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The Role of Infectious Diseases of the Lower Respiratory Tract in the Pathogenesis of Ischemic Stroke (Review)

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Summary

Objective: to clarify the pathogenesis of ischemic stroke in infectious diseases of the lower respiratory tract.

Material and methods. We searched the PubMed database for original research articles, clinical reports, review articles, editorials, commentaries, and short communications published before June 25, 2025. Additional studies that were not captured through the primary database search were analyzed after manually examining the reference lists of the selected articles. Articles were selected based on the relevance of the title and abstract to the purpose of this review. Data from 160 sources were included in the analysis.

Results. We have identified and analyzed in detail the mechanisms of ischemic stroke development in respiratory infections: activation of the coagulation system and disruption of natural anticoagulant and fibrinolytic mechanisms (1); interaction of the hemostasis system with innate immunity (2); the effect of infectious agents on the progression of atherosclerosis and the stability of the atherosclerotic plaque (3); the formation of thromboemboli in the pulmonary veins (4).

Conclusion. Both bacterial and viral infections can initiate a procoagulant state mediated by tissue factor, von Willebrand factor, platelet activation, neutrophil extracellular traps and decreased activity of endogenous anticoagulants. The infectious process localized in the lungs, characterized by damage to the pulmonary vascular endothelium, alveolocytes, intraalveolar fibrin deposition, edema, cellular infiltration, in concert with hemostasis alterations create conditions for the formation of thrombi in the pulmonary vessels. Thus, the pulmonary veins and venules can be a source of cerebral thromboembolism. This mechanism of thromboembolic stroke development largely explains causes of acute cerebrovascular events in patients with lower respiratory tract infection without cardiovascular risk factors. Another mechanism of ischemic stroke is associated with direct or indirect effects of pathogens on the stability of atherosclerotic plaques in cerebral vessels, which, together with systemic procoagulant imbalance, leads to the formation of atherothrombosis. Given the significant pathogenetic relationship between acute infectious lung diseases and thromboembolic and atherothrombotic strokes, clinical alertness regarding acute cerebrovascular events should be included in monitoring and management of such patients.

Key words: ischemic stroke; pneumonia; respiratory infection; atherosclerosis; thromboembolism; hemostasis; inflammation

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Understanding the relationship between acute cerebrovascular accidents (CVA), one of the leading causes of death worldwide, and lower respiratory tract infections, the leading cause of death among infectious diseases, is of global public health significance. The hypothesis linking acute infectious diseases and stroke emerged in the late 19th century, based on the first works of P. Marie and S. Freud [1], devoted to the problem of stroke in children. In 1930, S. Collins et al. first noted a link between seasonal influenza activity and mortality from cardiovascular diseases [2]. Data on the increased risk of ischemic stroke and myocardial infarction in respiratory infections, obtained on the basis of an analysis of large patient databases [3–5], as well as a number of modern publications on ischemic stroke in children associated with a preceding bacterial or viral infection, confirm the previously formulated hypotheses [6–10]. Infection, particularly respiratory infection, has been considered as a trigger for ischemic stroke in both elderly and young patients and children [11–13].

The significance of this problem has become especially evident during the COVID-19 pandemic, which is confirmed by a large number of published clinical reports of acute cerebrovascular accidents in patients hospitalized with the diagnosis of COVID-19. According to A. E. Merkler et al., approximately 1.6% of patients admitted to the emergency department or hospitalized with COVID-19 experienced ischemic stroke, which was incidence

was significantly higher than in patients with influenza [14]. In contrast, a study by Ward et al. demonstrated a similar risk of ischemic stroke in COVID-19 and influenza [15]. According to W. Luo et al., the prevalence of ischemic stroke in COVID-19 was 2% [16]. Similar results were obtained by us when analyzing fatal COVID-19 cases based on autopsy reports [17–18]. However, it is necessary to take into account the high heterogeneity of studies published during the pandemic [19].

Various pathogenetic types of strokes have been described in patients with respiratory infections. Wang et al. showed a high risk of predominantly ischemic stroke (atherothrombotic and cardioembolic) in patients with a recent respiratory tract infection [20]. M. C. Zurrú et al. found that recent respiratory tract infections were significantly associated with atherothrombotic stroke [21]. According to A. Paganini-Hill et al., respiratory tract infection increases the risk of cardioembolic ischemic stroke, even in patients without cardiovascular risk factors [22]. It should be noted that cardioembolic stroke was not associated with infective endocarditis in the mentioned studies.

Despite a large number of studies, data on a direct causal relationship between stroke and respiratory infectious diseases remain contradictory to this day [23]. For example, in a study by T. G. Beach et al., aimed at comparing the frequencies of ischemic and hemorrhagic strokes in patients with pneumonia confirmed at autopsy and without pneumonia, similar risks of stroke were demonstrated for patients in both groups [24].

The mechanisms linking acute respiratory infections and stroke have not been fully addressed in many studies published on this topic. The lack of a clear understanding of the pathogenesis of this association was particularly noticeable in studies conducted during the COVID-19 period. Increased interest in the properties of the Sars-CoV-2 virus and the molecular mechanisms of COVID-19 complications, without regard to morphological and pathological studies, has led to a focus on the «cytokine storm» and the «unique» neuroinvasive and epitheliotropic properties of the virus, interpreting most findings as specific to COVID-19. However, most hypotheses regarding the pathogenesis of stroke in COVID-19 have already been described in the context of other respiratory infections and are not unique to this infection. The uncertainty and inconsistency of data regarding the causal relationship between ischemic stroke and respiratory infections are largely due to an insufficient understanding of the pathogenesis of thrombi or thromboemboli that cause cerebral vascular occlusion.

The aim of the review was to clarify the pathogenesis of ischemic stroke in infectious diseases of the lower respiratory tract.

Material and Methods

To identify studies relevant to the aim of the review, a literature search was conducted in PubMed using the combinations listed in Table 1. Additional sources not identified through the primary database search were analyzed after examining the reference lists of the selected articles.

Results

Based on data from 160 sources, the mechanisms of ischemic stroke development in respiratory infections were identified, requiring detailed consideration and systematization: 1) activation of the blood coagulation system and disruption of natural anticoagulant and fibrinolytic mechanisms; 2) interaction of the hemostasis system with innate immunity; 3) the impact of infectious agents on the progression of atherosclerosis and the stability of atherosclerotic plaque; 4) formation of thromboemboli in the pulmonary veins.

Activation of the blood coagulation system. The lungs are involved in the regulation of the hemostatic system in both physiological and pathological conditions [25]. In pneumonia, inflammation and hemostasis are components of the host's antibacterial defense. Disruption of natural anticoagulant and fibrinolytic mechanisms has been described in detail in acute respiratory distress syndrome (ARDS), severe pneumonia, and sepsis [26, 27]. Some studies indicate hemostatic disorders in patients with moderate and even mild lower respiratory tract diseases [28, 29]. In a study by Milbrandt et al. aimed at studying blood coagulation markers in patients with community-acquired pneumonia over time, it was shown that hemostatic disorders (changes in D-dimer and thrombin-antithrombin complex [TAT] levels) were observed and progressed both in patients with severe disease and in patients with mild, disease without complications [30].

Based on the clot waveform analysis data (CWA — clot waveform using a modified activated partial thromboplastin time (APTT) analysis based on continuous recording of changes in the optical density of the test sample, Tan et al. showed that bacterial infections lead to a general prothrombotic state, while common respiratory viral infections do not have a significant effect on CWA parameters [31]. Studies assessing the effect of lipopolysaccharide (LPS) on hemostasis have noted activation of the Hageman factor, an increase in the content of von Willebrand factor, an increase in the activity of plasminogen activator inhibitor, and a decrease in the activity of tissue plasminogen activator [32, 33]. Procoagulant imbalance in patients with community-acquired pneumonia was noted not only during the disease but also during convalescence [34].

Activation of the tissue factor-thrombin pathway. The role of tissue factor (TF) in the pathogenesis

of respiratory infectious diseases and ARDS is given special attention, since TF is one of the main initiators of procoagulant activity during tissue alteration and inflammation [35–37]. TF is a transmembrane glycoprotein expressed by fibroblasts, vascular smooth muscle cells, mononuclear cells, and endothelial cells [38–40]. Under physiological conditions, TF comes into contact with blood and circulating coagulation factors only after vascular damage [41, 42]. TF activates the blood coagulation factor F VII to F VIIa. The TF-FVIIa complex promotes the additional formation of FVIIa from FVII and activates coagulation factors X and IX [43]. TF-dependent coagulation generates thrombin and induces pleiotropic cellular effects of thrombin on platelets via protease-activated receptors (PARs) [44].

Morphological immunohistochemistry (IHC) studies showed intense TF staining in alveolar epithelial cells, alveolar macrophages, and hyaline membranes of the lungs of patients with ARDS. In contrast, weak TF expression was observed in the lungs of control patients [45]. Exposure of alveolar cell cultures to edema fluid from patients with ARDS was accompanied by a dose-dependent and time-dependent TF expression. TF production during pulmonary infection is suggested to be mediated by tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β) [46].

TF was detected in the bronchoalveolar lavage (BAL) of patients with bacterial pneumonia [47]. Experimental studies indicate that bacterial antigens, both gram-positive and gram-negative, can directly activate the coagulation system [48, 49]. Bronchoscopic instillation of lipoteichoic acid (LTC), the main component of the membrane of gram-positive bacteria, and instillation of lipopolysaccharide (LPS) in healthy volunteers were shown to induce procoagulant changes in the human bronchoalveolar space. The authors explained the identified features of LTC- and LPS-induced lung inflammation by the action of LTC and LPS on various toll-like receptors, TLR2 and TLR4, respectively. The release of soluble TF in BAL was noted upon exposure to both LTC and LPS. However, increased TF mRNA expression in alveolar macrophages was associated with LTC but not LPS exposure [50–52].

The role of TF in viral infections is supported by studies that have revealed TF expression during infection of various cell types, including pulmonary epithelial and endothelial cells and monocytes [53, 54]. Furthermore, TF expression in endothelial cells is induced by activation of TLR3 (toll-like receptor 3), a pattern recognition receptor that detects single-stranded RNA [55]. Angiotensin II can also induce TF expression in vascular smooth muscle cells and endothelial cells [56]. RNA viruses penetrate cellular endosomes, stimulate endosomal formation and activation of NADPH oxidase complexes through RNA-sensitive toll-like receptors, inducing TF expression [57]. On the one hand, initiation of the procoagulant cascade may promote thrombosis, and on the other hand, TF-dependent activation of coagulation is part of the host's innate immune response to viral infection, which helps prevent intrapulmonary hemorrhage, as evidenced by an increase in alveolar hemorrhage with a genetic decrease in TF in epithelial cells [56].

Increased TF expression in ARDS, pneumonia, and ventilator-induced lung injury is associated with hypercoagulation and thrombus formation in the pulmonary vascular bed, as well as interalveolar fibrin deposition [47, 58–60]. Given the data indicating an elevated level of circulating TF as a potential risk factor for the development of ischemic stroke [61], and also taking into account the role of circulating TF on monocytes and cellular TF-positive microvesicles in thrombus formation after rupture of atherosclerotic plaques [62], TF should be considered as a component of the pathogenesis of ischemic stroke in respiratory infections.

Violation of natural anticoagulant and fibrinolytic mechanisms. Endothelial cells play a key role in maintaining intravascular patency due to their anticoagulant properties. They provide a favorable environment for plasma anticoagulant proteins, including antithrombin, tissue factor inhibitor, and protein C. Infectious diseases impair the anticoagulant properties of endothelial cells. Endothelial cells synthesize heparan sulfate, a component of the glycocalyx, which binds and potentiates anticoagulant plasma proteins, including tissue factor pathway inhibitor (TFPI) and antithrombin [63]. Endothelial

Table. Word combinations used for the PubMed database search strategy .

Keyword combinations
((pneumonia) OR (respiratory infection)) AND (stroke)
((acute respiratory distress syndrome) OR (ARDS)) AND (stroke)
((pneumonia) OR (respiratory infection)) AND (embolic stroke)
(((infection respiratory) OR (pneumonia))) AND (coagulation)
(((infection respiratory) OR (pneumonia))) AND (hemostasis)
((platelets) AND (stroke)) AND (infection)
((pneumonia) OR (respiratory infection)) AND (atherosclerosis)
((pneumonia) OR (respiratory infection)) AND (biomarkers)
((pneumonia) OR (respiratory infection)) AND (pathogenesis) AND (thrombosis)
(thrombosis) OR (immunothrombosis) OR (immunothrombosis) OR ((thromboinflammation) AND (pneumonia))

cells also produce thrombomodulin, which, by binding to thrombin, converts it from a procoagulant to an anticoagulant, activating anticoagulant protein C [64]. Activated protein C (APC), together with cofactor protein S, inactivates factors FVa and FVIIIa. In addition, endothelial cells synthesize and release tissue plasminogen activator (tPA), potentiating plasmin-mediated fibrinolysis in the vascular bed [63, 65].

Tissue factor pathway inhibitor (TFPI) is a central endogenous regulator of TF-thrombin pathway activity. This glycoprotein is produced primarily by endothelial cells and platelets. TFPI directly inhibits factor Xa forming the Xa-TFPI complex, which subsequently inhibits the TFVIIa complex [43]. The highest amount of TFPI mRNA is reported to be expressed in the human lung, while the lowest is expressed in the brain [66]. In the lung, TFPI is localized along the alveolar septa and in the alveolar epithelium, suggesting that decreased TFPI activity may play a significant role in coagulation disorders in the context of lung injury [67, 68]. The exact physiological mechanisms responsible for the decreased TFPI activity observed during infections are unclear. One common hypothesis is that TFPI is cleaved by endogenous or pathogen-derived proteases. Cleavage of TFPI by leukocyte elastase has been described [69]. A study by T. H. Yun et al. presented a mechanism for proteolytic inactivation of TFPI by omptins, the outer membrane aspartyl proteases of gram-negative bacteria, which, according to the authors, contributes to increased pathogen virulence [70]. However, S. Massberg et al. consider local proteolysis of TFPI by serine proteases and extracellular nucleosomes as part of the host's antimicrobial defense, promoting compartmentalization of bacteria in blood vessels with a resulting decrease in tissue invasion [71–72].

Elevated TFPI levels have been found in the lavage fluid of patients with ARDS or pneumonia [73]. However, the relationship of increased TFPI levels and decreased TFPI activity with coagulation remains unclear. To examine the effects of endogenous TFPI levels on coagulation, inflammation, and bacterial growth during *S. pneumoniae* pneumonia, F. E. Van Den Boogaard et al. conducted studies in genetically modified TFPI-deficient mice and in wild-type mice administered with a neutralizing anti-TFPI antibody. The results of the study refuted a significant role for endogenous TFPI in the antibacterial, inflammatory, and procoagulant responses in pneumococcal pneumonia, as none of the low TFPI groups showed altered procoagulant responses in the lungs or plasma during pneumonia [68].

J. A. Bastarache et al. suggested that although alveolar epithelial cells produce TFPI, the amount of this endogenous protein is insufficient to block the increased procoagulant activity of TF during inflammation [67]. Data from other studies also indicate that the increased procoagulant activity observed in various lung diseases is not counterbalanced by TFPI [73, 74]. Of clinical significance is that the recombinant TFPI (rh-TFPI) showed no beneficial effect in patients with severe community-acquired pneumonia [75].

The role of plasma TFPI in the development of cardiovascular diseases has not been determined, despite the fact that in atherosclerotic plaques TFPI is localized together with TF, where it is believed to suppress TF activity [76].

Thrombomodulin (TM) is a transmembrane glycoprotein found primarily on endothelial cells, but also found in immune cells, vascular smooth muscle cells, keratinocytes, and alveolar epithelial cells of the lung. TM is a potent anticoagulant that binds to thrombin and then deactivates it, triggering the anticoagulant cascade [77]. Thrombin interacts with thrombomodulin (TM), thereby mediating the activation of protein C, which binds to the endothelial cell protein C receptor (EPCR) [78, 79]. Transcriptional expression of TM occurs in high amounts in the vessels of the heart, pancreas, and lungs, and to a lesser extent in the brain [66].

It has been shown that TM (sTM) increases in blood plasma in community-acquired pneumonia, COVID-19, and mycoplasma pneumonia, and that TM level examination has prognostic value [80–82]. The informative value of sTM in relation to thrombotic risk in patients with COVID-19 has been noted [83].

A study by A. W. Rijneveld et al. on mice with a mutation in the TM gene (TM pro/pro) was aimed at elucidating the pathogenetic role of TM in bacterial pneumonia. Bacterial pneumonia was associated with fibrin deposits in the lungs, inflammatory infiltrates, and an increase in thrombin-antithrombin complexes in bronchoalveolar lavage fluid in both TM pro/pro mice and mice without the mutation. This data, according to the authors, indicates that the ability of TM to generate APS does not play an important role in the pulmonary response to respiratory pathogens or LPS [84].

Based on studies showing high levels of soluble thrombomodulin in pulmonary inflammation, it can be assumed that the release of thrombomodulin from the cell surface contributes to protein C deficiency [60, 85].

Impaired production and/or activation of protein C is another potential mechanism leading to thrombosis in pneumonia [86]. Relative deficiency of APS may be due to increased consumption and enhanced degradation of protein C by neutrophil elastase [87]. It should be taken into account that, although some APS is detected in bronchoalveolar fluid, the lungs are capable of producing only a small amount [88]. Since the main synthesis of APS occurs in liver cells, a decrease in its content in blood plasma may be due to liver cell damage due to tissue hypoxia caused by respiratory failure [89].

Ware et al. showed that in patients with ARDS, plasma APC concentrations were reduced, while plasminogen activator inhibitor type 1 (PAI-1) levels were increased, compared to a control group of patients with cardiogenic pulmonary edema [90]. Low APC and high PAI-1 concentrations associated with increased mortality in patients with ARDS [91]. Relatively low protein C activity was noted in COVID-19 [92]. Increased APC expression was shown to enhance host defense during experimental pneumococcal pneumonia [93].

T. Won et al. studied the expression of TM and endothelial protein C receptor (EPCR) in the lungs, kidneys, and hearts of patients who died from COVID-19. A significant difference between the control group and the group of patients who died from COVID-19 was a decrease in the expression of TM and EPCR in the lungs [77].

In scientific literature, there is data on impaired fibrinolysis and decreased protein C activation as hemostatic risk factors for cerebral infarction. The findings of the case-control study by R. F. Macko et al. indicate that protein C dysfunction and endogenous fibrinolysis may contribute to an increased risk of cerebral infarction after a recent (⩽1 week) infection [94].

When analyzing hemostasis mechanisms in infectious diseases, genetic predisposition to thrombosis should be taken into account. Single nucleotide polymorphisms of protein C, factor V (e. g., the Leiden mutation), and plasminogen activator inhibitor-1 have been found to be associated with an increased risk of deep vein thrombosis, pulmonary embolism, acute myocardial infarction, and stroke [95]. Therefore, a personalized approach to assessing the risk of thrombotic complications of infectious respiratory diseases is necessary.

Interaction of the hemostasis system and innate immunity. Since the onset of the COVID-19 pandemic, the previously existing terms «thromboinflammation» and «immunothrombosis» have gained widespread popularity and prevalence. The first mentions of «thromboinflammation» date back to the 1990s in experimental studies on cerebral air embolism models. It has been suggested that damage to the cerebral vascular endothelium results from secondary reactions involving the interaction of air emboli with blood elements (platelets, leukocytes), fibrinogen, and the endothelium, leading to local fibrin accumulation, as well as platelet and leukocyte adhesion to the endothelium. Thus, to describe the process of thrombus formation with a pronounced cellular reaction, the authors used the term «thromboinflammation» [96].

Later, with the emergence of a large amount of evidence of the involvement of the immune system, in particular proteins of the complement system, in the process of thrombus formation, the preconditions arose for the introduction of a term encompassing the interaction of the immune system and hemostasis [97]. Thus, in 2013, the term «immunothrombosis» appeared [98]. These terms are most often used in studies devoted to the pathogenesis of pulmonary artery thrombosis in ARDS. However, the interaction of the hemostatic system and innate immunity is an integral component of thrombus formation, which was studied even before the appearance of the term «immunothrombosis» [99–102].

Neutrophil extracellular traps, von Willebrand factor, ADAMTS-13. The association of acute infections with an increased risk of thrombotic complications, including ischemic stroke, has recently been increasingly explained by mechanisms of innate immunity, in particular, special attention is paid to neutrophil extracellular traps (NETs) [103]. Neutrophils are known to kill invading microorganisms using two strategies: phagocytosis and degranulation [104]. In a study by O. Porembskaya et al., in rats with normal neutrophil counts and neutropenia, showed that no thrombi were detected in the pulmonary artery in animals with neutropenia. Neutropenia caused a significant decrease in the size of the thrombus in the inferior vena cava and slowed the transition from fresh fibrin to mature fibrin and connective tissue within the thrombus [105].

NETosis is one of the mechanisms of neutrophil involvement in thrombosis. Brinkmann et al. first reported NETosis as an antimicrobial strategy of neutrophils, through which a mesh-like structure of chromatin with histones and granular proteins is released from neutrophils into the extracellular space to capture and destroy bacteria and protect the host from infection [106].

S. Massberg et al. showed that serine proteases, neutrophil elastase and cathepsin G, promote coagulation and thrombus formation by inducing TF-factor XII-dependent coagulation and suppressing endogenous anticoagulants [71]. Extracellular DNA derived from NETs mediates thrombin generation in an FXII- or FXI-dependent pathway. Histones induce thrombin generation in platelet-rich plasma (PRP) by activating platelets through TLR2 and TLR4 [107]. Furthermore, histones, especially H4, directly interact with platelets and activate integrin α IIb β3 on the platelet surface, inducing subsequent fibrinogen-mediated platelet aggregation [108].

Uncontrolled NET formation can lead to endothelial cell damage indirectly through NET-associated proteases, defensins, and histones. Endothelial damage and the release of von Willebrand factor (VWF) from Weibel-Palade bodies contribute to thrombus formation.

VWF is produced and secreted by endothelial cells, megakaryocytes, and platelets. The majority of VWF (80–90%) in plasma is produced by endothelial cells. VWF recruits circulating platelets at

sites of vascular injury and mediates subsequent platelet activation and aggregation [109]. VWF activity is size-dependent. Ultra-large VWF multimers (UL — VWF), released by endothelial cells in response to endothelial-damaging factors, can spontaneously recruit excess circulating platelets and other blood cells, promoting thrombosis [110].

ADAMTS metalloprotease 13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) specifically cleaves the Tyr 1605- Met 1606 bond in the VWF domain A2 regulating the size and activity of VWF multimers, preventing thrombus formation [111]. VWF directly binds and immobilizes extracellular DNA released from leukocytes [112]. Since NETs and VWF are involved in the inflammatory process, the interaction between NETs and VWF may contribute to the development of thrombosis in infectious diseases. An increase in NETs reduces ADAMTS13 activity, promoting the formation of UL-VWF, which leads to the formation of a vicious circle [113].

NETs are very large structures and may contribute to thrombus stability similar to von Willebrand factor (VWF) and fibrin. In vitro studies have shown that NETs provide a thrombolytic-resistant scaffold for blood clots [114]. Individual DNA and histones have been shown to have a more pronounced procoagulant effect than intact NETs [115].

An increase in the VWF factor content in combination with a decrease in the ADAMTS-13 content in blood plasma has been observed in respiratory infectious diseases of both viral and bacterial etiology [34]. The imbalance between VWF and ADAMTS-13 is explained by a relative deficiency of ADAMTS-13 due to a significant increase in the VWF level [116]. Thus, in patients with COVID-19, such an imbalance led to the appearance of large VWF multimers, which was associated with a high thrombotic risk [117, 118]. The important role of VWF in the development of thrombosis in COVID-19 is confirmed by significantly more intense immunohistochemical (IHC) staining of VWF in the pulmonary vascular endothelium in patients with thrombotic complications than in patients without thrombotic complications [119].

Patients with hospital-acquired pneumonia also exhibit a procoagulant imbalance, in particular the VWF/ADAMTS13 ratio was higher in patients with pneumonia than in healthy study participants [34]. The ability of Streptococcus pneumoniae, the most common causative agent of pneumonia, to induce Weibel-Palade body exocytosis and the release of VWF and interleukin 8 (IL-8) from pulmonary endothelial cells has been reported [120]. *Staphylococcus aureus* infection has been shown to be associated with an increase in NETs and VWF content, as well as a decrease in ADAMTS13 activity [121]. Considering that patients with severe acute respiratory infections may require artificial ventilation (AV), which in itself is associated with many complications, including thrombotic ones [122, 123], it is necessary to take into account studies that have shown an increase in VWF expression in the endothelium of patients on mechanical ventilation [124].

The role of NETs was noted in the pathogenesis of cardiovascular diseases, in particular in the formation of atherosclerotic plaques, arterial and venous thrombosis, as well as in the development and progression of aneurysms [125]. A significant increase in NETs markers was found in plasma of patients with ischemic stroke [126].

Excess neutrophils and NETs are observed in almost all thrombi obtained from patients with ischemic stroke [127]. Experimental targeting of NETs with DNase I or Cl-amidine significantly inhibited arterial thrombosis and improved stroke outcome [128]. Experiments in In vitro studies have shown that the addition of extracellular DNA and histones to fibrin increases the thickness, rigidity and stability of the fibrin network, making thrombolysis more difficult [129].

A study by R. B. Patel et al. confirmed the role of VWF-ADAMTS13 imbalance in stroke severity in respiratory infections in an experimental setting. Thus, Vwf -/- deficient mice infected with *S. aureus* or SARS-CoV-2 showed a reduced number of infarcts and improved functional outcomes, while infected Adamts13 -/- deficient mice showed greater stroke severity [130]. A study in patients also confirmed the effect of SARS — CoV -2 infection preceding ischemic stroke on coagulation and NETosis biomarkers, leading to an imbalance in the VWF — ADAMTS 13 axis [131].

Platelet activation. The complex interaction between NETs and platelets, characterized by the ability of NET components to enhance platelet aggregation and activation, which, in turn, under certain conditions, can activate neutrophils to form NETs [132]. A wide range of functional Pattern Recognition Receptors (PRR) receptors are present on the platelet surface, including TLR and Fc receptors. In response to pathogen invasion, activated platelets release their granules containing various immunomodulatory and antimicrobial molecules that either promote the differentiation and activation of immune cells or can directly kill pathogens [133]. Platelets have been shown to interact with Gram-negative and Gram-positive bacteria. LPS enhances the platelet response through interaction with TLR4 [134].

M. Mirsaeidi et al. showed an independent association of thrombocytosis with increased length of hospital stay and mortality in patients with community-acquired pneumonia [135]. Increased platelet reactivity and activation compared to controls was noted in patients with viral respiratory infections, including COVID-19 [136, 137]. P. D. McMullen et al.

performed an immunohistochemical study of autopsy material from the lungs of patients who died from COVID-19, influenza, bacterial and fungal infections using antibodies to CD 61. Almost all samples showed an increase in the area of CD 61 IHC staining compared to control lung tissue. The area of CD 61 staining in COVID-19 infection was higher than in influenza, but still comparable to many other infectious diseases. The highest area of CD 61 staining was observed in cases of aspiration pneumonia, *Staphylococcus aureus* infection, and blastomycosis [138].

The role of infections in the development of atherothrombosis and atherosclerotic plaque instability. The hypothesis suggesting a pathogenetic link between infection and atherosclerosis has existed for quite some time. It is believed that both viral and bacterial pathogens may be associated with the development and progression of atherosclerosis, as well as with disruption of atherosclerotic plaque stability [139]. Given the high prevalence of atherosclerosis, understanding the mechanisms by which infection influences existing atherosclerotic vascular changes in patients is important. We previously showed that COVID-19 patients who died from ischemic stroke had severe cardiovascular comorbidity, in particular atherosclerosis and stenosis of the arteries of the base of the brain [17, 140].

The most compelling evidence for a link between atherosclerosis and infections is presented in relation to *Chlamydia pneumoniae*. R. Ezzahiri et al. described increased T-cell infiltration and atherosclerotic plaque progression in *Chlamydia pneumoniae* infected hypercholesterolemic mice [141]. Currently, plaque progression is not considered to be a continuous process. Therefore, it is proposed that repeated infections throughout life are associated with multiple episodes of increased T cell infiltration, which contributes to plaque composition remodeling. *Chlamydia pneumoniae* bacterial antigens persist in tissues and remain accessible to immunocompetent cells, which is accompanied by a cellular response for at least 4 weeks. T cell lines derived from carotid artery plaques showed antigen specificity for chlamydial antigens in approximately 50% of plaques [142]. A comparative study of the walls of the aorta, coronary, and basilar arteries revealed intra- and extracellular deposition of *Chlamydia pneumoniae* in unstable atherosclerotic plaques, which were characterized by infiltration of the cap and intima adjacent to the atheromatous core, and infiltration by mononuclear cells, primarily T cells. *Chlamydia pneumoniae* was not detected in the intima of unchanged areas of the vascular wall, and insignificant amounts were detected in stable atherosclerotic plaques [143].

Pneumonia caused by *Streptococcus pneumoniae* has been shown to alter plaque characteristics and promote aortic wall remodeling in hypercholesterolemic mice [144].

M. Boumegouas et al. demonstrated for the first time the binding of *Staphylococcus aureus* and *Pseudomonas aeruginosa* with cholesterol crystals, which partially reveals the mechanism of bacterial adhesion to atherosclerotic plaques and their destabilization [145]. It has been shown that the flagellar protein FlgE *Pseudomonas aeruginosa* induces lipid uptake by macrophages and proinflammatory responses mediated by ATP 5 B/NF — kB/AP-1 signaling [146].

B. B. Lanter et al. showed that bacteria form biofilm deposits in carotid artery plaques, which, when exposed to physiologically relevant levels of norepinephrine in the presence of transferrin, could disperse, releasing bacterial enzymes. The authors suggested that these enzymes may damage surrounding tissue and promote plaque rupture. Thus, this study demonstrates a potential link between infections, atherothrombosis, and conditions associated with elevated adrenaline [147].

The role of a local cross-reactive immune response in human atherosclerotic plaques cannot be ruled out. Cross-reaction with bacterial outer membrane proteins *Proteus mirabilis* and *Klebsiella pneumoniae*, a well as with transgelin, cytoskeletal protein involved in atherogenesis, has been described [148].

For some viruses, data have also been obtained substantiating their involvement in the pathogenesis of atherosclerosis and plaque destabilization. Neuraminidase, a group of enzymes that cleave sialic acid during virus release from the host cell, can induce desialylation of lipoproteins, increase the uptake of low-density lipoproteins, and thus contribute to the progression of atherosclerosis [149–151]. A mechanism for the destabilization of vulnerable atherosclerotic plaques in arteries has been described, mediated by increased expression of matrix metalloproteinase-13 (MMP-13) in influenza A [152].

Some studies attribute a significant role in vascular damage to infection of perivascular adipose tissue (PAT). Under physiological conditions, PAT has potent antiatherogenic properties mediated by its ability to secrete various biologically active factors involved in thermogenesis and fatty acid metabolism. In pathological conditions, steatocytes lose their thermogenic capacity and release adipokines, which induce endothelial dysfunction and inflammatory cell infiltration, contributing to the development of atherosclerosis [153, 154].

Influenza A mRNA levels in the aortic AF in mice were shown to be ~4–8 times higher than in the vessel wall. Infection also increased the number of Ly6Clow and Ly6Chigh monocytes in the vessel wall, followed by more intense monocyte infiltration into the AF [155].

Ischemic stroke due to pulmonary venous thromboembolism. The pathogenesis of thrombus

formation in the pulmonary arteries and veins during respiratory infections has been described in detail. Local pulmonary factors associated with damage to endothelial cells, alveolar cells, fibrin deposition, and pulmonary edema, coupled with systemic hemostatic disorders characteristic of lower respiratory tract infections, especially severe ones, contribute to thrombus formation in the pulmonary vascular bed. Pulmonary vein thrombosis can cause thromboembolic stroke. However, the link between infection and pulmonary vein thrombosis is often overlooked.

A number of clinical reports have been published on pulmonary vein thromboembolism in respiratory infections, including COVID-19 [156–159]. An analysis of thrombotic complications of COVID-19 revealed pulmonary vein thrombosis in 5.8% of deceased patients [18].

It is important to note that the pulmonary veins are the most proximal source of thromboembolism. Therefore, careful evaluation of the pulmonary veins should be performed in all cases of arterial thromboembolism [160]. Understanding this mechanism of thromboembolism is important for both clinicians and pathologists, especially in cases where the source of embolism cannot be determined.

Conclusion

The pathogenesis of ischemic stroke in acute lower respiratory tract infections is at the intersection of alteration, inflammation, immunopathological processes, and circulatory impairment. Based on a review of the literature, it is clear that both bacterial and viral infections, despite differences in their mechanisms of action on the immune system and hemostasis, can initiate a procoagulant state mediated by tissue factor, von Willebrand factor, platelet activation, neutrophil extracellular traps, and decreased activity of endogenous anticoagulants. An infectious process localized in the lungs, characterized by damage to the pulmonary vascular endothelium and alveolar cells, interalveolar fibrin accumulation, edema, and cellular infiltration, combined with hemostatic disorders, creates conditions conducive to thrombus formation in the pulmonary vessels. Thus, the pulmonary veins and venules may be a source of cerebral thromboembolism. This mechanism of thromboembolic stroke development largely explains cases of acute cerebrovascular accidents in patients with lower respiratory tract infections without cardiovascular risk factors. Another mechanism of ischemic stroke is associated with the direct or indirect effects of pathogens on the stability of atherosclerotic plaques in cerebral vessels, which, combined with procoagulant imbalance, leads to the development of atherothrombosis.

Understanding the mechanisms of ischemic stroke in respiratory infectious diseases is essential for developing targeted therapeutic strategies and improving patient outcomes. Clinical awareness of ischemic stroke in acute infectious lung diseases is essential for the management of these patients.

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