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Review

Animal Models of Vascular Cognitive Disorder after Myocardial Infarction: Scoping Review

Artem V. Petrov [1], Natalia A. Shnayder [1,2*], Marina M. Petrova [1*], Aleksandr A. Evsyukov [1], Darya S. Kaskaeva[1], Diana V. Dmitrenko[1], Natalia A. Malinovskaya[1]

[1] V.F. Voino-Yasenetsky Krasnoyarsk State Medical University, 660022 Krasnoyarsk, Russia
[2] V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology, 192019 Saint Petersburg, Russia
*Correspondence: naschnaider@yandex.ru (N.A.S.); stk99@yandex.ru (M.M.P.)

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Abstract: Vascular cognitive disorders (VCD) are one of the most common forms of non-psychotic mental disorders with a variable phenotype and rate of progression, transformation into vascular dementia. VCD is characterized by development against the background of existing cardiovascular diseases (CVD), which explains the importance of an interdisciplinary approach to their diagnosis and treatment. The study of new mechanisms of development of VCD can help in finding the key to the development of innovative diagnostic methods and personalized treatment approaches. The purpose of this thematic review is to search, generalize and systematize domestic and foreign research in the field of fundamental neurology using methods of modeling VCD in experimental animals. The authors conducted a search for publications in the databases PubMed, Springer, Web of Science, ClinicalKeys, Scopus, OxfordPress, Cochrane, e-Library using keywords and their combinations. The publications for 2005-2024 were analyzed, including original studies of VCD and vascular dementia.

***Keywords**: fundamental neurology; cognitive functions; vascular cognitive disorders; experiment; animal model; disease modeling.*

1. INTRODUCTION

Vascular cognitive disorders (VCD) and vascular dementia are neurodegenerative diseases that are recognized as the second leading cause of dementia after Alzheimer's disease [1]. According to the National Institute of Neurological Disorders and Stroke - International Association for Research and Development of Neurology (NINDS-AIREN), the main signs of VCD include: 1) acute impairment of memory and at least two other cognitive areas; 2) neuroimaging evidence of cerebrovascular lesions; 3) evidence of a temporary link between stroke and loss of cognitive abilities [2].

Cardiovascular diseases (CVD), which are widespread in middle-aged and elderly people [3], are a recognized distinguishing feature and the leading background pathology in VCD. The prevalence of VCD tends to increase exponentially [4], with individuals with VCD likely to make up approximately 30% of the aging population [5]. Despite the high prevalence of VCD [6, 7], the sensitivity and specificity of early diagnosis methods and the effectiveness of existing therapeutic strategies for VCD and vascular dementia remain limited. Even with the appearance of clinically defined symptoms of moderate and severe VCD, there are no highly specific laboratory and neuroradiological biomarkers yet, although research in this direction has been actively conducted by domestic and foreign scientists over the past decade [8, 9, 10].

The most studied mechanisms of the pathogenesis and progression of VCD are: silver microvascular dysfunction, dilution of cerebral capillaries, violation of the blood-brain barrier (BBB), neuroinflammation, microhemorrhagia, etc. [4].

Modeling of VCD on biological test systems [11, 12, 13], including experimental animals, plays an important role in the study of pathophysiology and allows translating the results of fundamental research into real clinical practice, including the development of new algorithms for the diagnosis and treatment of VCD in humans.

However, to date, the creation of an animal model of VCD is a difficult task, since it is not always possible to reproduce the mechanisms of the pathogenesis of VCD and their symptoms with sufficient completeness in an experiment, especially taking into account the variability of background cardiovascular diseases in humans. Previously, it was shown that the variants of cognitive decline are diverse and have interindividual variability, they can occur in one or more domains. Therefore, when developing an animal model of VCD, in most cases only individual symptoms are reproduced [13]. Since neurotransmitter systems and neural networks involved in cognitive functioning are interconnected, when modeling VCD using experimental animals, it is important to use a sufficient number of tests to more accurately assess the profile of VCD and study their additive effect. Several approaches have been proposed to assess the validity of the animal model of VCD, including several parameters: constructive validity (correspondence of etiological factors of VCD in humans and experimental animals); substantive validity (reproduction of the main clinical manifestations of VCD in experimental animals); prognostic validity (suitability of the animal model of VCD for predicting the effectiveness and safety of medicines that will subsequently be used for the treatment of VCD in humans) [14].

The potential mechanisms of the relationship between ischemic heart disease (IHD) and myocardial infarction with VCD and vascular dementia are complex and insufficiently studied. These mechanisms are associated with a certain degree of dysregulation of tone and patency of cerebral vessels, which can lead to a two- to three-fold risk of transformation of the neurodegenerative process induced in the acute period of myocardial infarction into moderate and severe VCD over the following weeks and years. In VCD and vascular dementia caused by IHD and acute myocardial infarction (AMI), atherosclerosis and degeneration of small cerebral blood vessels can lead to clinically unnoticeable microinfarctions and dysfunctional damage to the white matter in the cerebral cortex due to cerebral hypoperfusion, microvascular cerebral ischemia, enlargement of periventricular spaces, cerebral amyloid angiopathy and hippocampal sclerosis [15].

In addition, left ventricular failure and decreased cardiac output in AMI can lead to arterial hypotension and clinically significant cerebral hypoperfusion [16], and increased platelet activation in patients with IHD can lead to perivascular neuroinflammation, cerebral vasoconstriction and an increase in the severity of carotid artery damage. Platelet activation in patients with IHD and AMI can lead to deposition of amyloid precursor protein and β–amyloid in the brain, which accelerates the processes of neurodegeneration, development and severity of cognitive disorders [17, 18]. Thus, the functions of the cardiovascular and central nervous systems are intricately intertwined, and the well-known heart-brain axis is based on the interaction of remote organs through changes in neural activity, neurohormonal response and vascular tone, which leads to a change in the multisystem response and the development of VCD and vascular dementia in patients with severe IHD and AMI [19, 20, 21].

The neurovascular system regulates central perfusion pressure, BBB permeability, and immune molecular pathways of β–amyloid transport and excretion to maintain normal homeostasis of brain neurons [19, 20, 21]. IHD and AMI can trigger or accelerate the aging of cerebral vessels by mechanisms that damage these sensitive regulatory systems, while atherosclerosis and neuroinflammation can lead to secondary dysfunction of the neurovascular unit, including neurons, pericytes, astrocytes, endothelial cells and peri-

vascular cells [22, 23], which leads to a violation of homeostasis and the subsequent development of VCD and vascular dementia [24, 25]. Some authors believe that AMI itself can lead to the development and progression of VCD, which is associated primarily with the mechanisms of chronic cerebral hypoperfusion after AMI as a result of a decrease in the left ventricular ejection fraction and a decrease in blood pressure. In addition, chronic cerebral hypoperfusion associated with AMI can initiate mechanisms of neuroinflammation and hyperexpression of pro-inflammatory cytokines in the brain, which causes dysfunction of neurovascular units, changes in metabolism in the brain and the subsequent development of microstructural changes, including white matter damage and gray matter atrophy of the brain [26, 27, 28, 29, 30].

It is known that AMI can cause chronic atrial fibrillation, which is a risk factor for the formation of intracardiac thrombi and subsequent cerebral cardioembolism, which can lead to the formation of subclinically mute myocardial infarctions and ischemic strokes, which, in turn, are associated with VCD and vascular dementia [26]. Finally, cardiogenic shock in patients with AMI can cause acute cerebral hypoperfusion, increasing the risk of heart attacks and microvascular ischemia of the brain [16].

Animal model studies have shown that high levels of oxidative stress at an early stage of AMI remodeling contribute to the loss of neurons and disruption of normal autoregulation mechanisms, contribute to the development of VCD and vascular dementia [31, 32, 33, 34, 35, 36, 37].

Animal studies have also shown that the behavior of mice after AMI repeats the behavior of humans with VCD and vascular dementia [38, 39].

The purpose of this review is to analyze fundamental studies of VCD with using animal models.

2. MATERIAL AND METHODS

A search was conducted for Russian and English-language publications in the databases eLibrary, PubMed, Springer, Web of Science, Clinicalkeys, Scopus, OxfordPress, Cochrain DataBase. The search was carried out using keywords and phrases in Russian and English: cognitive functions; vascular cognitive disorders; experiment; animal model; disease modeling. Full-text articles published between January 2000 and July 2024 were analyzed. A total of 358 publications were analyzed, from which duplicate publications and publications with no access to the full-text version were excluded. In total, this narrative review includes 11 studies that meet the purpose and criteria of the search.

3. RESULTS

As a result of the presented review, we found and analyzed 8 promising animal models of VCD that can be used in fundamental cardiology, including: model of hyperhomocysteinemia (HHC) [40]; model of common carotid artery stenosis [41, 42] and model of hypoperfusion [43] in common carotid artery basin; model of microvascular brain damage [44]; model of chronic hyperglycemia [44, 45]; model of cerebral amyloid angiopathy [41]; model of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [46]; model of chemic-induced cerebral hypoxia [47, 48]. However, only 2 animal models have been used in recent years to study the mechanisms of pathogenesis and develop new approaches to the pharmacotherapy of VCD after AMI, including: a model of unilateral transient occlusion of the coronary artery [49]; a model of coronary atherosclerosis [50].

3.1. Animal Models of Vascular Cognitive Disorders

3.1.1. Model of Hyperhomocysteinemia

The HHC refers to independent modifiable risk factors for CVD and cerebrovascular diseases [40]. At the same time, isolated HHC in rodents is sufficient to simulate VCD in

them [41], which can be achieved by using: 1) genetic models (knockout of genes encoding folate cycle enzymes, including cystathionine beta-synthase and methylenetetrahydrofolate reductase); 2) dietary models with chronic (long-term) deficiency of B vitamins (pyridoxine, cyanocobalamin, folic acid) and/or prolonged excess of methionine for a period of 14 weeks to 6 months. [40]. When transgenic mice of the 3XTg line are kept, which is more often used for the animal model of Alzheimer's type cognitive disorders, the conditions of chronic folate, pyridoxine and cyanocobalamin deficiency are additionally modulated, which is associated with the development of HHC in experimental animals and the development of pronounced memory disorders in them [51]. Chronic excessive administration of methionine to experimental animals leads to pronounced suppression of microglia and moderate HHC, but with chronic deficiency of B vitamins, suppression of microglia activity is insignificant, and HHC is more pronounced. Moderate and severe HHC in rodents are the cause of repeated micro-strokes, chronic neuroinflammation and VCD [52].

3.1.2. Model of Common Carotid Artery Stenosis

Bilateral stenosis of the common carotid arteries (CCA) in rodents is a well-known method for modeling subcortical vascular dementia, which is achieved by positioning microspirals outside the CCA to achieve their variable degree of occlusion. Against the background of the achieved decrease in cerebral blood flow in the carotid basins, the permeability of the BBB increases, microglia is activated, and the level of pro-inflammatory cytokines in ischemic foci increases. The above-mentioned links in the pathogenesis of VCD develop in the period from 3 to 14 days after the procedure, and foci of damage to the white matter form no earlier than 2 weeks later. Hippocampal neurons in the CA1 and CA3 layers, involved in the mechanisms of short-term memory and memory consolidation, undergo atrophy, which leads to the progression of VCD in experimental animals of gray matter over the next 6 months [41]. Unilateral stenosis of the CCA belongs to a less popular model of VCD and subcortical vascular dementia in rodents. In this case, the microspiral is applied only to one of the CCA to achieve a chronic decrease in cerebral blood flow for 7 days. An ameroid constrictor made of hygroscopic casein and a steel shell is applied to the contralateral CCA to achieve a gradual increase in the decrease in blood flow in this vessel until complete occlusion, which develops approximately 28 days after the procedure. As a result, experimental animals develop numerous cerebral infarctions in subcortical areas, microglia are activated, hippocampal neurons die on the side of the constrictor location, which leads to the formation of VCD (violations of spatial working memory, coordination of movements, spontaneous activity) [42].

3.1.3. Model of Hypoperfusion in Common Carotid Artery Basin

Short but repeated periods of decreased cerebral blood flow in the carotid basin can lead to long-term damage to neurons and neuroglia and the development of VCD. Transient hypoperfusion in the basins of four vessels (CCA and vertebral arteries) with a duration of about 10-20 minutes is proposed as an experimental model of VCD in rodents. At the same time, in experimental animals, a pronounced cognitive deficit is achieved against the background of acute death (necrosis) of hippocampal neurons and delayed death (apoptosis) of oligodendrocytes in the cerebral cortex and thalamus. The severity of VCD and associated behavioral disorders in young rodents are less pronounced than in middle-aged animals [43]. However, the problem of this model is the difficulty of translating the results obtained into real clinical practice due to simultaneous bilateral transient hypoperfusion in the carotid and vertebrobasilar basins.

3.1.4. Model of Microvascular Brain Damage

The model of microvascular brain injury is based on the consequences of remodeling of small cerebral vessels under the influence of prolonged elevated blood pressure, which

leads to the development and progression of VCD in experimental animals. For this model, spontaneously hypertensive rats under the age of 10 weeks are used, in which the functioning of the BBB is disrupted, microglia is activated and the white matter of the brain is damaged during the first third of their life, as well as neuroatrophy develops and progresses, intracerebral ventricles expand, the wall of arterioles thickens and perivascular spaces increase, small multiple foci of ischemia and hemorrhages. The clinical symptoms of this VCD model are impaired spatial working memory and attention. However, this model of VCD is characterized by the development and progression of motor disorders, which can have a negative impact on the performance of cognitive tests by experimental animals [44].

3.1.5. Model of Chronic Hyperglycemia

Type 2 diabetes mellitus is a known risk factor for VCD and vascular dementia in humans due to various mechanisms, including the formation of repeated small foci of ischemia and atherosclerotic lesions of cerebral vessels of medium and large caliber [53, 54]. An animal model of VCD has been proposed using the offspring of leptin-resistant rodents (mice) suffering from obesity and diabetes mellitus (db/db) and knockout mice serving as a model of Alzheimer's type cognitive disorders (db/AD) [45]. As a result, the experimental animals develop pronounced VCD by the age of 12 months. Similarly, a VCD model was created in APP23/ob/ob knockout mice, in which the number of axons of cholinergic neurons in the hippocampus is significantly reduced, astrogliosis, neuroinflammation, angiopathy and brain atrophy develop [44].

3.1.6. Model of Cerebral Amyloid Angiopathy

Gooch J. and Wilcock D.M. [41] as an animal model of VCD and vascular dementia, they proposed using an animal model of amyloid angiopathy of the brain, which is characterized by the deposition of β-amyloid in the walls of cerebral vessels, which leads to a gradual narrowing of their lumen, chronic cerebral ischemia and neurodegeneration. In laboratory animals (mice), the authors recreated previously known models of amyloid angiopathy, the essence of which is the hyperexpression of β-amyloid in animals with mutations (Swedish APP, Dutch E22Q, Iowa D23 N, E693Δ Osaka) in the gene encoding this protein. The model proposed by the authors is characterized by the early development of memory disorders, spatial orientation, and impaired executive functions in experimental animals, which are characteristic of people with VCD and vascular dementia [41].

3.1.7. Model of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

The animal model of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is based on knockout of the *Notch3* gene, since this causal mutation is the cause of one of the most common hereditary monogenic diseases associated with recurrent ischemic strokes and the early development of VCD and vascular dementia. In transgenic TgPAC-Notch3R169C mice, multiple segmental ischemic foci of white matter damage are formed without loss of oligodendrocytes [46].

3.1.8. Model of Chemic-Induced Cerebral Hypoxia

The chronic hypoxia model is used by various research groups to study the mechanisms of development and new therapeutic strategies related to VCD and vascular dementia. As is known, chronic hypoxia is one of the important pathogenetic mechanisms of the formation of VCD due to hypoxia, hypercapnia and ischemia. This model consists in the fact that experimental animals (rats – for 12 seconds, mice – for 8 seconds) are surrounded by pure CO_2 (carbon dioxide) and then for 5 minutes in conditions of hypercapnia, which leads to the rapid development of memory disorders and posture maintenance.

Table 1. Animal models of vascular cognitive disorders.

Animal Model of VCD	Methodology	Mechanisms of development of VCD	References
Model of Hyperhomocysteinemia	Variants: 1) Genetic model (knockout of genes encoding folate cycle enzymes, including cystathionine β - synthase and methylenetetrahydrofolate reductase); 2) a dietary model with a chronic deficiency of B vitamins (pyridoxine, cyanocobalamin, folic acid) and/or a prolonged excess of methionine for a period of 14 weeks to 6 months	Moderate HHC on the background of excessive methionine administration in experimental animals leads to pronounced suppression of microglia. Severe HHC in chronic vitamin B deficiency leads to suppression of microglial activity	[40]
Model of Common Carotid Artery Stenosis	Unilateral/bilateral CCA stenosis, which is achieved by placing microspirals outside the CCA	Chronic cerebral decrease in the carotid basin leads to increased BBB permeability, activation of microglia, hyperexpression of pro-inflammatory cytokines in ischemic foci, damage to the white matter of the brain	[41, 42]
Model of Hypoperfusion in Common Carotid Artery Basin	Three-stage occlusion in the basins of four vessels (CCA and vertebral arteries)	Transient global cerebral hypoperfusion leads to the formation of foci of necrosis of hippocampal neurons, apoptosis of oligodendrocytes in the cerebral cortex and thalamus	[43]
Model of Microvascular Brain Damage	Remodeling of small cerebral vessels under the influence of prolonged elevated blood pressure in spontaneously hypertensive rats	Arterial hypertension leads to impaired functioning of the BBB, activation of microglia, damage to white matter, development and progression of neurodegeneration, expansion of intracerebral ventricles, thickening of arteriole walls, expansion of perivascular spaces, formation of multiple small foci of ischemia and hemorrhages	[44]
Model of Chronic Hyperglycemia	Variants: 1) knockout leptin-resistant rodents (mice) suffering from obesity and diabetes mellitus (db/db) 2) knockout mice serving as a model of Alzheimer's type cognitive disorders (db/AD)	Chronic hyperglycemia leads to the formation of multiple small foci of ischemia, atherosclerosis of cerebral vessels of medium and large caliber, the development of astrogliosis, induction of neuroinflammation, progressive angiopathy and neurodegeneration	[44, 45]
Model of Cerebral Amyloid Angiopathy	Hyperexpression of β-amyloid in animals with mutations (Swedish APP, Dutch E22Q, Iowa D23 N, E693Δ Osaka) in the gene encoding this protein	Excessive deposition of β-amyloid in the walls of cerebral vessels leads to progressive narrowing of their lumen, chronic cerebral ischemia and neurodegeneration Excessive deposition of β-amyloid in the walls of cerebral vessels leads to progressive narrowing of their lumen, chronic cerebral ischemia and neurodegeneration Excessive deposition of β-amyloid in the walls of cerebral vessels leads to progressive narrowing of their lumen, chronic cerebral ischemia and neurodegeneration	[41]
Model of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy	Knockout of the *Notch3* gene in rodents	Complete suppression of the expression of the NOTCH3 protein, which plays a key role in the functioning and survival of smooth muscle cells of cerebral vessels, leads to the formation of multiple segmental ischemic foci of white matter damage without loss of oligodendrocytes	[46]
Model of Chemic-Induced Cerebral Hypoxia	Variants: 1) finding an experimental animal surrounded by pure carbon dioxide, followed by staying in hypercapnia conditions 2) three-time stay of an experimental animal surrounded by pure carbon monoxide 3) intraperitoneal administration of sodium nitrite solution	Cerebral hypoxia leads to the accumulation of β-amyloid in the wall of cerebral vessels and neurons, impaired degradation and clearance of β-amyloid, impaired BBB permeability, hyperproduction of tau protein and subsequent neurodegeneration	[47, 55]

Note: *BBB - blood-brain barrier; CCA - common carotid arteries; HHC - hyperhomocyste-inemia.*

A three-time stay of laboratory animals surrounded by pure CO (carbon monoxide) with a duration of one exposure for 1 minute and a break between exposures for one hour is also used as an animal model of chronic hypoxia and VCD [47].

In addition, the use of $NaNO_2$ (sodium nitrite) has been proposed, which leads to disruption of O_2 transport and the development of memory and learning disabilities in experimental animals. Secondary cerebral hypoxia as an animal model of VCD can be achieved using hydroxylamine.

All of the above models of cerebral hypoxia contribute to the accumulation of β-amyloid in the wall of cerebral vessels and neurons, impaired degradation and clearance of β-amyloid, and also lead to impaired BBB permeability and affect the phosphorylation of tau protein, which leads to subsequent neurodegeneration. Hypoxia can have a significant negative effect on cerebral circulation and trigger neuroinflammation processes, which leads to impaired filtration of β–amyloid through the BBB into the systemic circulation and contributes to its accumulation in the brain [48].

3.2. Animal Models of Vascular Cognitive Disorders Associated with Acute Myocardial Infarction

3.2.1. Model of Unilateral Transient Occlusion of Coronary Artery

The model of unilateral transient coronary artery occlusion is used by various research groups to study the mechanisms of development and new therapeutic strategies related to VCD and vascular dementia associated with AMI. This model consists in the fact that in experimental animals (rats) after thoracotomy under general anesthesia, the left anterior coronary artery was clamped for 40 minutes using silk thread and a plastic loop. The achievement of acute myocardial ischemia is verified using an electrocardiogram (ECG) and the presence of epicardial cyanosis. The ligature from the coronary artery is removed 40 minutes after occlusion is achieved to initiate the processes of myocardial reperfusion, after which the chest of the experimental animal is sutured.

An antibiotic (15,000 IU of penicillin G subcutaneously) is used to prevent postoperative infectious complications, and an analgesic (2 mg/kg, 0.2 ml of buprenorphine subcutaneously) is used to treat postoperative pain on the day of surgery and the next day.

Analgesia method: combined anesthesia was achieved with ketamine/xylazine (50 mg/kg and 5 mg/kg intramuscularly, respectively) and was supported by inhalation of 1.5% isoflurane [49].

3.2.2. Model of Coronary Atherosclerosis

The mechanisms of development of atherosclerotic lesions of the coronary arteries consist in the accumulation of oxidized particles of low-density lipoproteins (LDL) in the intima of the artery, which leads to an immune response, as well as the formation and accumulation of foam cells [56].

Atherosclerosis causes narrowing of the coronary vessels, thereby limiting blood flow and reducing the ability of these vessels to expand. The final stage of coronary atherosclerosis usually leads to acute coronary syndrome (ischemia) and AMI without or with the development of acute cerebral ischemia.

Mice usually do not develop coronary atherosclerosis, therefore, transgenic animals with knockout genes *ApoE*, *ApoB* and *LDLr* are used for this model. However, when using these genetic animal models of coronary atherosclerosis, there is a difference in vulnerability between strains to the development of atherosclerosis. At the same time, C57BL/6 transgenic mouse lines are the most susceptible to the inbred strain [57]. As in humans, the severity of atherosclerotic coronary artery disease in these models (mice) depends on long-term use of a diet high in fat and cholesterol. The Paigen diet with or without cholic acid (cholate) content is most often used in such VCD modeling [58].

The ApoE$^{-/-}$ mouse model is a classic model of coronary atherosclerosis. These mice develop severe hypercholesterolemia against the background of using the Paigen diet, followed by atherosclerotic damage to both the coronary arteries and the aorta, pulmonary arteries and carotid arteries. The cardiovascular effects of this animal model have previously been well studied, but only a few publications have used it to model VCD after AMI.

In ApoE$^{-/-}$ mice fed a diet high in fat and cholate for 8 weeks (Paigen diet: 18.5% fat, 0.9% cholesterol, 0.5% cholate, 0.26% sodium), a significant increase in intracerebral expression of vascular adhesion molecules, intercellular adhesion molecules and vascular cell adhesion molecules, which are markers of activation of the endothelium of large and medium-sized vessels [50]. Chronic decrease in blood circulation in these vessels, localized in the cerebral cortex, striatum, thalamus and hippocampus, is one of the leading mechanisms of the development of VCD. In addition, lipid deposition is noted in the walls of cerebral vessels, which leads to the recruitment of leukocytes and activation of microglia, also related to one of the mechanisms of development of VCD.

4. DISCISSION

The presented narrative review demonstrates that the modeling of VCD associated with AMI is carried out using rodents (mice or rats), which normally do not develop atherosclerotic lesions of the coronary vessels. This makes it difficult to translate the results of experimental studies of VCD associated with transferred AMI (**Table 2**) into real clinical practice. In addition, the risk factors and mechanisms for the development of this disease in humans are more complex than in the proposed animal models. On the one hand, the animal model of unilateral transient occlusion of the coronary artery requires thoracotomy under general anesthesia, which may be an additional factor in the development of cognitive disorders associated with the negative effects of intravenous and inhaled central anesthetics [49].

Table 2. Animal Models of Vascular Cognitive Disorders Associated with Acute Myocardial Infarction

Animal Model of VCD	Methodology	Mechanisms of development of VCD	References
Model of Unilateral Transient Occlusion of Coronary Artery	Ligation of the left anterior coronary artery for 40 minutes Anesthesia: combined anesthesia with ketamine/xylazine and isoflurane	Forced swimming test (4 months after AMI) Morris Water Maze test (4 months after AMI)	[49]
Model of Coronary Atherosclerosis	For 8 weeks, laboratory animals are on a high fat/high cholate diet (Paigen diet)	Morris Water Maze test (2 months after AMI)	[50]

Note: *AMI – acute myocardial infarction.*

On the other hand, the animal model of coronary atherosclerosis requires long-term use of the Paigen diet with a regulated content of its components (fatty acids, cholesterol, cholates), which is not feasible in real clinical conditions, since patients with AMI have variable eating behavior and diet.

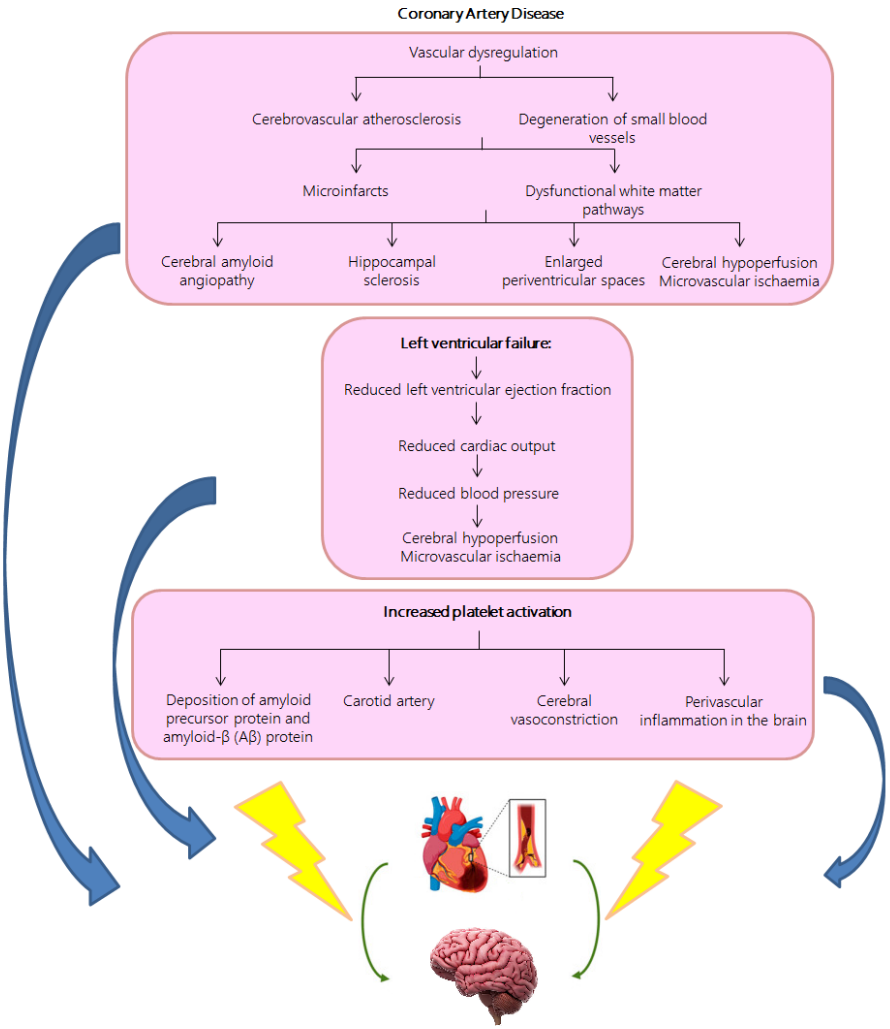
To study the impairment of global cognitive functioning after AMI, the VCD models presented in Table 1 are promising. It is noteworthy that these models are very variable in methodology. Despite the fact that they have not previously been used to study VCD associated with transferred AMI, these models can be used to solve problems of studying the mechanisms of formation of VCD after AMI (**Appendix, Figure 1**).

The interest in these models in experimental cardiology and neurology is explained by the fact that they all lead to impaired functioning of the neurovascular unit in acute myocardial infarction (**Appendix, Figure 2**).

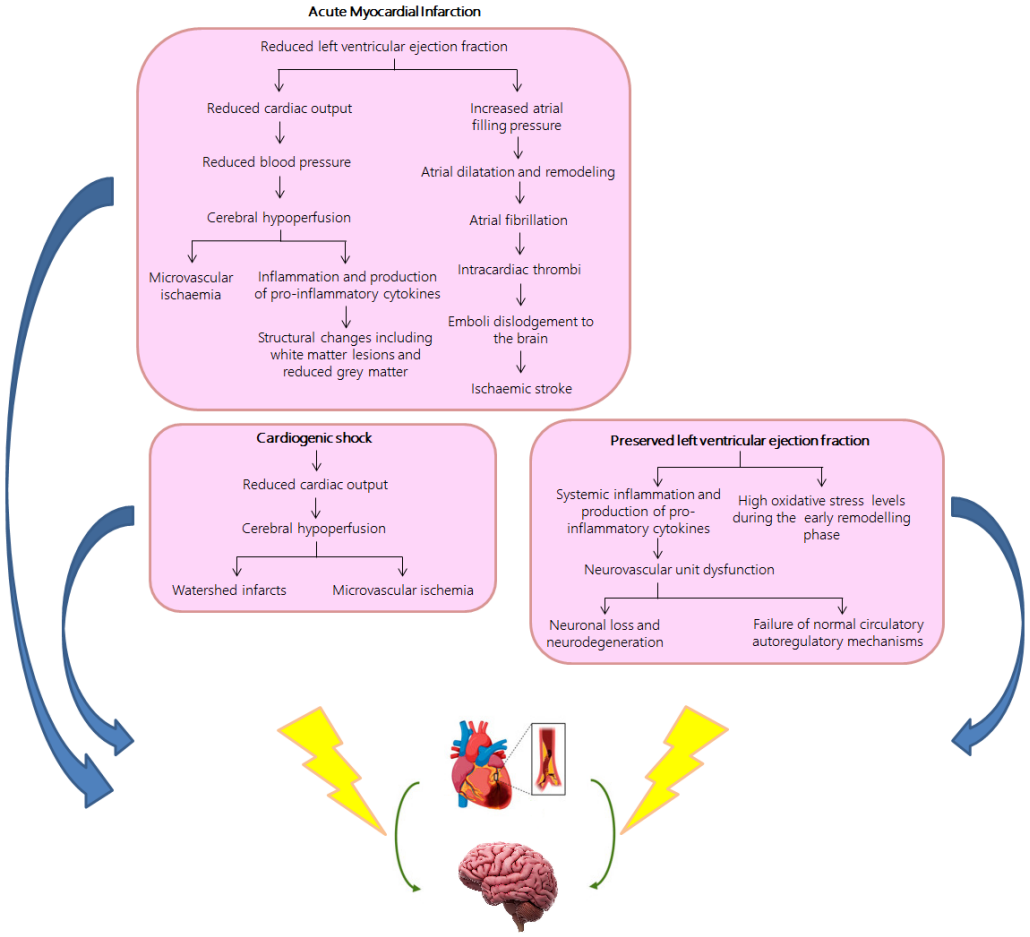
5. CONCLUSION

Modeling VCD after undergoing AMI is a difficult and not yet solved task. Direct transmission of the results of basic research using animal models of this disease is not possible due to the interspecific features of the formation of carotid atherosclerosis, AMI and secondary damage to the neurovascular unit in rodents and humans. Nevertheless, all of the animal models of VCD presented in this review have scientific and clinical interest in experimental cardiology and neurology.

6. APPENDIX



(a)



(b)

Figure 1. Mechanisms of formation of vascular cognitive disorders associated with acute myocardial infarction (Thong E.H.E. [15], modified by Petrov A.V. et al.): (a) – coronary artery disease; (b) – acute myocardial infarction

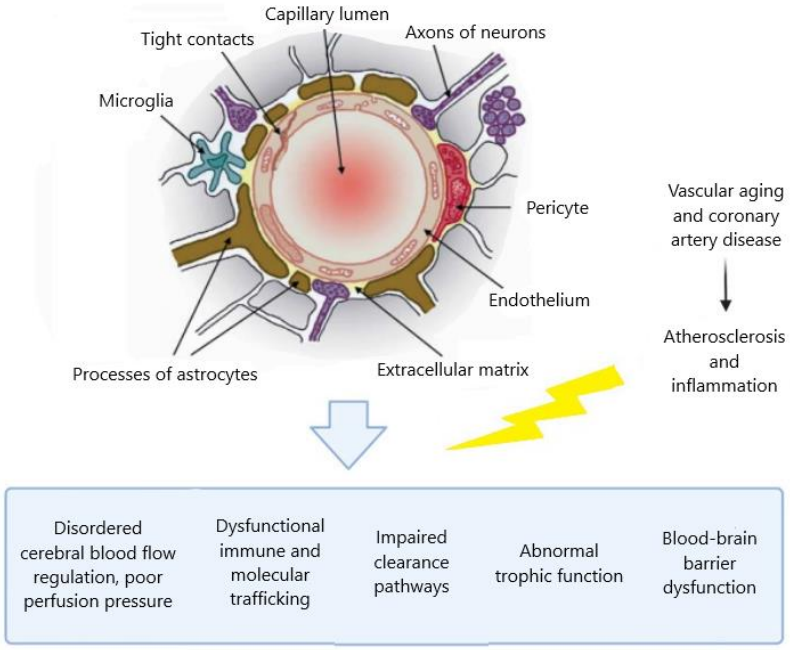


Figure 2. Mechanisms of damage to the neurovascular unit in acute myocardial infarction ([15]., modified by Petrov A.V. et al.)

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