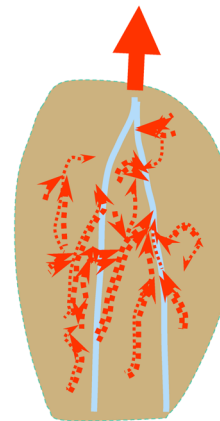
Fig. 4 Anatomical features of the gastrocnemius muscle, soleus muscle, gastrocnemius vein, and soleal vein.

Gastrocnemial muscle



- The blood flow is extruding to the central side by the pump action.

Soleus muscle



- The blood flow is ejected to the central side while diffusing, like squeezing lemon.

Fig. 5 Difference in hemodynamics during muscle contractions between the gastrocnemius and soleal veins.

side does not run as a pair and has many branches (Fig. 6).

The peripheral side of the soleal vein plays an important role as a venous sinus that can temporarily store blood by extending itself. Thus, the soleal vein has few valves and many junctions; however, these characteristics predispose this vein to venous stagnation. Once thrombosis has occurred on the peripheral side of the soleal vein, the thrombus tends to propagate to other branches via various anastomoses.

Differences in the anatomical structure of venous valves

The venous valve of the gastrocnemius vein is mainly

present on the trunk side and runs toward the center. The venous valve of the gastrocnemius vein is bifurcated and firm, with valves present in both the main trunk and vein junction. In the trunk of the soleal vein, multiple thin veins gather, with few and incomplete venous valves. A small valve is present just before the gathering site of a thin vein that joins the trunk (Fig. 6). This small valve prevents backward flow during muscle pumping; however, if severe venous dilation occurs because of blood flow stagnation, the valve function is lost.

In summary, soleal muscle pumping is necessary for blood perfusion and does not sufficiently function in bedridden patients. The vein and venous valve structures

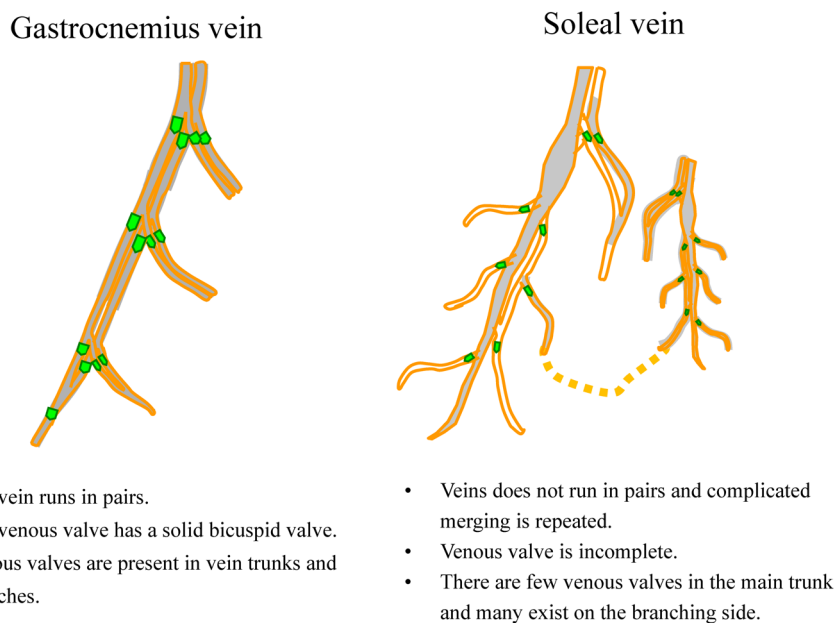


Fig. 6 Difference in the anatomical structure between the gastrocnemius and soleal veins.

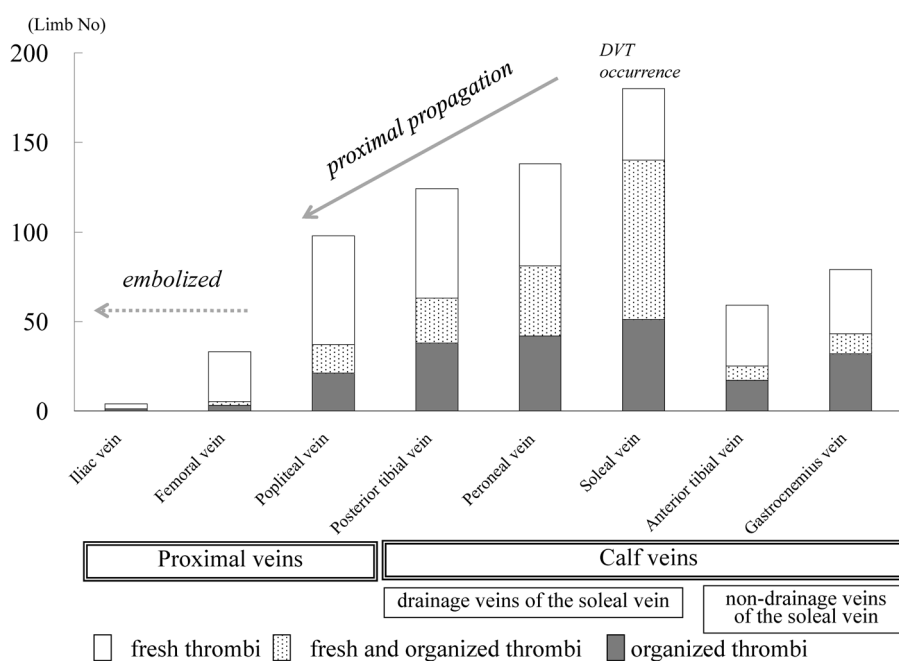


Fig. 7 Distribution and chronology of deep vein thrombosis in eight deep venous segments of 189 limbs, and the suspected mechanism of venous thromboembolism, resulting in lethal pulmonary thromboembolism (from ref. 1, Fig. 2).

can cause venous perfusion disturbances in patients with excessive venous stasis. Therefore, the soleal vein tends to be the initial site for DVT formation in bedridden patients.

In our study of 100 autopsy cases of acute pulmonary thromboembolism, >90% of cases had a soleal vein thrombus¹⁾ (Fig. 7). Furthermore, on histological examination of the thrombi, the soleal vein had the highest proportion of organized thrombi formed before the onset of

the fatal thromboembolism¹⁾ (Fig. 7). The study revealed that the soleal vein is a site of thrombus development in patients with pulmonary embolism.

A previous study in space science examined the anti-gravity action of the soleus muscle and observed a change in the lower leg muscle, which was induced by bed rest in a simulation of a zero gravity environment. When subjects wearing antigravity suits restrained by bed, their soleal

muscle atrophied, which could be prevented by adding dorsiflexing the ankle joint.²⁾

Growth of a Soleal Vein Thrombus

The soleal vein thrombus itself is not a directly lethal embolus which can occlude the proximal pulmonary artery. A soleal vein thrombus easily forms, but it is quickly organized and does not become a substantially large embolus because of the vessel structure. Rather, a secondary thrombus, which propagates to the proximal side, would be serious. The reported rate of such thrombus propagation is 20%.³⁾

The soleal vein has many branches and is classified into six types on the basis of the confluence site: a proximal soleal vein, which drains to the popliteal vein level; a medial soleal vein, which drains to the proximal posterior tibial vein; a central soleal vein, which drains to the tibio-peroneal vein; a lateral soleal vein, which drains to the proximal peroneal vein; a distal medial soleal vein, which drains to the distal posterior tibial vein; and a distal lateral soleal vein, which drains to the distal peroneal vein.⁴⁾

The most frequent branch of the soleal vein is the central soleal vein, and the detection rate of thrombi is highest in these central veins.⁴⁾ Then the central soleal vein is the most important vein for thromboembolism.

The deep veins of lower limbs can be classified on the basis of the drainage route of the central soleal vein. The

central soleal vein merges with the peroneal vein near the popliteal trunk, immediately enters the posterior tibial vein, and travels through the popliteal trunk to drain to the proximal thigh veins. These are the drainage veins of the soleal vein and have a high thrombus detection rate.^{1,5)} Conversely, the anterior tibial and peroneal veins do not join the drainage veins of the soleal vein but instead directly pour into the popliteal trunk. These two veins are the nondrainage veins of the soleal vein and have a low thrombus detection rate.

Examination of autopsy cases of acute pulmonary embolism revealed that the soleus muscle vein most frequently has an aged thrombus. Furthermore, based on the detection rates of thrombi in the deep veins of lower limbs, classified by the drainage route of the soleal vein, a thrombus that forms in the soleal vein develops on the proximal side along the drainage veins and embolizes into the thigh veins¹⁾ (Figs. 7 and 8). When a thrombus is formed in the soleal vein, it slowly progresses through the calf veins along the drainage route and grows.^{1,6)} However, once a secondary thrombus has formed in a thigh vein via the popliteal vein, there is the risk for developing a free-floating thrombus, which can be widely propagated in a short time period. A free-floating thrombus can be easily released from the vessel wall with knee joint flexion, resulting in a lethal embolus. Thus, although the soleal vein is an important structure for primarily preventing lethal thromboembolism, assessing for femoral or iliac vein

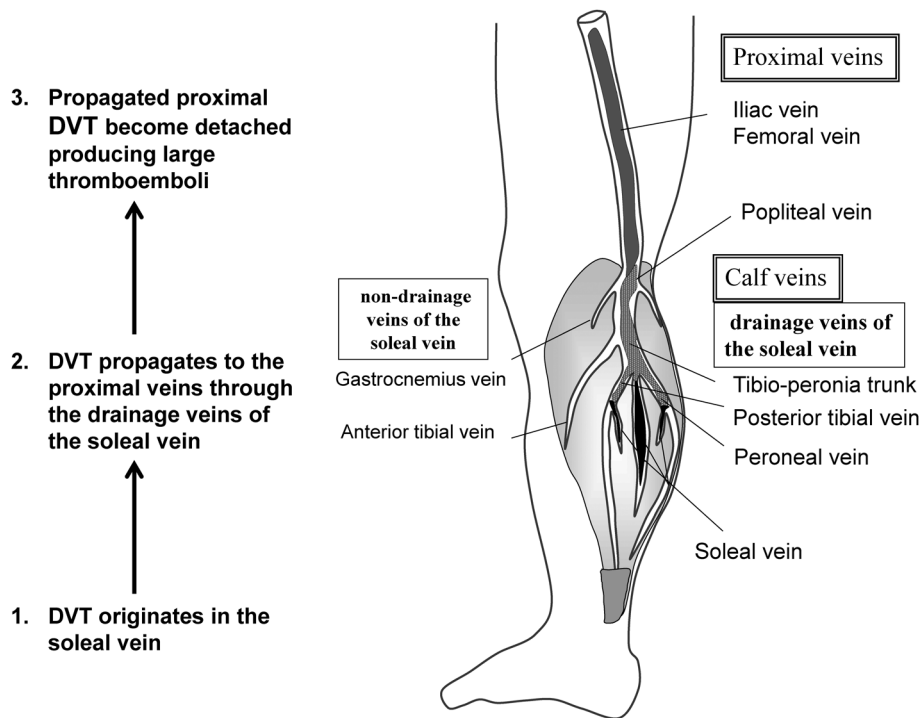


Fig. 8 Suspected mechanism of venous thromboembolism, resulting in lethal pulmonary thromboembolism (from ref. 1, Fig. S).

thrombus as the actual embolization source in patients with symptomatic massive pulmonary thromboembolism is useful.

Fate and Recurrence of Acute DVT

When a thrombus is formed in the soleal vein, it may disappear by thrombolysis, embolization, or organization (Fig. 9). Thrombus organization from the vein wall is a biological reaction necessary for recanalization but may result in a risk for venous stenosis. In addition, the organization is often accompanied by venous valve destruction, which seriously affects venous perfusion of the calf.

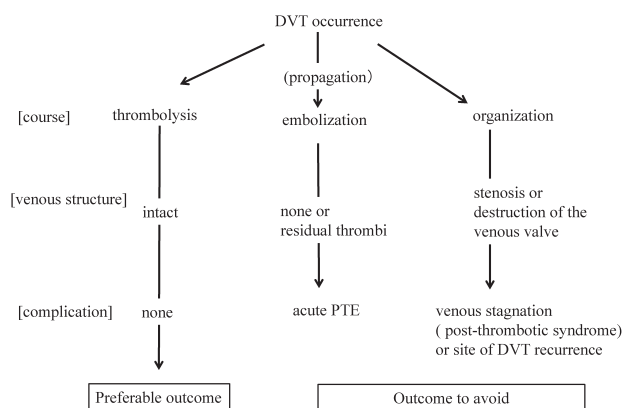


Fig. 9 Fate of the deep vein thrombosis.

Organization, as well as embolization, must be avoided when treating a venous thrombus. The development of leg symptoms caused by perfusion failure of the lower deep veins secondary to venous thrombus organization is defined as a postthrombotic syndrome, and it is known that blood flow stagnation contributes to thrombus recurrence.

When DVT relapses because of an old organized thrombus in the calf vein, a new thrombus often forms on the proximal side.⁷⁾ A repeating cycle of thrombus recurrence and organization owing to persistent blood flow stagnation, which is caused by the organized thrombus, can cause the thrombus formation site to shift to the proximal side. In addition, during lung embolization, which can also occur in the pulmonary artery, the thrombus is captured on the proximal side from the subsegmental artery, and the effect of thromboembolism is more severe.⁸⁾ To interrupt this cycle, preventing lower limb DVT formation, which is the initial lesion, and ensuring that no residual organization is present are important.

A typical autopsy case is shown in Fig. 10. A fresh thrombus that escaped embolization was observed in the femoral and popliteal veins. Further examination showed an organized thrombus at the base of the popliteal vein, suggesting that these fresh thrombi were secondary thrombi. Furthermore, an occlusive organized primary thrombus was confirmed in the soleal vein. Many sudden deaths secondary to pulmonary thromboembolism occur

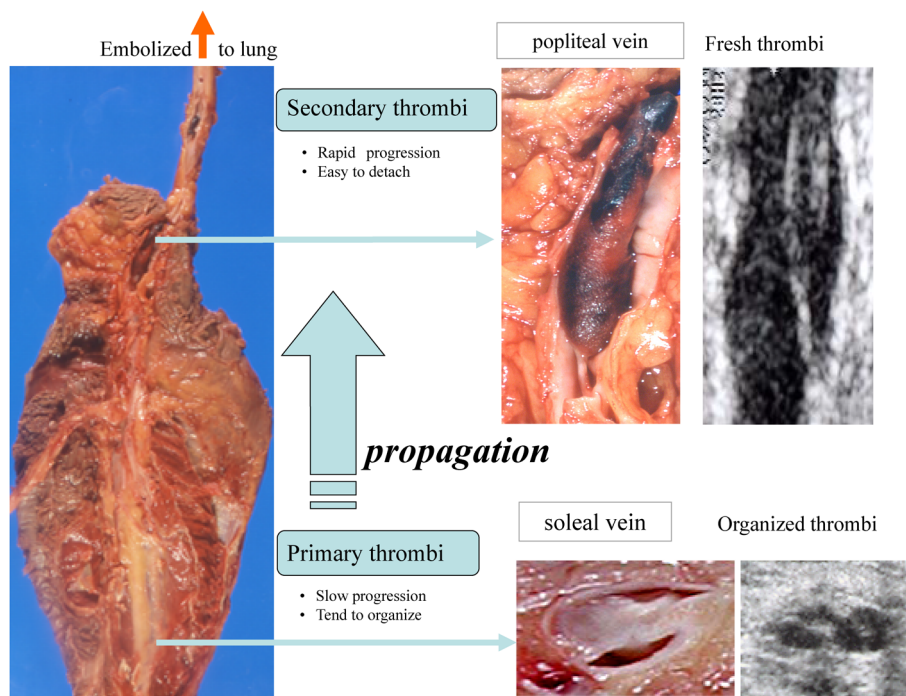


Fig. 10 Mechanism of thrombus propagation in fatal pulmonary thromboembolism (from ref. 6, Fig. 15).

after an acute-to-chronic clinical course wherein a thrombus first forms in a deep calf vein. The thrombus then propagates to the proximal thigh veins, forming repeated small thromboemboli with few clinical symptoms. Finally, the massive development of thromboemboli becomes lethal. This clinical course can be confirmed by medicolegal autopsy.⁸⁾ Understanding these thrombus growth processes for effectively treating venous thromboembolism is important.

Conclusion

The pathological condition of lower limb DVT is affected by the anatomical structure of the involved veins.

A thrombus is less likely to form in the thigh veins compared with that in the calf veins, but clinical symptoms are more common in the thigh veins because of vascular occlusion.

During bed rest, thrombosis is more likely to occur in the intramuscular veins, which require active muscle pumping and adequate venous valve functioning.

Thrombi are more prone to develop in the soleal veins compared with the gastrocnemius vein because of the unique characteristics of the vein and muscle structure. A soleal vein thrombus grows toward the proximal veins along the drainage routes.

To prevent sudden pulmonary thromboembolism-related death in patients with immovable limbs, preventing soleal vein thrombus formation and observing the proximal progression of the thrombi through the drainage veins of the central soleal veins are clinically important.

When DVT occurs, avoiding both embolization and the sequela caused by organization is necessary.

A thorough understanding of the anatomical structure and pathophysiology enables more effective prevention and treatment of venous thromboembolism.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Writing: AR

Funding acquisition: AR, TM

Critical review and revision: all authors

Final approval of the article: all authors

Accountability for all aspects of the work: all authors

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