UDC 616.151.5-072.7+612.115+616.13/.14-005.6-092-084-085+578.834.1
DOI: 10.56871/RBR.2023.85.16.008

CONTEMPORARY CONCEPT OF ARTERIAL THROMBOSIS MECHANISMS. ARTERIAL THROMBOSIS IN CASE OF COVID INFECTION

© Iskander Albertovich Latypov[1], Sarng Sanalovich Purveev[1, 2], Mikhail S. Nekrasov[1], Nikolay S. Dedanishvili[1], Nair Sabirovich Tagirov[1]

[1] Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100
[2] Institute of Experimental Medicine. Academician Pavlova st., 12, Saint Petersburg, Russian Federation, 19702

Contact information: Sarng S. Pyurveev — Senior Assistant Department of pathological physiology with immunopathology course. E-mail: dr.purveev@gmail.com ORCID ID: 0000-0002-4467-2269 SPIN: 5915-9767

For citation: Latypov IA, Purveev SS, Nekrasov MS, Dedanishvili NS, Tagirov NS. Contemporary concept of arterial thrombosis mechanisms. Arterial thrombosis in case of COVID infection // Russian biomedical research (St. Petersburg). 2023; 8(3): 61-68. DOI: https://doi.org/10.56871/RBR.2023.85.16.008

Received: 22.05.2023 **Revised: 17.07.2023** **Accepted: 21.09.2023**

Abstract. Complex mechanisms of thrombosis are traditionally regarded within the so called Virchov's pathogenic thriade consisting of blood vessel injury + hypercoagulation + blood-flow slowing down. On spite of multiple additions and attempts at sophistications its essence remaiтs unchanged. However this threenominal scheme which is more or less applicable for explaining the pathogeny of venous thrombosis can be used in case of arterial ones only to a limited degree. Of late a different concept is under discussion namely that of arterial thriade consisting of different components: 1. Arterial stenosis and acceleration of bloodflow; 2. Platelets activation and their interaction with Von Willebrand factor (VWF); 3. Blood vessel wall injury. This composition of arterial thriade is more successfully explaining thrombosis mechanisms in case of arterial stenosis especially in case of atherosclerosis. Of late the attention is focused also at the association between new COVID-infection and increased risk of thrombosis. The new "arterial thriade" concept in addition to classical "Virchov's thriade" or even that of "tetrade" will help pathophysiologists to better discriminate pathogenetical features of arterial thromboses vs the venous ones and for the clinical doctors to improve prophylaxis and treatment of these separate conditions.

Key words: venous thrombosis; arterial thrombosis; Virchow triad; COVID-19.

СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ О МЕХАНИЗМАХ АРТЕРИАЛЬНОГО ТРОМБОЗА. АРТЕРИАЛЬНЫЙ ТРОМБОЗ ПРИ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ

© Искандер Альбертович Латыпов[1], Сарнг Саналович Пюрвеев[1, 2], Михаил Сергеевич Некрасов[1], Николай Сергоевич Деданишвили[1], Наир Сабирович Тагиров[1]

[1] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2
[2] Институт экспериментальной медицины. 197022, г. Санкт-Петербург, ул. Академика Павлова, 12

Контактная информация: Сарнг Саналович Пюрвеев — старший лаборант кафедры патологической физиологии с курсом иммунопатологии. E-mail: dr.purveev@gmail.com ORCID ID: 0000-0002-4467-2269 SPIN: 5915-9767

Для цитирования: Латыпов И.А., Пюрвеев С.С., Некрасов М.С., Деданишвили Н.С., Тагиров Н.С. Современные представления о механизмах артериального тромбоза. Артериальный тромбоз при новой коронавирусной инфекции // Российские биомедицинские исследования. 2023. Т. 8. № 3. С. 61–68. DOI: https://doi.org/10.56871/RBR.2023.85.16.008

Поступила: 22.05.2023 **Одобрена: 17.07.2023** **Принята к печати: 21.09.2023**

Резюме. Сложные механизмы тромбообразования традиционно принято рассматривать в рамках так называемой патогенетической триады Вирхова: повреждение сосуда + гиперкоагуляция + замедление кровотока. Несмотря на многократные дополнения и усовершенствования данной концепции, ее суть оставалась прежней. Однако

эта трехчленная схема, более или менее применимая для объяснения патогенеза тромбообразования в венах, в классическом ее виде для артериальных тромбозов имеет ограниченное значение. В последнее время начали обсуждать несколько иную концепцию артериальной триады, включающую другие компоненты: 1 — стеноз артерии и ускорение кровотока, 2 — активация тромбоцитов и их взаимодействие с фактором фон Виллебранда (VWF), 3 — повреждение сосудистой стенки. Эта компоновка артериальной триады успешнее объясняет механизмы тромбообразования при стенозах артерий, в первую очередь, при атеросклерозе. С недавних пор также повысилось внимание к связи между заболеваемостью новой коронавирусной инфекцией (COVID-19) и повышением риска тромбообразования. Введение понятия «артериальная триада» в дополнение к «триаде Вирхова» или «тетраде» позволит патофизиологам лучше разделить патогенетические особенности артериальных и венозных тромбозов, а для клиницистов — профилактику и терапию этих состояний в отдельности.

Ключевые слова: венозный тромбоз; артериальный тромбоз; триада Вирхова; COVID-19.

The complex mechanisms of thrombosis have been commonly considered as part of the so-called classical Virchow triad, including: 1) vascular injury; 2) hypercoagulability and 3) slowing of blood flow. Despite repeated additions and improvements of this concept, its essence remained the same. Besides damage to the vascular wall, hypercoagulation is still considered to be one of the main elements of thrombosis. Activation of the coagulation link of hemostasis leads to fibrin filaments formation on vessel endothelial lining. In addition, platelet aggregates are more often found on the outer side of the clot and additionally contribute to its growth. Moreover, there are factors that increase blood clotting, they are congenital and acquired ones. Congenital factors include deficiencies of antithrombin III, protein C, protein S, as well as mutations of factors V (Leiden) and prothrombin 20210A. Acquired factors include surgery, trauma, cancer, medications (hormonal contraceptives), autoimmune diseases (lupus anticoagulant), prolonged bed rest, and so on. Processes which are close to neoplasia are also a typical example of acquired hypercoagulability [16, 26].

The relationship between slower blood flow and thrombosis has not yet been definitively elucidated. There are various hypotheses explaining how this factor may increase thrombosis. There is evidence that decreased blood flow velocity favors the accumulation of procoagulant proteins [4, 8]. Venous hyperemia and hypoxia induce inflammatory changes in the endothelium, release of reactive oxygen species and expression of cell adhesion molecules. In addition, hypoxia induces a complex of changes leading to a decrease in nitric oxide (NO) synthesis. However, it is worth noting that activation of thrombosis is largely driven by the release of tissue factor as a result of gross damage to the vascular endothelium. However, it is difficult to fully explain the mechanism of fibrin formation in the absence of endothelial damage. There is evidence that tissue factor expression is increased upon exposure to bacterial toxins as well as on the vascular endothelium of malignant tumors [5]. Nevertheless, no tissue factor expression has been found in microcirculation disorders only [5, 36].

An important factor affecting the hemostasis system is pregnancy. The balance of hemostasis is shifted towards physiological hypercoagulation to prevent major blood loss during delivery [1, 2, 25]. Pregnant women have increased activity of coagulation factors, decreased levels of protein S. Moreover, resistance of factor V to protein C is formed [20]. The fibrinolysis system is suppressed due to an increase in plasminogen activator inhibitor-1 (IAP-1), as well as the appearance of placental plasminogen activator inhibitor (IAP-2) [8, 25]. Decrease in the number of platelets is compensated by their increased activity. Similar effects are observed when taking outdated drugs of exogenous sex steroids in order to contracept, to obtain non-contraceptive effects or as perimenopausal therapy. The concentration of clotting factors increases, anticoagulants decrease, and acquired (or congenital) resistance of factor V to protein C occurs [3, 6].

Recently, the attention of researchers to von Willebrand factor (VWF) has increased [4, 14, 22] (Fig. 1), which enhances platelet fixation on fibrin filaments during blood flow disorders.

Anyway, Virchow's pathogenetic triad describes the mechanisms of venous clot formation quite well. These clots are predominantly composed of fibrin and erythrocytes. At the same time, when describing the pathogenesis of arterial thrombi,

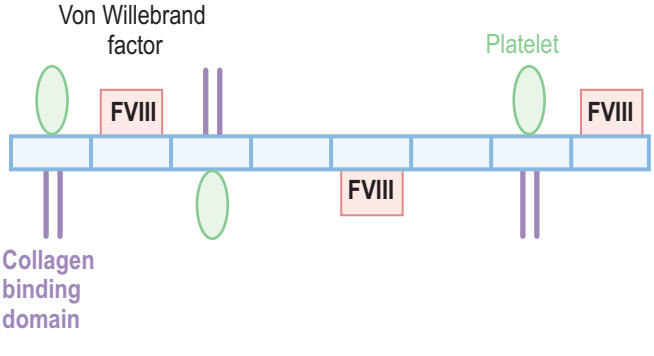

Fig. 1. Von Willebrand factor enhances platelet fixation on fibrin filaments

Virchow's triad is often not mentioned in its original form, or its interpretation differs from the original version. Thus, instead of the term "blood flow slowdown" or "stasis", the broader concept of "blood flow disturbance" is more often used [13].

It should be kept in mind that ideas resembling the arterial triad existed long before its modern description: "For some time scientists hoped to explain the interesting connection between kidney disease on the one hand and increased blood pressure and arteriolosclerosis on the other hand by the newly discovered properties of adrenaline" [5, 27]. More than 100 years ago, experts already noted the relationship between changes in blood flow as a result of vasospasm and thrombosis and the development of atherosclerosis, which often leads to the formation of large wall clots [27]. Accordingly, the doctrine of the arterial triad of thrombosis should not be considered unique and something completely new.

It may seem strange that hypercoagulability is less significant within arterial clotting: for example, the *20210A* gene mutation does not affect the risk of arterial thrombosis. However, it is associated with the risk of acute myocardial infarction and pregnancy complications [9, 14]. In any case, hypercoagulability, as interpreted by the classical Virchow triad, has much less influence on arterial clot formation.

In contrast to the two factors mentioned above, blood flow velocity occupies central role in the pathophysiology of arterial thrombosis. The effect of blood flow velocity is assessed by two parameters: *shear rate* and *shear stress*.

Shear rate is the rate at which neighboring fluid layers move in relation to each other. It is directly proportional to the blood flow velocity and inversely proportional to the vessel diameter. Accordingly, the higher the blood flow velocity and smaller the vessel diameter, the greater the value of shear rate [5].

Shear stress is the frictional force generated by the blood current along the endothelium of the vessel and directed along the blood flow.

In case of arterial vasoconstriction and corresponding increase in blood flow velocity, platelet hemostasis is activated, which, in turn, promotes the formation of "white" clot. VWF normally circulates in the blood in globular form as huge proteins (more than 20 000 kDa) and has a unique property to change its geometry when blood flow velocity increases. The factor spreads from its globular form and becomes filamentous, opening up hundreds of additional sites for binding to platelet receptors and their subsequent activation and aggregation. At high shear rates, VWF is capable of so-called *self-association* — the protein multimers begin to bind to each other as a result of A2 domain opening [3, 5]. Self-association leads to the formation of grid-like structures, which is an excellent place for platelet attachment and further clot growth.

It is worth mentioning that VWF is cut by the enzyme called ADAMTS-13 in the A2 domain to inhibit excessive platelet activity. When the enzyme is not active enough, less VWF is exposed to it, which, again, leads to an increased risk of thrombosis. In some cases, a condition called thrombotic thrombocytopenic purpura (TTP) occurs. TTP is a rare, acute, and life-threatening condition resulting from thrombocytopenia consumption in diffuse thrombosis processes in microvessels. As a consequence of mechanical intravascular hemolysis, non-immune hemolytic anemia occurs, as well as multi-organ failure. A key link in the pathogenesis of TTP is congenital or acquired ADAMTS-13 enzyme deficiency [13, 19, 28].

The conditions of clot formation in arterial vessels do not have an absolute correspondence to Virchow's triad in its classical interpretation. Several different components have been proposed to describe the pathogenesis of arterial thrombosis: 1) vessel stenosis, 2) endothelial damage, 3) prothrombotic processes (VWF and platelet activation, decreased ADAMTS-13 activity) [6, 21, 28]. We can say that this concept has a connection with Virchow's classical triad in terms of endothelial damage. The platelet response is undoubtedly one of the elements of arterial thrombogenesis and is to some extent equivalent to the presence of hypercoagulability in Virchow's triad (Fig. 2). In contrast to venous thrombosis, the presence of initially high platelet activity is not necessary for arterial clot formation.

Considering specifically arterial clotting, platelet activation with increased blood flow velocity in stenosed vessels should be assumed. Various types of erythrocyte pathology should also be taken into account. The new coronavirus infection COVID-19 [30] may cause the possible complications, as well as preventive vaccination against it [31] (Table 1). There are pathologic reactions that occur after administration of recombinant adenovirus vector [32, 39] and mRNA vaccines [33, 34]. These reactions include thrombocytopenia, thrombosis, and hemorrhage, and are associated with sex and age, life history, the vaccine administered, and concomitant use of other drugs. Thrombi are most often localized in the cerebral venous system. Women are most commonly affected [37]. The main risk factors are anticoagulant therapy, pregnancy, brain infections, head trauma, and use of medication contraceptives. Therefore, the use of Astrazeneca vaccine has been temporarily restricted in European countries [38, 39].

Understanding the pathogenesis of arterial and venous thrombosis has become particularly important in clinical practice after the COVID-19 pandemic, which, according to WHO, lasted from January 30, 2020, to May 5, 2023. According to various reports, the incidence of acute thrombosis as a complication of coronavirus infection ranged from 0.39% to 11.1% [7, 18, 24, 35].

The discovery of SARS-CoV-2 virus tropism to vascular endothelium [11, 12, 20] radically changed the approach to therapy of this infection. In general, when analyzing the literature data for 2020-2021, the association of the incidence of thrombosis as a complication of COVID-19 with gender

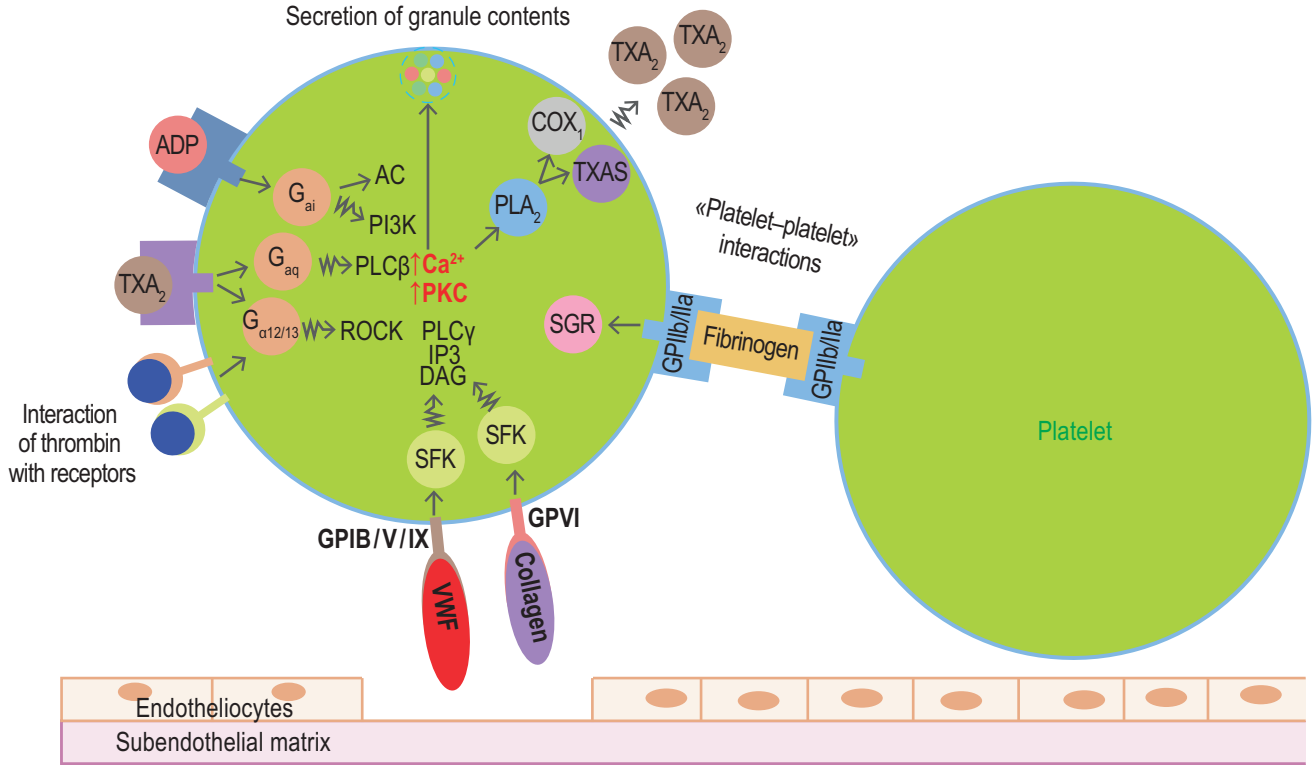

Fig. 2. **Schematic of platelet activation. ADP, adenosine diphosphate; TXA2, thromboxane A2; Gai, α subunit of G-protein; Gaq, αq subunit of G-protein; Gα12/13, α12/13 subunits of G-protein; AC, adenylate cyclase; PI3K, phosphoinositide-3-kinase; PLCβ, phospholipase C β; PLCγ, phospholipase C γ; PLA2, phospholipase A2; ROCK, Rho-associated protein kinase; IP3, inositol-3-phosphate; DAG, diacylglycerol; SFK, Src-family kinase; GP (IB, IIa, IIb V, VI, IX), glycoproteins; VWF, von Willebrand factor; SGR, small regulatory G-protein; COX1, cytochrome oxidase subunit 1; TXAS, thromboxane A synthase**

Table 1

Association of thrombosis with COVID-19 vaccination

Vaccine	Number of patients	Type of vaccine	Age	Women, %	Venous sinus thrombosis, %	Mortality, %
Astrazeneca [32]	11	Vector	22–49	18%	82%	55%
Moderna [33]	23	mRNA	21–77	61%	57%	30%
Pfizer [34]	19	mRNA	20–89	63%	58%	5%

and age is revealed. Men over 50 y.o. are significantly more prone to thrombosis. However, the mortality rate due to acute thrombosis is many times and sometimes 10 times higher in women [7, 17, 23, 29, 37].

The correlation between risks of thrombosis and severity of the disease remains a matter of debate. According to numerous data [18, 25, 29], thrombosis is more likely to develop in moderate and severe course of infection. However, some sources report that thrombosis also occurs in the mild course of COVID-19 [28]. Criteria for assessing severity may vary not only between countries but also between physicians themselves. It is quite possible that thrombosis in the mild course of infection was an isolated incident and not reliably associated with the severity of the disease course. In addition, there are no reliably identified cases of thrombosis in outpatients. This could be attributed to various factors: death of patients from other causes, development of acute thrombosis as iatrogenic complications (which are more likely to occur in inpatient care rather than outpatient care), and asymptomatic course and spontaneous resolution of thrombosis during recovery. In general, the development of coagulopathies at any severity of coronavirus infection is associated with a significant increase in D-dimer levels [15, 18, 24]. Meanwhile, studies of platelet levels, activated partial thromboplastin time (APTT) and

prothrombin time (PTT) did not reveal statistically significant changes, which suggests a different mechanism of COVID-associated coagulopathies.

There is evidence that SARS-CoV-2 particles are capable to adhere to erythropoiesis precursor cells [7, 28, 35]. Erythroid cells showed significant expression of arginases and reactive oxygen species exerting a damaging effect on the endothelium. The virus is able to penetrate erythrocytes, leaving S1 spike proteins, CD147 receptors and band 3 transmembrane proteins on their surface. In general, these changes lead to a decrease in erythrocyte ATP activity, impaired erythrocyte deformability and consequently tissue hypoxia, which can lead to hypercoagulability. Shear stress increases, VWF activity rises, which, as described above, enhances thrombosis even more. As a result, erythrocyte adhesion to the endothelium increases, and huge VWF multimers attach, which initiates blood stasis [10, 14].

Analyzing the data on venous and arterial thromboses, it is possible to distinguish them as complications of the new coronavirus infection. Taking into account the above mentioned, it is possible to put forward the question whether thromboses in COVID-19 are a new form of pathologic processes that unite both components of Virchow's triad and arterial triad. Perhaps it even makes sense to identify a new pathogenetic chain of thrombosis in form of a tetrad rather than a triad, including hypercoagulability, decreased or increased blood flow velocity, endothelial damage, and platelet activation, which we would suggest labeling as the "Virchow tetrad" (Fig. 3).

CONCLUSION

Presumably, a new interpretation of the pathophysiologic patterns of thrombosis will allow clinicians to take a closer look at the tactics of treatment of arterial thrombosis, including those associated with COVID-19. In any case, the introduction of the concept of "arterial triad" in addition to the "Virchow triad" or "tetrad" instead of it will allow pathophysiologists to separate pathogenetic features of arterial and venous thrombosis better. As for clinicians, it will help to prevent and treat these conditions separately.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования

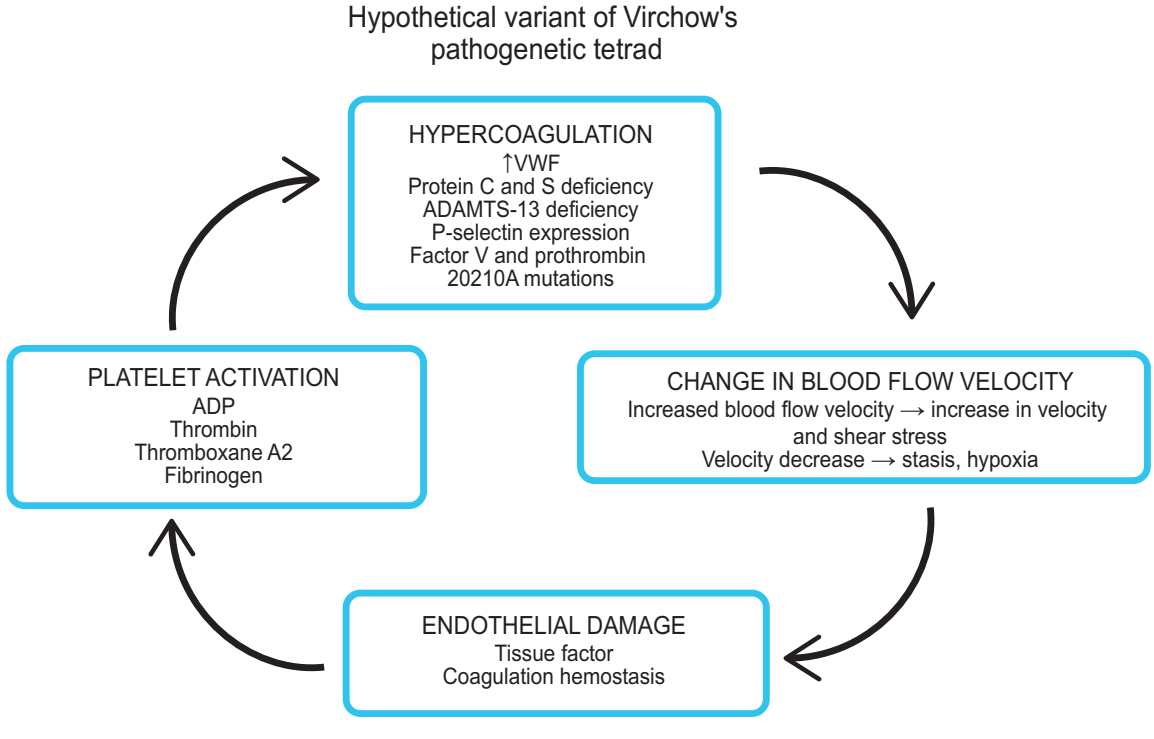

Fig. 3. Hypothetical variant of the scheme of thrombosis formation within the framework of pathogenetic "tetrad"

и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

REFERENCES

1. Vasil`ev A.G., Komyakov B.K., Tagirov N.S., Musaev S.A. Chreskozhnaya nefrolitotripsiya v lechenii korallovidnogo nefrolitiaza. [Percutaneous nephrolithotripsy in the treatment of staghorn nephrolithiasis] Vestnik Sankt-Peterburgskoj gosudarstvennoj meditsinskoj akademii im. I.I. Mechnikova. 2009; 4(33): 183–186. (in Russian).
2. Vasina L.V., Vlasov T.D., Petrishhev N.N. Funktsional`naya geterogennost` e`ndoteliya (obzor) [Functional heterogeneity of the endothelium (review)]. Arterial`naya gipertenziya. 2017; 23(2): 88–102. (in Russian).
3. Vlasov T.D., Petrischev N.N., Lazovskaya O.A. Disfunktsiya endoteliya. Pravil`no li my` ponimaem e`tot termin? Vestnik anesteziologii i reanimatologii. 2020; 17(2): 76–84.
4. Vlasov T.D., Yashin S.M. Arterial'nye i venoznye trombozy. Vsegda li primenima triada Virhova? [Arterial and venous thromboses. Is Virchow's triad always applicable?]. Regionarnoe krovoobrashchenie i mikrocirkuljacija. 2022; 21(1): 78–86. (in Russian).
5. Gagun V.E., Luk'janov N.G., Osmanov Z.A. Retrospektivnyj analiz chastoty arterial'nyh trombozov, associirovannyh s virusom SARS-CoV-2. [Retrospective analysis of the frequency of arterial thrombosis associated with the SARS-CoV-2 virus]. Izvestija Rossijskoj voenno-medicinskoj akademii. 2022; 41(2): 103–107. (in Russian).
6. Dutova T.I., Banin I.N., Sazonov I.E. i dr. Geneticheski determinirovannaja predraspolozhennost' k razvitiju sosudistoj katastrofy: est' li svjaz' s tjazhelym techeniem novoj koronavirusnoj infekcii COVID-19? [Genetically determined predisposition to the development of vascular catastrophe: is there a connection with the severe course of the new coronavirus infection COVID-19?]. Tromboz, gemostaz i reologija. 2023; 1: 12–22. (in Russian).
7. Kruchinina M.V., Gromov A.A., Logvinenko I.I., Kruchinina E.V. Izmenenija kletok krasnoj krovi, svjazannye s razvitiem serdechno-sosudistyh oslozhnenij, u pacientov s koronavirusnoj infekciej COVID-19. [Changes in red blood cells associated with the development of cardiovascular complications in patients with coronavirus infection COVID-19]. Ateroskleroz. 2023; 19(1): 35–46. (in Russian).
8. Magamedov I.D., Pivovarova L.P., Noxrin S.P. i dr. Klinicheskij sluchaj ostroj ishemii nizhnih konechnostej, associirovannoj s novoj koronavirusnoj infektsiej COVID-19. [A clinical case of acute ischemia of the lower extremities associated with a new coronavirus infection COVID-19]. Dzhanelidzevskie chteniya — 2023: Sbornik nauchny`kh trudov nauchno-prakticheskoj konferentsii, Sankt-Peterburg, 01–03 marta 2023 goda. Sankt-Peterburg: Gosudarstvennoe byudzhetnoe uchrezhdenie "Sankt-Peterburgskij nauchno-issledovatel`skij institut skoroj pomoschi im. I.I. Dzhanelidze", 2023; 103–105. (in Russian).
9. Mukanova A.D., Mukanova A.D., Erekesh A. A.i dr. D-dimer — potencial'nyj biomarker tiazhesti COVID-19. [D-dimer is a potential biomarker for COVID-19 severity]. Farmacija Kazahstana. 2021; 5: 17–21. (in Russian).
10. Tagirov N.S., Nazarov T.X., Vasil`ev A.G., Lichtschanghof A.Z., Lazarenko I.B., Madzhidov S.A., Ahmedov M.A. Opy`t primeneniya chreskozhnoj nefrolitotripsii i kontaktnoj ureterolitotripsii v kompleksnom lechenii mochekamennoj bolezni. [Experience in the use of percutaneous nephrolithotripsy and contact ureterolithotripsy in the complex treatment of urolithiasis]. Profilakticheskaya i klinicheskaya medicina. 2012; 4(45): 30–33. (in Russian).
11. Trashkov A.P., Brus T.V., Vasil`ev A.G., Artemenko M.R., Pechatnikova V.A., Gumennaya M.A. Bioximicheskij profil` kry`s s nealkogol`noj zhirovoj bolezn`yu pecheni razlichnoj stepeni tyazhesti i ego korrekciya preparatom Remaksol. [Biochemical profile of rats with non-alcoholic fatty liver disease of varying severity and its correction with Remaxol]. Pediatr. 2017; 8(4): 78–85. (in Russian).
12. Hajcev N.V., Vasil`ev A.G., Trashkov A.P., Kravtsova A.A., Balashov L.D. Vliyanie vozrasta i pola na harakter otvetny`h reakcij bely`h kry`s pri dejstvii hronicheskoj gipoksicheskoj gipoksii [Influence of age and sex on the nature of response reactions of white rats under the action of chronic hypoxic hypoxia]. Pediatr. 2015; 6(2): 71–77. (in Russian).
13. Abou-Ismail M.Y., Citla Sridhar D., Nayak L. Estrogen and thrombosis: A bench to bedside review. Thromb Res. 2020; 192: 40–51.
14. Alam W. COVID-19 vaccine-induced immune thrombotic thrombocytopenia: A review of the potential mechanisms and proposed management. Sci Prog. 2021; 104(2): DOI: 10.1177/00368504211025927.
15. Al-Ali D., Elshafeey A., Mushannen M. et al. Cardiovascular and haematological events post COVID-19 vaccination: A systematic review. J Cell Mol Med. 2022; 26(3): 636–653.
16. Ali MAM, Spinler S.A. COVID-19 and thrombosis: From bench to bedside. Trends Cardiovasc Med. 2021; 31(3): 143–160.
17. Bank I., Libourel E.J., Middeldorp S. et al. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine. 2004; 164(17): 1932–1937. DOI: 10.1001/archinte.164.17.
18. Bank I., Libourel E.J., Middeldorp S. et al. Elevated levels of FVIII:C within families are associated with an increased risk for venous and arterial thrombosis. Journal of Thrombosis and Haemostasis. 2003; (3): 79–84.
19. Bennett P.C., Silverman S.H., Gill P.S. et al. Peripheral arterial disease and Virchow's triad. Thrombosis and Haemostasis. 2009; 101(6): 1032–1040. DOI: 10.1160/TH08-08-0518.
20. Brill A. Multiple Facets of Venous Thrombosis. Int J Mol Sci. 2021; 22(8): 3853.
21. Bilotta C., Perrone G., Adelfio V. et al. COVID-19 Vaccine-Related Thrombosis: A Systematic Review and Exploratory Analysis. Front Immunol. 2021; 12:729251. DOI: 10.3389/fimmu.2021.729251.

22. Bjarne Osterud, Eirik Bjorklid. Tissue factor in blood cells and endothelial cells. Frontiers in Bioscience (Elite Edition). 2012; 4(1): 289–299. DOI: 10.2741/e376.
23. Dr. Adolf Strumpell, Lehrbuch der speciel'en Pathologie und Therapie der inneren Krankheiten. Neunzehnte vielvach cerbesserte und vermehrte Auflage. Erster Band. Leipzig. 1914.
24. Furie K.L., Cushman M., Elkind M.S.V. et al. American Heart Association/American Stroke Association Stroke Council Leadership. Diagnosis and Management of Cerebral Venous Sinus Thrombosis With Vaccine-Induced Immune Thrombotic Thrombocytopenia. Stroke. 2021; 52(7): 2478–2482. DOI: 10.1161/STROKEAHA.121.035564.
25. Gonzalez-Fajardo J.A., Ansuategui M., Romero C. et al. Mortality of COVID-19 patients with vascular thrombotic complications. Med Clin (Engl Ed). 2021; 156(3): 112–117.
26. Greinacher A., Thiele T., Warkentin T.E. et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med. 2021; 384(22): 2092–2101.
27. Malik B., Kalantary A., Rikabi K. et al. Pulmonary embolism, transient ischaemic attack and thrombocytopenia after the Johnson & Johnson COVID-19 vaccine. BMJ Case Reports. 2021; 14(7): e243975. Published 2021 Jul 14. DOI: 10.1136/bcr-2021-243975.
28. Iba T., Levy J.H. Thrombosis and thrombocytopenia in COVID-19 and after COVID-19 vaccination. Trends Cardiovasc Med. 2022; 32(5): 249–256.
29. Pyurveev S.S., Sizov V.V., Lebedev A.A. et al. Registration of Changes in the Level of Extracellular Dopamine in the Nucleus Accumbens by Fast-Scan Cyclic Voltammetry during Stimulation of the Zone of the Ventral Tegmental Area, Which Also Caused a Self-Stimulation. Journal of Evolutionary Biochemistry and Physiology. 2022; 58(5): 1613–1622.
30. Sadler J.E. Pathophysiology of thrombotic thrombocytopenic purpura. Blood. 2017; 130(10): 1181–1188.
31. Sastry S., Cuomo F., Muthusamy J. COVID-19 and thrombosis: The role of hemodynamics. Thromb Res. 2022; (212): 51–57.
32. Sahu K.K., Borogovac A., Cerny J. COVID-19 related immune hemolysis and thrombocytopenia. J Med Virol. 2021; 93(2): 1164–1170.
33. Scully M., Singh D., Lown R. et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021; 384(23): 2202–2211. DOI: 10.1056/NEJMoa2105385.
34. Shankaran H., Alexandridis P., Neelamegham S. Aspects of hydrodynamic shear regulating shear-induced platelet activation and self-association of von Willebrand factor in suspension. Blood. 2003; 101(7): 2637–45.
35. Silvis S.M., de Sousa D.A., Ferro J.M. et al. Cerebral venous thrombosis. Nature Reviews. Neurology. 2017; 13(9): 555–565. DOI: 10.1038/nrneurol.2017.104.
36. Tsygan N.V., Trashkov A.P., Litvinenko I.V. et al. Autoimmunity in acute ischemic stroke and the role of blood-brain barrier: the dark side or the light one? Frontiers of Medicine. 2019. 13(4): 420–426.
37. Veyre F., Poulain-Veyre C., Esparcieux A. et al. Femoral Arterial Thrombosis in a Young Adult after Nonsevere COVID-19. Ann Vasc Surg. 2020; 69: 85–88. DOI: 10.1016/j.avsg.2020.07.013.
38. Wells P.S., Anderson D.R., Rodger M. et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003; 349(13): 1227–1235. DOI: 10.1056/NEJMoa023153.
39. Wool G.D., Miller J.L. The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology. 2021; 88(1): 15–27.

ЛИТЕРАТУРА

1. Васильев А.Г., Комяков Б.К., Тагиров Н.С., Мусаев С.А. Чрескожная нефролитотрипсия в лечении коралловидного нефролитиаза. Вестник Санкт-Петербургской государственной медицинской академии им. И.И. Мечникова. 2009. 4(33): 183–186.
2. Васина Л.В., Власов Т.Д., Петрищев Н.Н. Функциональная гетерогенность эндотелия (обзор). Артериальная гипертензия. 2017; 23(2): 88–102.
3. Власов Т.Д., Петрищев Н.Н., Лазовская О.А. Дисфункция эндотелия. Правильно ли мы понимаем этот термин? Вестник анестезиологии и реаниматологии. 2020; 17(2): 76–84.
4. Власов Т.Д., Яшин С.М. Артериальные и венозные тромбозы. Всегда ли применима триада Вирхова? Регионарное кровообращение и микроциркуляция. 2022; 21(1): 78–86.
5. Гагун В.Э., Лукьянов Н.Г., Османов З.А. Ретроспективный анализ частоты артериальных тромбозов, ассоциированных с вирусом SARS-CoV-2. Известия Российской военно-медицинской академии. 2022; 41(S2): 103–107.
6. Дутова Т.И., Банин И.Н., Сазонов И.Э. и др. Генетически детерминированная предрасположенность к развитию сосудистой катастрофы: есть ли связь с тяжелым течением новой коронавирусной инфекции COVID-19? Тромбоз, гемостаз и реология. 2023; 1: 12–22.
7. Кручинина М.В., Громов А.А., Логвиненко И.И., Кручинина Э.В. Изменения клеток красной крови, связанные с развитием сердечно-сосудистых осложнений, у пациентов с коронавирусной инфекцией COVID-19. Атеросклероз. 2023; 19(1): 35–46.
8. Магамедов И.Д., Пивоварова Л.П., Нохрин С.П. и др. Клинический случай острой ишемии нижних конечностей, ассоциированной с новой коронавирусной инфекцией COVID-19. Джанелидзевские чтения — 2023: Сборник научных трудов научно-практической конференции, Санкт-Петербург, 01–03 марта 2023 года. Санкт-Петербург: Государственное бюджетное учреждение «Санкт-Петербургский научно-исследовательский институт скорой помощи им. И.И. Джанелидзе», 2023. 103–105.
9. Муканова А.Д., Муканова А.Д., Ерекеш А.А. и др. D-димер — потенциальный биомаркер тяжести COVID-19. Фармация Казахстана. 2021; 5: 17–21.
10. Тагиров Н.С., Назаров Т.Х., Васильев А.Г., Лихтшангоф А.З., Лазаренко И.Б., Маджидов С.А., Ахмедов М.А. Опыт применения чрескожной нефролитотрипсии и контактной уретеролитотрипсии в комплексном лечении мочекаменной болезни. Профилактическая и клиническая медицина. 2012. 4(45): 30–33.
11. Трашков А.П., Брус Т.В., Васильев А.Г., Артеменко М.Р., Печатникова В.А., Гуменная М.А. Биохимический профиль крыс с неалкогольной жировой болезнью печени различной степени

тяжести и его коррекция препаратом Ремаксол. Педиатр. 2017. 8(4): 78–85.
12. Хайцев Н.В., Васильев А.Г., Трашков А.П., Кравцова А.А., Балашов Л.Д. Влияние возраста и пола на характер ответных реакций белых крыс при действии хронической гипоксической гипоксии. Педиатр. 2015. 6(2): 71–77.
13. Abou-Ismail M.Y., Citla Sridhar D., Nayak L. Estrogen and thrombosis: A bench to bedside review. Thromb Res. 2020; 192: 40–51.
14. Alam W. COVID-19 vaccine-induced immune thrombotic thrombocytopenia: A review of the potential mechanisms and proposed management. Sci Prog. 2021; 104(2): DOI: 10.1177/00368504211025927.
15. Al-Ali D., Elshafeey A., Mushannen M. et al. Cardiovascular and haematological events post COVID-19 vaccination: A systematic review. J Cell Mol Med. 2022; 26(3): 636–653.
16. Ali MAM, Spinler S.A. COVID-19 and thrombosis: From bench to bedside. Trends Cardiovasc Med. 2021; 31(3): 143–160.
17. Bank I., Libourel E.J., Middeldorp S. et al. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine. 2004; 164(17): 1932–1937. DOI: 10.1001/archinte.164.17.
18. Bank I., Libourel E.J., Middeldorp S. et al. Elevated levels of FVIII:C within families are associated with an increased risk for venous and arterial thrombosis. Journal of Thrombosis and Haemostasis. 2003; (3): 79–84.
19. Bennett P.C., Silverman S.H., Gill P.S. et al. Peripheral arterial disease and Virchow's triad. Thrombosis and Haemostasis. 2009; 101(6): 1032–1040. doi: 10.1160/TH08-08-0518
20. Brill A. Multiple Facets of Venous Thrombosis. Int J Mol Sci. 2021; 22(8): 3853
21. Bilotta C., Perrone G., Adelfio V. et al. COVID-19 Vaccine-Related Thrombosis: A Systematic Review and Exploratory Analysis. Front Immunol. 2021; 12:729251. DOI: 10.3389/fimmu.2021.729251.
22. Bjarne Osterud, Eirik Bjorklid. Tissue factor in blood cells and endothelial cells. Frontiers in Bioscience (Elite Edition). 2012; 4(1): 289–299. DOI: 10.2741/e376.
23. Dr. Adolf Strumpell, Lehrbuch der speciel'en Pathologie und Therapie der inneren Krankheiten. Neunzehnte vielvach cerbesserte und vermehrte Auflage. Erster Band. Leipzig. 1914.
24. Furie K.L., Cushman M., Elkind M.S.V. et al. American Heart Association/American Stroke Association Stroke Council Leadership. Diagnosis and Management of Cerebral Venous Sinus Thrombosis With Vaccine-Induced Immune Thrombotic Thrombocytopenia. Stroke. 2021; 52(7): 2478–2482. DOI: 10.1161/STROKEAHA.121.035564.
25. Gonzalez-Fajardo J.A., Ansuategui M., Romero C. et al. Mortality of COVID-19 patients with vascular thrombotic complications. Med Clin (Engl Ed). 2021; 156(3): 112–117.
26. Greinacher A., Thiele T., Warkentin T.E. et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med. 2021; 384(22): 2092–2101.
27. Malik B., Kalantary A., Rikabi K. et al. Pulmonary embolism, transient ischaemic attack and thrombocytopenia after the Johnson & Johnson COVID-19 vaccine. BMJ Case Reports. 2021; 14(7): e243975. Published 2021 Jul 14. DOI: 10.1136/bcr-2021-243975.
28. Iba T., Levy J.H. Thrombosis and thrombocytopenia in COVID-19 and after COVID-19 vaccination. Trends Cardiovasc Med. 2022; 32(5): 249–256.
29. Pyurveev S.S., Sizov V.V., Lebedev A.A. et al. Registration of Changes in the Level of Extracellular Dopamine in the Nucleus Accumbens by Fast-Scan Cyclic Voltammetry during Stimulation of the Zone of the Ventral Tegmental Area, Which Also Caused a Self-Stimulation. Journal of Evolutionary Biochemistry and Physiology. 2022; 58(5): 1613–1622.
30. Sadler J.E. Pathophysiology of thrombotic thrombocytopenic purpura. Blood. 2017; 130(10): 1181–1188.
31. Sastry S., Cuomo F., Muthusamy J. COVID-19 and thrombosis: The role of hemodynamics. Thromb Res. 2022; (212): 51–57.
32. Sahu K.K., Borogovac A., Cerny J. COVID-19 related immune hemolysis and thrombocytopenia. J Med Virol. 2021; 93(2): 1164–1170.
33. Scully M., Singh D., Lown R. et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021; 384(23): 2202–2211.
34. Shankaran H., Alexandridis P., Neelamegham S. Aspects of hydrodynamic shear regulating shear-induced platelet activation and self-association of von Willebrand factor in suspension. Blood. 2003; 101(7): 2637–45.
35. Silvis S.M., de Sousa D.A., Ferro J.M. et al. Cerebral venous thrombosis. Nature Reviews. Neurology. 2017; 13(9): 555–565. DOI: 10.1038/nrneurol.2017.104.
36. Tsygan N.V., Trashkov A.P., Litvinenko I.V. et al. Autoimmunity in acute ischemic stroke and the role of blood-brain barrier: the dark side or the light one? Frontiers of Medicine. 2019; 13(4): 420–426.
37. Veyre F., Poulain-Veyre C., Esparcieux A. et al. Femoral Arterial Thrombosis in a Young Adult after Nonsevere COVID-19. Ann Vasc Surg. 2020; 69: 85–88.
38. Wells P.S., Anderson D.R., Rodger M. et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003; 349(13): 1227–1235. DOI: 10.1056/NEJMoa023153.
39. Wool G.D., Miller J.L. The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology. 2021; 88(1): 15–27.