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University of Novi Sad, Faculty of Medicine Novi Sad[1]
Clinical Center of Vojvodina, Novi Sad[2]

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A NEOTERIC APPROACH TO UNDERSTANDING THROMBOSIS

SAVREMENI PRISTUP RAZUMEVANJU TROMBOZE

Biljana VUČKOVIĆ[1,2]

Summary

Pathophysiology of thrombosis. Thrombosis, a leading cause of morbidity and mortality worldwide, results from an imbalance between procoagulant, anticoagulant, and fibrinolytic factors. Virchow's triad – endothelial injury, stasis of blood flow, and hypercoagulability – has long been the cornerstone for understanding thrombosis. However, evolving knowledge has refined our interpretation of how these factors contribute to venous and arterial thrombosis. **Arterial thrombosis.** Historically, arterial and venous thromboses were viewed as distinct pathophysiological entities. Over the past two decades, research has highlighted the complexity of etiopathogenesis of the thrombotic process, recognizing mutual risk factors offering a more comprehensive understanding the pathophysiological mechanism behind these diseases. **Venous thrombosis.** Recent insights focus on thrombotic potential, defined as an individual's susceptibility to thrombosis resulting from a combination of congenital and acquired risk factors.. It has become clear that the interaction of these factors is not merely additive but synergistic, significantly increasing the risk of thrombosis. The significant social impact of thrombosis underscores the necessity of thoroughly understanding its underlying mechanisms to develop effective preventive and therapeutic strategies.

Key words: Thrombosis; Arteries; Venous Thrombosis; Pathology; Risk Factors

Sažetak

Patofiziologija tromboze. Tromboza predstavlja krajnji produkt disbalansa između prokoagulantnih, antikoagulantnih i fibrinoliznih faktora i jedan od vodećih uzroka morbiditeta i mortaliteta širom sveta. Kamen temeljac razumevanja patofiziološkog mehanizma ove bolesti je koncept Virhovljeve trijade, koji je već vekovima neosporni postulat. Ipak, interpretacija načina na koji individualne komponente ove trijade doprinose pojavi venskih i arterijskih tromboza menja se tokom vremena u skladu sa napretkom saznanja na ovom polju. **Arterijska tromboza.** Arterijska i venska tromboza dugo su smatrane odvojenim patofiziološkim entitetima. Tokom poslednje dve dekade kompleksnost etiopatogeneze tromboze potvrđena je prepoznavanjem zajedničkih faktora rizika koji nude značajno sveobuhvatniji koncept razumevanja patofiziološkog mehanizma odgovornog za pojavu ove bolesti. **Venska tromboza.** Jedna od novina u vezi sa razumevanjem ove teme fokusira se na trombozni potencijal definisan kao individualni „potencijal" pojedinca da doživi trombozu kao rezultat kombinovanja svih urođenih i stečenih faktora rizika za pojavu ove bolesti prisutnih kod ove osobe. Takođe, postalo je očigledno da tokom delovanja različitih etioloških faktora uključenih u patofiziološki mehanizam odgovoran za pojavu tromboze ne dolazi do njihovog jednostavnog sumiranja, nego kombinovanja po tipu multipliciranja uticaja. Veliki negativni socioekonomski uticaj tromboze postavlja imperativ za što bolje razumevanje mehanizma u osnovi nastanka ove bolesti kako bi se postigle što efikasnije preventivne i terapijske strategije.

Ključne reči: tromboza; arterije; venska tromboza; patologija; faktori rizika

ORCID NUMBER
Biljana Vučković 0000-0001-6018-1219

Pathophysiology of thrombosis

Thrombosis is the formation of an obstructive coagulum, resulting from an imbalance among procoagulant, anticoagulant, and fibrinolytic factors. Rudolph Virchow established the foundational concept known as Virchow's triad, which includes changes in the blood vessel wall, blood flow, and blood composition [1]. There three components are integral to the etiopathogenesis of both arterial and venous thrombosis, though the dominance of each component varies, adding complexity to understanding different types of thrombosis.

Historically, arterial and venous thromboses were seen as distinct pathophysiological entities. Arterial thrombosis was thought to result to result

Corresponding Author: Biljana Vučković, Univerzitet u Novom Sadu, Medicinski fakultet, Univerzitetski klinički centar Vojvodine, 21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: biljana.vuckovic@mf.uns.ac.rs

Abbreviations
NO – nitric oxide
FV – factor V

primarily from the changes in the blood vessel wall due to factors like hypertension, hyperlipoproteinemia, smoking, and carbohydrate metabolism disorders, all of which promote endothelial dysfunction. Venous thrombosis, conversely, was attributed to changes in blood flow (venous stasis) and blood composition favoring procoagulant factors. However, recent research over the past two decades has revealed mutual risk factors spanning all three components of Virchow's triad, offering a much more comprehensive understanding of thrombosis [2–4].

Arterial thrombosis

Arterial thrombosis is a leading cause of morbidity and mortality globally, with significant social implications. It causes an acute imbalance between the blood supply and the oxidative demand of organs due to a sudden drop in arterial blood flow, leading to necrosis in the affected organ segment [5].

The primary component of Virchow's triad in arterial thrombosis is damage to the blood vessel wall. This damage is now understood not just as a mechanical defect but as any change in the functionality of the blood vessel wall, particularly endothelial dysfunction, which precedes atherosclerotic plaque formation [6].

Endothelial dysfunction

The endothelium should not be seen merely as a mechanical barrier that separates the blood inside the vascular bed from the subendothelial structures. Healthy endothelium provides a protective, nonthrombogenic surface with vasodilatory and anti-inflammatory characteristics, which is metabolically extremely active tissue maintaining blood homeostasis. Endothelial cells produce antithrombotic molecules (e.g., heparan sulfate, thrombomodulin, prostacyclin, nitric oxide (NO), plasminogen activators) and prothrombotic and antifibrinolytic molecules as needed [7]. Maintaining the balance between these factors is crucial for physiological hemostasis, and a shift towards prothrombotic factors increases the risk of thrombosis. Endothelial cells also modulate smooth muscle cell media through both vasodilators (e.g., NO and prostacyclin) and vasoconstrictors (e.g., endothelin), with a slight physiological predominance of vasodilators. Furthermore, they play a role in immune response modulation during local inflammation, expressing adhesion molecules that bind mononuclear cells and secreting chemokines to recruit leukocytes to the damage site [8]. From the above, it is evident that maintaining hemostatic balance at the endothelial level is highly complex. Subtle disruptions, caused by various etiological factors, are the most common drivers in the pathophysiological mechanism initiating arterial thrombosis.

A wide range of factors can lead to endothelial damage and dysfunction, including mechanical forces and various other etiological factors. Hydrodynamic circumstances play a significant role, as certain arterial regions (such as branching sites) have a greater predisposition for atheroma development. In straight arterial sections, laminar blood flow creates a protective environment by favoring the production of nitric oxide [7], an endogenous vasodilator with anti-inflammatory properties that inhibits platelet aggregation and promotes production of antioxidant enzymes opposing reactive oxygen radicals. These protective functions are compromised at arterial bifurcations, which are predominant sites for atheroma formation. Endothelial dysfunction can also result from chemical irritants, such as smoking, which leads to the production of reactive superoxide anions. These anions interact with intracellular molecules, causing metabolic and synthetic dysfunction in endothelial cells and resulting in local inflammation.

Disruption of endothelial homeostasis due to various factors leads to increased permeability, proinflammatory cytokine release, increased production of surface adhesion molecules, leukocyte recruitment, increased release of vasoactive substances, and loss of antithrombotic characteristics [6]. This endothelial dysfunction is the initial step in atherosclerotic plaque formation, forming the basis for arterial thrombus.

Venous thrombosis

Venous thrombosis, encompassing deep vein thrombosis and pulmonary embolism, has significant population importance [9]. This importance is not just reflected in the incidence rate of 1-3 per 1000 persons per year but also in the high mortality rate of 21% during the first year after the initial episode. Additionally, there is a very high recurrence rate of over 30% in the first ten years and a substantial disability rate due to post-thrombotic syndrome, which affects approximately 20% of venous thrombosis patients [10, 11].

Etiological factors

Understanding the etiopathogenesis of venous thrombosis involved recognizing and comprehending the interplay of various etiological factors [12]. These factors can be congenital or acquired. Key congenital factors include gene mutations like FV Leiden and the prothrombin gene G20210A mutation, and deficiencies in natural coagulation inhibitors such as antithrombin, protein C, and protein S. Important acquired factors include immobilization, surgical procedures, trauma, pregnancy, and antiphospholipid syndrome. Moreover, many factors traditionally associated with arterial thrombosis also increase the risk of venous thrombosis [13–15]. Despite recognizing many etiological factors, it remains unclear why some individuals develop venous thrombosis under certain circumstances while others do not [16].

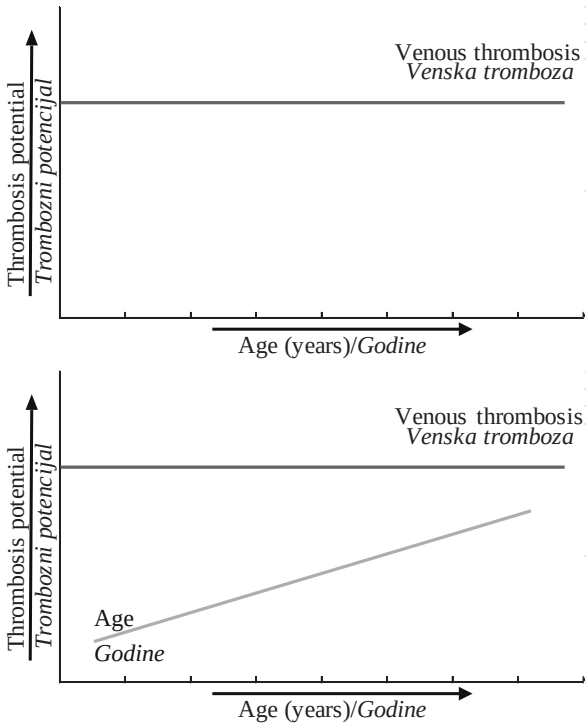

Figure 1. The relationship between thrombotic potential and thrombotic threshold in the light of years as an etiology factor
Slika 1. *Odnos tromboznog potencijala i tromboznog praga u slučaju godina kao etiološkog činioca*

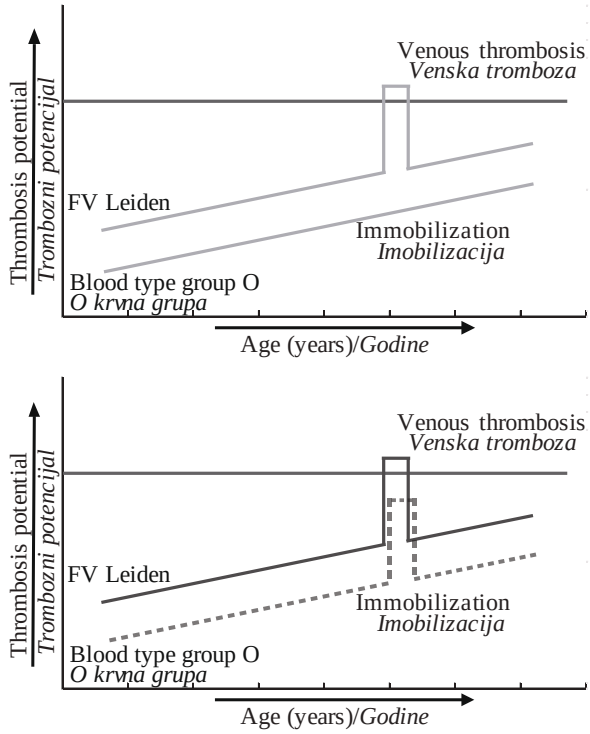

Figure 2. The relationship between thrombotic potential and thrombotic threshold is shown in the case of transient etiological factor action
Slika 2. *Odnos tromboznog potencijala i tromboznog praga u slučaju dejstva tranzitornog etiološkog faktora*

Understanding the impact of etiological factors

The term "thrombotic potential" defines the individual's likelihood of experiencing venous thrombosis, considering all congenital and acquired risk factors. Given the multitude of risk factors, each individual has a unique combination and associated risk [17]. The "thrombotic threshold" is reached when this combination results in a venous thrombosis event. For example, age significantly increases venous thrombosis risk, increasing linearly with aging, implying that everyone would eventually experience venous thrombosis if they lived long enough [18, 19]. The individual's thrombotic potential determines whether the disease occurs within their lifespan. Those with a higher thrombotic potential due to an unfavorable combination of risk factors will experience venous thrombosis sooner than those with a lower thrombotic potential **(Figure 1).**

Transient etiological factors, like immobilization or pregnancy, uniformly increase thrombotic potential across individuals. Whether venous thrombosis occurs in such transient situation depends on the individual's pre-existing thrombotic potential. The thrombotic threshold is reached only in those with a sufficiently high pre-existing thrombotic potential **(Figure 2).**

Understanding how etiological factors combine is crucial. For instance, the heterozygous FV Leiden mutation increases venous thrombosis sevenfold, while oral contraceptive use increases it threefold. If both factors are present simultaneously, the risk increases by over thirty times. This illustrates that the influence of various etiological combines multiplicatively rather than additively [20].

Pathophysiological mechanism

In addition to understanding how etiological factors combine, it is essential to understand how each risk factor contributes to the disease's pathogenesis. Each factor typically increases thrombotic potential in several ways simultaneously. The following examples of various effects of a single etiological factor shed light on this very fact.

Malignancy is a significant etiological factor for venous thrombosis. Mechanisms include a humoral effect, disputing hemostatic homeostasis towards a procoagulant state due to tissue factor production by malignant cells and increased apoptosis leading to microparticle formation. Larger tumors can cause direct venous compression and obstruction. Additionally, immobilization, often associated with malignancy, leads to venous stasis, and chemotherapy further increases thrombotic potential [21].

Pregnancy and the puerperium are significant acquired etiological factors for venous thrombosis. This involves a complex combination of factors from Virchow's triad. Pregnancy increases body weight and the compressive effect of the pregnant uterus on pelvic and lower extremity veins, increasing thrombotic potential. Simultaneously, thrombin

activity stimulation increased as a physiological preparation for bleeding control during labor [22].

These examples highlight the complexity of the pathophysiological mechanism responsible for venous thrombosis and the synergistic combination of synergistic combination of various etiological factors. Considering all the above, it is evident that individual thrombotic potential is the key to understanding this disease.

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