Review Article

Hypertension-Induced Cerebral Small Vessel Disease Leading to Cognitive Impairment

Yang Liu[1,2], Yan-Hong Dong[2], Pei-Yuan Lyu[1,2], Wei-Hong Chen[1,2], Rui Li[1,2]

[1]Graduate School, Hebei Medical University, Shijiazhuang, Hebei 050017, China
[2]Department of Neurology, Hebei General Hospital, Shijiazhuang, Hebei 050051, China

Abstract

Objective: Alzheimer's disease and vascular dementia are responsible for more than 80% of dementia cases. These two conditions share common risk factors including hypertension. Cerebral small vessel disease (CSVD) is strongly associated with both hypertension and cognitive impairment. In this review, we identify the pathophysiological changes in CSVD that are caused by hypertension and further explore the relationship between CSVD and cognitive impairment.

Data Sources: We searched and scanned the PubMed database for recently published literatures up to December 2017. We used the keywords of "hypertension", "cerebral small vessel disease", "white matter lesions", "enlarged perivascular spaces", "lacunar infarcts", "cerebral microbleeds", and "cognitive impairment" in the database of PubMed.

Study Selection: Articles were obtained and reviewed to analyze the hypertension-induced pathophysiological changes that occur in CSVD and the correlation between CSVD and cognitive impairment.

Results: In recent years, studies have demonstrated that hypertension-related changes (e.g., small vascular lesions, inflammatory reactions, hypoperfusion, oxidative stress, damage to autoregulatory processes and the blood-brain barrier, and cerebral amyloid angiopathy) can occur over time in cerebral small vessels, potentially leading to lower cognitive function when blood pressure (BP) control is poor or lacking. Both isolated and co-occurrent CSVD can lead to cognitive deterioration, and this effect may be attributable to a dysfunction in either the cholinergic system or the functionality of cortical and subcortical tracts.

Conclusions: We explore the currently available evidence about the hypertensive vasculopathy and inflammatory changes that occur in CSVD. Both are vital prognostic indicators of the development of cognitive impairment. Future studies should be performed to validate the relationship between BP levels and CSVD progression and between the numbers, volumes, and anatomical locations of CSVD and cognitive impairment.

Key words: Cerebral Microbleeds; Cerebral Small Vessel Disease; Cognitive Impairment; Hypertension

Introduction

Hypertension affects more than 60% of individuals aged 65 years old or older and more than 80% of people aged older than 85 years old.[1] Of note, the brain and its functions are early targets of hypertension-induced organ damage. By 2050, 135.5 million people are predicted to be living with dementia worldwide.[2] This will place a substantial burden on the society, economy, and family happiness. In addition, cerebral small vessel disease (CSVD) can manifest as hypertensive vascular lesions and is a major contributor to cognitive impairment and dementia.[3,4] Despite its devastating effects, the pathogenesis of CSVD and the association between CSVD and cognitive impairment remain incompletely understood. Developing a method to identify cognitive decline early in patients with hypertension may provide a unique opportunity to implement preventive therapies before overt dementia develops. Moreover, silent CSVD, which is usually ignored, is characterized by white matter lesions (WMLs), enlarged perivascular spaces (EPVSs), lacunar infarcts (LIs), and cerebral microbleeds (CMBs). The ability to observe these signs

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.226069

Address for correspondence: Prof. Pei-Yuan Lyu, Department of Neurology, Hebei General Hospital, 348 Heping West Road, Shijiazhuang, Hebei 050051, China
E-Mail: peiyuanlu@163.com

Received: 06-11-2017 **Edited by:** Li-Shao Guo
How to cite this article: Liu Y, Dong YH, Lyu PY, Chen WH, Li R. Hypertension-Induced Cerebral Small Vessel Disease Leading to Cognitive Impairment. Chin Med J 2018;131:615-9.

on magnetic resonance imaging (MRI) has improved over the past decade with advances in neuroimaging. Therefore, in this review, we aimed to evaluate the pathological mechanisms in CSVD that are affected by hypertension and to further explore the relationship between CSVD and cognitive impairment.

White Matter Lesion

WML or WM hyperintensities are usually located around the ventricles, especially close to the ventricular horns. WML is defined as hyperintensities on fluid-attenuated inversion recovery (FLAIR) and proton density/T2-weighted images, without prominent hypointensity on T1-weighted images.[5] WML refers to the entire spectrum of such lesions from mild perivascular tissue damage surrounding the lipohyalinotic arterioles which result in minimal axonal loss, to more severe ischemic damage, which can cause extensive myelin and axonal loss.[6]

It is generally thought that the most important risk factors for WML progression are age and hypertension.[7] On the one hand, long-term hypertension results in lipohyalinosis of the media and thickening of the vessel walls, and narrowing of the lumen of the arterioles and small perforating arteries that are derived from cortical and leptomeningeal arteries and nourish the deep WM.[8] On the other hand, hypertension increases blood vessel fibrosis, altering the distribution of Type 4 collagen and other extracellular matrix and resulting in stiffening of the vessel walls and a reduction in cerebral blood flow (CBF), especially at times of increased need.[9] It has previously been reported that hypertension modifies the relationship between amyloid and WML, in that patients with either current or past evidence of hypertension have more WML for a given burden of amyloid.[10] High systolic blood pressure (SBP) stiffens aortic roots, favoring upstream left ventricular hypertrophy and downstream WML as a result of an increase in the intensity of the propagation of pulse waves to the smallest cerebral vessels.[11] Furthermore, the deep WM has a watershed-like blood supply and is therefore more vulnerable than other regions' impairment in CBF. This suggests that hypoperfusion and hypoxia may be early features of the development of WML.[12,13] Interestingly, hypertension influences the autoregulation of CBF by narrowing the range of the autoregulatory process instead of its speed, resulting in a steeper CBF–BP curve.[14]

Both the occurrence and the progression of WML are associated with cognitive decline, dementia, stroke, and mortality.[15] A longitudinal cohort study conducted over 4 years by Uiterwijk *et al*.[16] suggested that, in hyperintensive patients, the progression of periventricular WML was related to cognitive impairment (especially executive function), whereas there was no association between baseline periventricular WML and cognitive dysfunction. Thus, preventing the progression of WML should be emphasized as a therapeutic goal in hypertensive patients. Moreover, WML-associated reductions in gray matter volume were significantly more substantial and executive function, and memory was worse in uncontrolled hypertensives than in normotensives.[6] In addition, cognitive decline was more associated with the degree of periventricular WML than that of subcortical WML. Intriguingly, the former may disrupt the long associative tracts that connect more distant cortical areas, whereas the latter may cause more limited damage to short cortico-cortical connections.[16] A recent study based on a three-dimensional FLAIR showed that performance on the Mini Mental State Examination (MMSE) was associated with an increase in the total WML volume. However, only parietal WML volumes were independently correlated with Montreal Cognitive Assessment scores.[17] The effects of WML on memory are fully mediated by acetylcholinesterase activity. Data suggest that the effect of WML on the dysfunction of the cholinergic system in Alzheimer's disease (AD) patients with mild cognitive impairment (MCI) depends on the WML distribution.[18] The results of this study suggest that further pharmacological studies are warranted to explore whether WML influences responses to cholinergic treatment. For example, Blume *et al*.[19] found that, in Parkinson's disease, a higher WML volume was associated with the rapid onset of dementia within the 1st year of treatment with deep brain stimulation. In contrast, a previous study failed to find a relationship between total WML volume and MMSE performance.[20] Future studies should be performed to validate the relationship between WML volume and cognitive impairment, and these studies should extend their follow-up periods as long as possible.

Enlarged Perivascular Spaces

Perivascular spaces surround perforating arterioles and venules as they course from the subarachnoid space through the brain parenchyma and serve as an important drainage system for interstitial fluids and solutes in the brain. EPVS, also known as Virchow–Robin spaces, are most likely to be identified in T2-weighted MRI and are characterized by punctate or linear signal intensities similar to cerebrospinal fluids.[21,22]

Long-term hypertension damages the blood vessels and initiates the expression of hypoxia-sensitive genes (HIF-1α, *etc*.) and molecular cascades during its hypoxic phase. Inflammation is ultimately induced by the release of cytokines, inflammatory matrix metalloproteinases, and cyclooxygenase-2, and these, in turn, open the blood-brain barrier (BBB) resulting in the induction of the expression of adhesion molecules in endothelial cells and thereby contributing to leukocyte and platelet adhesion and microvascular occlusion.[13,23,24] The disarrangement of the BBB leads to the leakage of plasma components through the BBB into the vessel wall and perivascular space, and this is thought to cause EPVS.[25,26] Although Yao *et al*.[27] previously suggested that hypertension may promote the development of EPVS throughout the brain including the basal ganglia (BG) and WM in addition to the hippocampus. Multiple recent studies that have focused on the association

between ambulatory BP levels and EPVS have found that higher SBP levels are independently associated with EPVS in the BG but not the WM. These results support the notion that EPVS in the BG may be a marker of CSVD.[22,28] The results of a prospective cohort study showed that WM-EPVS was associated with cerebral amyloid angiopathy (CAA) and superficial siderosis.[29] Conversely, a prospective, multicenter, hospital-based study published by Zhang *et al*.[30] showed that hypertension was an independent risk factor for EPVS in WM but not in BG or hippocampus. Future studies should further explore the relationship between BP levels and EPVS progression.

Patients with a high degree of EPVS at baseline experience greater declines in processing speed and have an increased likelihood of developing vascular dementia.[31] Huijts *et al*.[32] conducted a 5-year study of 189 patients with a high risk of CSVD and found that an increase in BG-EPVS was associated with a decrease in information processing speed and that this relationship was independent of age and WML. In addition, a study conducted by Arba *et al*.[33] revealed that the total EPVS number was not associated with cognitive impairment. While a case report published in 2017 suggested that widespread enlarged PVS could potentially cause neurological deficits and that the effect of EPVS on perivascular circulation could lead to focal brain dysfunction.[34] However, in patients with different degrees of CSVD, BG-EPVS seemed to depend on the presence of other markers of CSVD.[35] In addition, Yao *et al*.[27] surprisingly failed to find any significant association between the load of hippocampal load of EPVS and baseline cognitive performance or incident dementia over an 8-year follow-up period, although functional and structural changes in the hippocampus have long been demonstrated to play critical roles in memory, learning, and cognitive impairments.[36] Hence, the presence of EPVS in different anatomic sites indicates different levels of clinical significance.

Lacunar Infarct

LI is defined as infarction lesions of 3–15 mm in diameter that are located in the internal capsule, BG, corona radiata, thalamus, or brainstem and are caused by the occlusion of a perforating artery.[37]

These LIs are rarely fatal during the acute phase, and there is, therefore, a paucity of pathological data regarding this condition. While hypertension is the principal risk factor for stroke, it may be even more important in LI than large artery atherosclerosis and non-LIs with the same clinical severity.[38,39] A growing amount of evidence suggests that the anatomical location of LI is important to its etiology. Hypertension and an increasing WML volume independent of other vascular risk factors are significant risk factors for new LI in the deep WM. However, hyperhomocysteinemia has been associated an increased risk of LI in the BG, and hyperlipidemia always leads to isolated LI in the deep gray nuclei/internal capsule.[40,41] In patients with diabetes, LI is more frequently caused by branch orifice atheromatous disease than hypertensive arteriopathy, the latter of which is the predominant vascular pathology underlying strictly deep/mixed CMB.[42]

LI is usually considered benign and appropriate secondary preventive measures are, therefore, often neglected despite the fact that LI is associated with a higher risk of subsequent stroke and dementia.[37] Indeed, the impact of CSVD on dementia could be much more substantial than the impact of cerebral large vessel disease. A prospective cohort study conducted by Kitagawa *et al*.[43] revealed that the incidence of dementia was more substantially affected by the presence of LI than carotid stenosis. One key complication associated with this condition might be diffuse cerebrovascular endothelial failure, which leads to BBB damage, local inflammation, and reduced CBF as a result of the loss of autoregulation. A study that focusing on BP and poststroke cognitive impairment found that high home BP and multiple LI were significantly independent predictors for the progression of both cognitive impairment and stroke recurrence.[44] Finally, the Ohasama study revealed that, at a 7-year follow-up appointment, LI was a better indicator than WML of declines in motivation, interest, and reaction to the environment.[45]

Cerebral Microbleed

CMB, cerebral microhemorrhages, refers to homogeneous, small (<10 mm in diameter), round, or ovoid hypointensities evident on susceptibility-weighted imaging or T2* Gradient-Recall Echo MRI sequences. These signs correspond to areas of hemosiderin deposits that are themselves caused by the prior leakage of blood from small arteries, arterioles, and/or capillaries.[46]

Kwon *et al*.[47] focused on hypertensive stroke patients and found that exposure of the vascular endothelium to sustained hypertensive stress, particularly during reverse dipping at night, could be a rational explanation for the higher prevalence of CMB. Previous data showed that hypertension increases the expression of the cytokine tumor necrosis factor-α (TNF-α),[48] which is a pivotal regulatory cytokine that is secreted primarily by macrophages/microglia, the main cell types found to underlie CMB in pathologic/autopsy samples. In addition, a higher level of TNF receptor 2 promotes the pathogenesis of CMB.[49] The results of The Atherosclerosis Risk in Communities Study indicated that hypertensive disease (indicated by LI and WML) may contribute to deep or mixed-deep and lobar CMB, whereas CAA may drive the development of lobar-only CMB.[50] Indeed, hypertension may also be a causative factor for future CAA-related hemorrhages, which act synergistically on recurrent stroke in patients with strictly lobar CMB.[51] Alternatively, Jia *et al*.[52] found that hypertension increased the risk of CMB in the territory near the posterior cerebral artery (in the temporal, parietal, and occipital lobe) and deep and infratentorial locations.

The results of the population-based AGES–Reykjavik Study suggested that hypertensive vasculopathy and the

combined effects of hypertensive and CAA play roles in the pathogenesis of cognitive deterioration.[53] They also found that patients with ≥3 CMB exhibited steeper declines in a composite measure of global cognitive function, memory, and speed than did those without CMB. In addition, deep and mixed CMB was associated with memory, whereas strictly lobar CMB was associated with speed and visuospatial executive functions.[53,54] Nevertheless, Heringa *et al*.[55] reported that there was no difference in cognitive functions between patients without CMB and those with ≥1 or ≥3 CMB. Furthermore, Rabelo *et al*.[56] also reported that, in mild AD patients, those with amnestic MCI, and cognitively normal elderly subjects, there was no significant difference between groups with and without CMB, indicating that CMB is not a good candidate neuroimaging biomarker for these diseases, especially in their early phases. Longitudinal studies may provide more robust information about CMB progression and its prognostic clinical significance. Multiple CMB (≥3) may disrupt connections between functionally important cortical and subcortical tracts that are critical for cognitive processes, ultimately damaging these neural networks and interfering with cognition. However, the direct impact of CMB on cognitive functions appears to be limited.[55]

Conclusion

Studies in the literature have confirmed that multiple hypertensive vasculopathies and changes in inflammatory status play pivotal roles in the pathological mechanisms underlying CSVD. The neuroimaging markers for CSVD, including WML, EPVS, LI, and CMB, have independent or combined effects on cognitive impairment. Therefore, in patients with CSVD, carefully monitoring and treating hypertension may provide a benefit by preventing cognitive impairment. More attention should be paid to this issue, and targeted efforts are needed to increase our understanding of the relationship between BP levels and CSVD progression and between the numbers, volumes, and anatomical locations of CSVD and cognitive impairment.

Financial support and sponsorship

This study was supported by the grants from the Science & Technology Pillar Program of Hebei Province, China (No. 14277787D), and the Science & Technology Plan Program of Hebei Province, China (No. 16397795D).

Conflicts of interest

There are no conflicts of interest.

References

1. Banegas JR, Graciani A, de la Cruz-Troca JJ, León-Muñoz LM, Guallar-Castillón P, Coca A, *et al.* Achievement of cardiometabolic goals in aware hypertensive patients in Spain: A nationwide population-based study. Hypertension 2012;60:898-905. doi: 10.1161/HYPERTENSIONAHA.112.19308.
2. Robinson L, Tang E, Taylor JP. Dementia: Timely diagnosis and early intervention. BMJ 2015;350:h3029. doi: 10.1136/bmj.h3029.
3. Rouhl RP, Mertens AE, van Oostenbrugge RJ, Damoiseaux JG, Debrus-Palmans LL, Henskens LH, *et al.* Angiogenic T-cells and putative endothelial progenitor cells in hypertension-related cerebral small vessel disease. Stroke 2012;43:256-8. doi: 10.1161/STROKEAHA.111.632208.
4. De Silva TM, Miller AA. Cerebral small vessel disease: Targeting oxidative stress as a novel therapeutic strategy? Front Pharmacol 2016;7:61. doi: 10.3389/fphar.2016.00061.
5. Teng Z, Dong Y, Zhang D, An J, Lv P. Cerebral small vessel disease and post-stroke cognitive impairment. Int J Neurosci 2017;127:824-30. doi: 10.1080/00207454.2016.1261291.
6. Kern KC, Wright CB, Bergfield KL, Fitzhugh MC, Chen K, Moeller JR, *et al.* Blood pressure control in aging predicts cerebral atrophy related to small-vessel white matter lesions. Front Aging Neurosci 2017;9:132. doi: 10.3389/fnagi.2017.00132.
7. Mok V, Kim JS. Prevention and management of cerebral small vessel disease. J Stroke 2015;17:111-22. doi: 10.5853/jos.2015.17.2.111.
8. Pantoni L, Garcia JH. The significance of cerebral white matter abnormalities 100 years after Binswanger's report. A review. Stroke 1995;26:1293-301. doi: 10.1161/01.STR.26.7.1293.
9. Faraco G, Iadecola C. Hypertension: A harbinger of stroke and dementia. Hypertension 2013;62:810-7. doi: 10.1161/HYPERTENSIONAHA.113.01063.
10. Scott JA, Braskie MN, Tosun D, Thompson PM, Weiner M, DeCarli C, *et al.* Cerebral amyloid and hypertension are independently associated with white matter lesions in elderly. Front Aging Neurosci 2015;7:221. doi: 10.3389/fnagi.2015.00221.
11. Muscari A, Faccioli L, Ghinelli M, Napoli C, Pirazzoli E, Puddu GM, *et al.* Hypertension and other determinants of white matter lesions in stroke patients. J Clin Hypertens (Greenwich) 2016;18:907-12. doi: 10.1111/jch.12788.
12. O'Sullivan M, Lythgoe DJ, Pereira AC, Summers PE, Jarosz JM, Williams SC, *et al.* Patterns of cerebral blood flow reduction in patients with ischemic leukoaraiosis. Neurology 2002;59:321-6. doi: 10.1212/WNL.59.3.321.
13. Rosenberg GA. Extracellular matrix inflammation in vascular cognitive impairment and dementia. Clin Sci (Lond) 2017;131:425-37. doi: 10.1042/CS20160604.
14. Novak V, Hajjar I. The relationship between blood pressure and cognitive function. Nat Rev Cardiol 2010;7:686-98. doi: 10.1038/nrcardio.2010.161.
15. Kloppenborg RP, Nederkoorn PJ, Geerlings MI, van den Berg E. Presence and progression of white matter hyperintensities and cognition: A meta-analysis. Neurology 2014;82:2127-38. doi: 10.1212/WNL.0000000000000505.
16. Uiterwijk R, Staals J, Huijts M, de Leeuw PW, Kroon AA, van Oostenbrugge RJ, *et al.* MRI progression of cerebral small vessel disease and cognitive decline in patients with hypertension. J Hypertens 2017;35:1263-70. doi: 10.1097/HJH.0000000000001294.
17. Ai Q, Pu YH, Sy C, Liu LP, Gao PY. Impact of regional white matter lesions on cognitive function in subcortical vascular cognitive impairment. Neurol Res 2014;36:434-43. doi: 10.1179/1743132814Y.0000000354.
18. Richter N, Michel A, Onur OA, Kracht L, Dietlein M, Tittgemeyer M, *et al.* White matter lesions and the cholinergic deficit in aging and mild cognitive impairment. Neurobiol Aging 2017;53:27-35. doi: 10.1016/j.neurobiolaging.2017.01.012.
19. Blume J, Lange M, Rothenfusser E, Doenitz C, Bogdahn U, Brawanski A, *et al.* The impact of white matter lesions on the cognitive outcome of subthalamic nucleus deep brain stimulation in Parkinson's disease. Clin Neurol Neurosurg 2017;159:87-92. doi: 10.1016/j.clineuro.2017.05.023.
20. Delano-Wood L, Abeles N, Sacco JM, Wierenga CE, Horne NR, Bozoki A, *et al.* Regional white matter pathology in mild cognitive impairment: Differential influence of lesion type on neuropsychological functioning. Stroke 2008;39:794-9. doi: 10.1161/STROKEAHA.107.502534.
21. Potter GM, Doubal FN, Jackson CA, Chappell FM, Sudlow CL, Dennis MS, *et al.* Enlarged perivascular spaces and cerebral small vessel disease. Int J Stroke 2015;10:376-81. doi: 10.1111/ijs.12054.
22. Yang S, Qin W, Yang L, Fan H, Li Y, Yin J, *et al.* The relationship between ambulatory blood pressure variability and enlarged

perivascular spaces: A cross-sectional study. BMJ Open 2017;7:e015719. doi: 10.1136/bmjopen-2016-015719.
23. Iadecola C. The pathobiology of vascular dementia. Neuron 2013;80:844-66. doi: 10.1016/j.neuron.2013.10.008.
24. Wallin A, Ohrfelt A, Bjerke M. Characteristic clinical presentation and CSF biomarker pattern in cerebral small vessel disease. J Neurol Sci 2012;322:192-6. doi: 10.1016/j.jns.2012.07.068.
25. Doubal FN, MacLullich AM, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. Stroke 2010;41:450-4. doi: 10.1161/STROKEAHA.109.564914.
26. Wardlaw JM. Blood-brain barrier and cerebral small vessel disease. J Neurol Sci 2010;299:66-71. doi: 10.1016/j.jns.2010.08.042.
27. Yao M, Zhu YC, Soumaré A, Dufouil C, Mazoyer B, Tzourio C, *et al.* Hippocampal perivascular spaces are related to aging and blood pressure but not to cognition. Neurobiol Aging 2014;35:2118-25. doi: 10.1016/j.neurobiolaging.2014.03.021.
28. Yang S, Yuan J, Zhang X, Fan H, Li Y, Yin J, *et al.* Higher ambulatory systolic blood pressure independently associated with enlarged perivascular spaces in basal ganglia. Neurol Res 2017;39:787-94. doi: 10.1080/01616412.2017.1324552.
29. Charidimou A, Boulouis G, Pasi M, Auriel E, van Etten ES, Haley K, *et al.* MRI-visible perivascular spaces in cerebral amyloid angiopathy and hypertensive arteriopathy. Neurology 2017;88:1157-64. doi: 10.1212/WNL.0000000000003746.
30. Zhang C, Chen Q, Wang Y, Zhao X, Wang C, Liu L, *et al.* Risk factors of dilated Virchow-Robin spaces are different in various brain regions. PLoS One 2014;9:e105505. doi: 10.1371/journal.pone.0105505.
31. Ding J, Sigurðsson S, Jónsson PV, Eiriksdottir G, Charidimou A, Lopez OL, *et al.* Large perivascular spaces visible on magnetic resonance imaging, cerebral small vessel disease progression, and risk of dementia: The age, gene/Environment susceptibility-Reykjavik study. JAMA Neurol 2017;74:1105-12. doi: 10.1001/jamaneurol.2017.1397.
32. Huijts M, Duits A, Staals J, Kroon AA, de Leeuw PW, van Oostenbrugge RJ, *et al*. Basal ganglia enlarged perivascular spaces are linked to cognitive function in patients with cerebral small vessel disease. Curr Neurovasc Res 2014;11:136-41. doi: 10.2174/1567202611666140310102248.
33. Arba F, Quinn TJ, Hankey GJ, Lees KR, Wardlaw JM, Ali M, *et al.* Enlarged perivascular spaces and cognitive impairment after stroke and transient ischemic attack. Int J Stroke 2018;13:47-56. doi: 10.1177/1747493016666091.
34. Taniguchi D, Shimura H, Watanabe M, Hattori N, Urabe T. Widespread enlarged perivascular spaces associated with dementia and focal brain dysfunction: Case report. BMC Neurol 2017;17:210. doi: 10.1186/s12883-017-0997-9.
35. Riba-Llena I, Nafría C, Mundet X, López-Rueda A, Fernández-Cortiñas I, Jarca CI, *et al.* Assessment of enlarged perivascular spaces and their relation to target organ damage and mild cognitive impairment in patients with hypertension. Eur J Neurol 2016;23:1044-50. doi: 10.1111/ene.12979.
36. Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, *et al.* Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 2011;472:466-70. doi: 10.1038/nature09817.
37. Li Y, Liu N, Huang Y, Wei W, Chen F, Zhang W, *et al.* Risk factors for silent lacunar infarction in patients with transient ischemic attack. Med Sci Monit 2016;22:447-53. doi: 10.12659/MSM.895759.
38. Lv P, Jin H, Liu Y, Cui W, Peng Q, Liu R, *et al.* Comparison of risk factor between lacunar stroke and large artery atherosclerosis stroke: A Cross-sectional study in china. PLoS One 2016;11:e0149605. doi: 10.1371/journal.pone.0149605.
39. Altmann M, Thommessen B, Rønning OM, Reichenbach AS, Fure B. Blood pressure differences between patients with lacunar and nonlacunar infarcts. Brain Behav 2015;5:e00353. doi: 10.1002/brb3.353.
40. Kloppenborg RP, Nederkoorn PJ, Grool AM, De Cocker LJ, Mali WP, van der Graaf Y, *et al.* Do lacunar infarcts have different aetiologies? Risk factor profiles of lacunar infarcts in deep white matter and basal ganglia: The second manifestations of ARTerial disease-magnetic resonance study. Cerebrovasc Dis 2017;43:161-8. doi: 10.1159/000454782.
41. Rutten-Jacobs LCA, Markus HS, UK Young Lacunar Stroke DNA Study. Vascular risk factor profiles differ between magnetic resonance imaging-defined subtypes of younger-onset lacunar stroke. Stroke 2017;48:2405-11. doi: 10.1161/STROKEAHA.117.017813.
42. Shoamanesh A, Pearce LA, Bazan C, Catanese L, McClure LA, Sharma M, *et al.* Microbleeds in the secondary prevention of small subcortical strokes trial: Stroke, mortality, and treatment interactions. Ann Neurol 2017;82:196-207. doi: 10.1002/ana.24988.
43. Kitagawa K, Miwa K, Yagita Y, Okazaki S, Sakaguchi M, Mochizuki H, *et al.* Association between carotid stenosis or lacunar infarction and incident dementia in patients with vascular risk factors. Eur J Neurol 2015;22:187-92. doi: 10.1111/ene.12553.
44. Yamamoto Y, Nagakane Y, Tomii Y, Akiguchi I. High morning and bedtime home blood pressures strongly predict for post-stroke cognitive impairment. J Stroke Cerebrovasc Dis 2016;25:1856-63. doi: 10.1016/j.jstrokecerebrovasdis.2016.04.001.
45. Tsubota-Utsugi M, Satoh M, Tomita N, Hara A, Kondo T, Hosaka M, *et al.* Lacunar infarcts rather than white matter hyperintensity as a predictor of future higher level functional decline: The Ohasama study. J Stroke Cerebrovasc Dis 2017;26:376-84. doi: 10.1016/j.jstrokecerebrovasdis.2016.09.036.
46. Yates PA, Villemagne VL, Ellis KA, Desmond PM, Masters CL, Rowe CC, *et al.* Cerebral microbleeds: A review of clinical, genetic, and neuroimaging associations. Front Neurol 2014;4:205. doi: 10.3389/fneur.2013.00205.
47. Kwon HM, Lim JS, Kim YS, Moon J, Park H, Kim HY, *et al.* Cerebral microbleeds are associated with nocturnal reverse dipping in hypertensive patients with ischemic stroke. BMC Neurol 2014;14:8. doi: 10.1186/1471-2377-14-8.
48. Granger JP. An emerging role for inflammatory cytokines in hypertension. Am J Physiol Heart Circ Physiol 2006;290:H923-4. doi: 10.1152/ajpheart.01278.2005.
49. Shoamanesh A, Preis SR, Beiser AS, Vasan RS, Benjamin EJ, Kase CS, *et al.* Inflammatory biomarkers, cerebral microbleeds, and small vessel disease: Framingham heart study. Neurology 2015;84:825-32. doi: 10.1212/WNL.0000000000001279.
50. Graff-Radford J, Simino J, Kantarci K, Mosley TH Jr. Griswold ME, Windham BG, *et al.* Neuroimaging correlates of cerebral microbleeds: The ARIC study (Atherosclerosis risk in communities). Stroke 2017;48:2964-72. doi: 10.1161/STROKEAHA.117.018336.
51. Dumas A, Dierksen GA, Gurol ME, Halpin A, Martinez-Ramirez S, Schwab K, *et al.* Functional magnetic resonance imaging detection of vascular reactivity in cerebral amyloid angiopathy. Ann Neurol 2012;72:76-81. doi: 10.1002/ana.23566.
52. Jia Z, Mohammed W, Qiu Y, Hong X, Shi H. Hypertension increases the risk of cerebral microbleed in the territory of posterior cerebral artery: A study of the association of microbleeds categorized on a basis of vascular territories and cardiovascular risk factors. J Stroke Cerebrovasc Dis 2014;23:e5-11. doi: 10.1016/j.jstrokecerebrovasdis.2012.12.016.
53. Ding J, Sigurðsson S, Jónsson PV, Eiriksdottir G, Meirelles O, Kjartansson O, *et al.* Space and location of cerebral microbleeds, cognitive decline, and dementia in the community. Neurology 2017;88:2089-97. doi: 10.1212/WNL.0000000000003983.
54. Chung CP, Chou KH, Chen WT, Liu LK, Lee WJ, Chen LK, *et al.* Strictly lobar cerebral microbleeds are associated with cognitive impairment. Stroke 2016;47:2497-502. doi: 10.1161/STROKEAHA.116.014166.
55. Heringa SM, Reijmer YD, Leemans A, Koek HL, Kappelle LJ, Biessels GJ, *et al.* Multiple microbleeds are related to cerebral network disruptions in patients with early Alzheimer's disease. J Alzheimers Dis 2014;38:211-21. doi: 10.3233/JAD-130542.
56. Rabelo AG, Teixeira CV, Magalhães TN, Carletti-Cassani AFM, Amato Filho AC, Joaquim HP, *et al.* Is cerebral microbleed prevalence relevant as a biomarker in amnestic mild cognitive impairment and mild Alzheimer's disease? Neuroradiol J 2017;30:477-85. doi: 10.1177/1971400917720465.

高血压相关性脑小血管病引起认知障碍

摘要

目的：80%痴呆为阿尔茨海默病和/或血管性痴呆，两者的共同危险因素包括高血压。脑小血管病（cerebral small vessel disease，CSVD）与高血压和认知功能障碍均密切相关。本文对高血压引起CSVD的病理机制及CSVD与认知功能障碍的额关系进行综述，以期更好的了解CSVD与高血压、认知障碍的关系。

方法：通过使用高血压、脑小血管病、白质病变、扩大的血管周围间隙、腔隙性脑梗塞、脑微出血和认知障碍等关键词检索PubMed数据库最新文献。对相关文章进行回顾分析，整理并分析高血压引起CSVD的病理生理变化及CSVD与认知障碍的关系。

结果：近年研究表明，高血压相关性病理改变：小血管病变、炎症反应、氧化应激、低灌注，自身调节障碍，血脑屏障破坏及脑淀粉样血管病等可致CSVD，进而引起认知功能障碍。血压控制欠佳时，单一或多种CSVD可致认知功能下降，这种作用可能是由于胆碱能系统功能障碍或皮质与皮质下传导束功能紊乱所致。

结论：高血压相关性血管病变和炎症反应可引起CSVD。两者均是认知功能障碍发展的重要预后指标。不同解剖部位CSVD，CSVD数量等对认知功能领域的影响尚存在争议。血压水平与EPVS的发生发展，CSVD数量、体积及解剖位置的变化与认知功能障碍的关系需进一步探索。