·脑卒中研究进展·

脑小血管病血流动力学损害研究进展

刘娜 薛扬 唐杰 张苗怡 任雪 付建辉

【摘要】 脑血流动力学损害是小动脉硬化型脑小血管病发病机制的重要环节，包括血压变异性升高、血管搏动性改变、脑血流量降低等，并可能通过加重内皮功能障碍、血-脑屏障破坏等使疾病进展加快。本文对小动脉硬化型脑小血管病血流动力学损害进展进行综述。

【关键词】 大脑小血管疾病； 血流动力学； 综述

Research progress of impaired cerebral hemodynamics in cerebral small vessel disease

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【Abstract】 Cerebral hemodynamic damage is an important mechanism in the pathogenesis of arteriolosclerotic cerebral small vessel disease (CSVD). The hemodynamic damage of cerebral small vessel disease includes the changes of blood pressure variability (BPV), vascular pulsatility, cerebral blood flow (CBF) and so on. Impaired cerebral hemodynamics may promote the progression of the disease by aggravating the damage of endothelial dysfunction and the disruption of blood-brain barrier (BBB). This paper reviews progress of impaired cerebral hemodynamics in arteriolosclerotic cerebral small vessel disease.

【Key words】 Cerebral small vessel diseases; Hemodynamics; Review

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脑小血管病（CSVD）系指各种原因导致的颅内小血管病变引起的缺血性或出血性病变，可累及小动脉、微动脉、毛细血管和小静脉。典型影像学改变包括腔隙性梗死（LACI）、脑微出血（CMBs）、扩大的血管周围间隙（EPVS）、脑白质高信号（WMH）等。以高血压和老龄为主要危险因素的小动脉硬化型脑小血管病为最常见类型[1]，其血管重构的主要病理学表现为小动脉管壁增厚、内径减小同时伴纤维素样坏死、脂质透明样变、血管平滑肌细胞丢失、各型细胞外基质（ECM）在小动脉管壁沉积增加等[1-2]。脑小血管病的发病机制目前尚未明确，阻碍了动物模型的建立以及有效治疗方法的探索。目前认为，血-脑屏障破坏和内皮功能障碍是高血压相关脑小血管病发病机制的重要环节[3]。近年来，高血压和老龄相关的血流动力学改变在脑小血管病发生发展中的作用逐渐被认识，血流动力学改变可进一步加重血-脑屏障破坏和内皮功能障碍，最终加速脑小血管病进展。本文重点阐述小动脉硬化型脑小血管病血流动力学损害的研究进展。

一、血压变异性改变

人体血压日常呈一定节律性波动，单一静态血压并不能完全反映整体血压情况，仅以静态血压作为观察或治疗目标相对局限[4-5]。血压变异性（BPV）是反映血压在一定时间内波动的指标，根据监测时间可以分为超短期（每个心动周期内）、短期（24小时内）、中期（day by day）和长期（随访间）4种类型，其中，通过24小时动态血压监测（ABPM）计算短期血压变异性广泛应用于临床，观察指标包括标准差（SD）、变异系数（CV）、平均真实变异性（ARV）

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等。研究显示，血压变异性升高与脑小血管病进展密切相关[4-5]。Filomena等[6]对487例无症状性原发性高血压患者的观察显示，24小时平均真实变异性（*OR* = 1.16，95%CI：1.02～1.33；*P* = 0.024）和夜间平均真实变异性（*OR* = 1.11，95%CI：1.02～1.22；*P* = 0.020）升高是腔隙性梗死和脑白质高信号的危险因素。Yang等[7]发现，基底节区扩大的血管周围间隙严重程度与血压变异性升高呈正相关（*P* < 0.05）。de Heus等[4]指出，收缩期变异系数升高是脑小血管病总负荷增加的危险因素（*OR* = 1.29，95%CI：1.04～1.60；*P* = 0.022）。Liu等[8]的前瞻性研究显示，血压变异性升高是脑深部和幕下区域脑微出血进展的独立预测因素（*P* < 0.05）。血压变异性升高与脑小血管病进展的相关性可能与脑组织供血稳态失衡有关。脑小血管病患者常伴有脑血流自动调节（CA）能力下降，脑血管反应性（CVR）降低，神经血管单元（NVU）损害，血压变异性升高即血压波动增强，进一步增加了患者维持脑组织供血稳态的难度，使脑低灌注或血管壁机械应力超负荷的发生更加频繁[4]，从而加剧脑小血管病进展。值得注意的是，血压变异性改变也可能是脑小血管病进展的结果，血压变异性受自主神经系统的调节，而脑小血管病可影响自主神经调控相关脑区和神经环路，导致交感神经-副交感神经活性失衡，从而影响血压的调控[9]。

二、动脉僵硬度及血管搏动改变

慢性高血压或老龄等因素可使正常血管壁结构损害，包括血管平滑肌细胞丢失、细胞外基质沉积增加等[10-11]，使动脉僵硬度增加、弹性下降，从而导致血流脉动性和血管搏动变化。颅内外大动脉硬化，削弱了Windkessel效应对系统性动脉压脉冲的抑制，导致高脉动血流传入颅内小血管。脑是高流量、低阻抗器官，对血流脉动性增加的影响较为敏感[12]，传入颅内小血管的高脉冲能量可损害血管内皮，最终引起或加重颅内小血管损害。目前，临床主要以脉搏波传导速度（PWV）和搏动指数（PI）评价动脉僵硬度，可行TCD或MRI等无创性检查。

多项横断面研究显示，高脉搏波传导速度和颅内外大动脉高搏动指数与脑白质高信号、扩大的血管周围间隙、陈旧性腔隙性梗死、脑微出血进展相关[13-18]。一项在社区老年人群中开展的前瞻性研究显示，脉搏波传导速度可以预测脑白质高信号的进展[19]，但相关前瞻性研究仍相对较少。静脉方面，晚近有学者利用磁共振相位对比法（PC-MRI）进行研究，发现颅内静脉搏动指数升高与脑白质高信号和基底节区扩大的血管周围间隙增多有关[13,20]。脑小血管病的动脉病变与静脉病变是因果关系还是并存关系，目前尚无统一结论，一方面，动脉搏动改变可能通过毛细血管或脑脊液自动脉传递至静脉，导致静脉病变，因此颅内静脉搏动指数升高可能是动脉病变与静脉病变之间的联系[20-21]；另一方面，静脉病变也可能反过来增加毛细血管搏动性，造成内皮功能障碍或影响血管周围间隙代谢产物的清除，导致脑小血管病进展[20]。颅内小血管方面，Schnerr等[22]采用7T MRI在体记录脑穿支动脉或小血管血流速度和搏动指数，发现老年人大脑中动脉至豆纹动脉的脉搏波衰减明显减弱。Geurts等[23]发现，伴腔隙性梗死和深部脑出血的脑小血管病患者脑穿支动脉搏动指数升高。这些新技术的应用有助于更好地了解颅内小血管血流动力学变化。

三、脑血流量及脑血管反应性改变

在小动脉硬化型脑小血管病中，随着颅内小血管重构和动脉僵硬度的进行性加重，患者可逐渐出现脑低灌注和缺氧缺血现象[3]，多项横断面研究提示静息态脑血流量（CBF）降低与脑小血管病进展相关。对24项横断面研究进行的Meta分析表明，脑白质高信号患者静息态脑血流量降低（*SMD* = -0.71，95%CI：-1.12～-0.30；*P* = 0.0006）[24]，提示脑白质高信号的发生与慢性脑低灌注（CCH）和脑组织缺氧缺血密切相关[3]。亦有研究显示，静息态脑血流量降低与腔隙性梗死、脑微出血和扩大的血管周围间隙进展有关[25-27]。Yu等[28]发现，脑小血管病负荷总评分与静息态脑血流量呈负相关（*r* = -0.33，*P* = 0.001）。颅内小血管重构致形态学变化如内径缩小，以及功能学改变如血管收缩舒张能力下降是脑小血管病患者静息态脑血流量降低的重要原因，脑血流量降低可能通过脑组织缺氧缺血和低剪切力损伤等作用机制而加重血-脑屏障破坏和内皮功能障碍，促进脑小血管病进展[29]。应注意的是，静息态脑血流量对脑小血管病早期评价或进展预测的价值相对有限，一方面，疾病早期静息态脑血流量可保持正常或因代偿而无明显降低；另一方面，静息态脑血流量仅反映一个时间节点信息，不能很好地反映脑血管反应性变化或脑组织动态供血、供氧能力，而后者在疾病更早期可能已发生变化[3]。

由此可见，判断脑灌注对脑小血管病病情评估

和进展预测的价值需观察动态脑血流动力学变化，如脑血管反应性。脑血管反应性系指小动脉和毛细血管在神经元活动增强或代谢改变时，发生适应性舒张或收缩以维持脑血流稳定的能力，是衡量脑血管储备能力的重要指标。临床通过乙酰唑胺试验或诱导生理负荷，再采用TCD、CT或MRI等观察兴趣区（ROI）脑血流量变化以定量评估脑血管反应性。多项横断面研究显示，脑血管反应性下降与腔隙性梗死、脑白质高信号、扩大的血管周围间隙、脑微出血等脑小血管病的影像学改变密切相关[30-34]。脑小血管病早期即可能已经存在脑血管反应性降低[3]。Kozera等[35]发现，中年无症状性高血压患者存在脑血管反应性降低，而此类患者仅有非常早期脑白质病变。前瞻性研究结果提示，脑血管反应性降低可以预测脑白质高信号的发生，Sam等[36]在对中至重度脑白质高信号患者的观察中发现，伴脑血管反应性降低的表观正常脑白质（NAWM）患者随访期间转变为脑白质高信号的可能性明显增加。

四、脑小血管病血流动力学改变的部位异质性

脑小血管病存在多种病理学表现，且分布在多个脑区。同种病理改变发生于不同脑区可能代表不同的发病机制，其中不同脑区血流动力学差异可能发挥关键作用。例如，Poels等[37]的研究结果显示，腔隙性梗死和脑白质高信号与脑深部和幕下脑微出血有关，而与脑叶微出血不存在关联性，提示脑深部或幕下脑微出血的病因与脑叶微出血不同，前者可能主要归因于高血压相关小动脉硬化型脑小血管病。脑白质高信号可发生于脑室周围或脑深部，Sachdev等[38]发现脑深部白质高信号的进展明显快于侧脑室旁；Blair等[33]的研究显示，脑血管反应性降低与脑室周围白质高信号的相关性强于脑深部白质高信号。上述研究表明，不同脑区的小血管可能受不同血流动力学特点的影响。一项数值模拟研究提示，脑表面与脑深部存在血压梯度差，有助于解释高血压相关腔隙性梗死或脑出血好发于基底节区、内囊、丘脑等脑深部的原因；同样是大脑中动脉分支，相同管径下中央支血压明显高于皮质支，推测这种血压梯度差可能是由于中央支自动脉主干直接发出，故血压降低不明显，而皮质支经过在脑表面不断延伸、分支，血液流动黏性耗散更多，故血压下降显著；同样的血压梯度差亦存在于二者下级小动脉，且高血压状态下血压梯度差增加[39]。高血压状态下，脑深部小血管即中央支受高血压的冲击更为明显，而皮质支由于血压下降明显而受高血压的冲击较中央支相对减弱，因此，研究者进一步认为这种血压梯度差可能是高血压状态下大脑中动脉中央支更倾向于表现为高血压相关小动脉重构特征的原因之一[40]。然而，目前尚无直接的动物实验或临床研究提供更多的证据，而且这种中央支与皮质支的血压梯度差是否伴随其他血流动力学改变，如环形张力、剪切力、搏动性差异等，以及这些差异是否与脑小血管病的病理改变部位差异性相关，尚待进一步研究加以证实。

五、脑小血管病血流动力学改变与类淋巴系统动力学改变的关系

类淋巴系统是脑组织液体引流和代谢产物清除的重要系统。脑血管与类淋巴系统在解剖学上联系紧密，血管周围间隙是类淋巴通路的重要组成部分[41]，因此，脑小血管病病程中伴随类淋巴系统动力学改变。

一方面，脑小血管病血流动力学改变影响类淋巴系统动力学。脑小血管病中扩大的血管周围间隙增多即证实这一点，血管周围间隙可反映类淋巴系统功能[42-43]，扩大的血管周围间隙增多提示液体引流障碍，其中重要原因是动力来源的减弱，而动脉搏动被认为是脑脊液循环和类淋巴系统的重要动力来源[43]。动脉节律性搏动将脉压直接传递给脑脊液，促使其在脑组织内循环。动物实验显示，老龄或高血压模型动物存在类淋巴系统引流或清除障碍[44-45]，且与小动脉搏动幅度减弱相关[45-46]。在临床研究方面，Zhou等[47]通过鞘内注射对比剂证实类淋巴系统循环障碍与老龄化呈正相关（$P<0.05$）。同时，脉搏波传导速度、搏动指数和脑血管反应性变化均与扩大的血管周围间隙相关[20,33,48]，但目前尚缺乏直接的临床证据证实动脉搏动性异常在其中的作用。另一方面，脑脊液循环和类淋巴系统动力学障碍也反过来加剧脑小血管病进展。多项横断面研究显示，扩大的血管周围间隙与脑白质高信号、腔隙性梗死、脑微出血、脑萎缩、脑卒中后复发、认知功能减退等相关[42-43,49]。前瞻性队列研究结果显示，扩大的血管周围间隙与皮质下梗死、脑微出血和脑白质高信号进展相关，使随访5年时血管性痴呆风险增加4倍以上（$OR=4.19$，95%CI：1.81～9.69；$P<0.001$）[50]。究其原因，炎性细胞聚集和激活以及代谢产物清除率降低可能是重要机制[43,50]。亦有研究尝试探索脑脊液搏动与脑

小血管病影像学进展的关系。Blair等[33]的研究发现，脑小血管病患者枕骨大孔脑脊液每搏量降低与基底节区血管周围间隙评分增加相关，血管周围间隙评分每增加1分、脑脊液每搏量降低0.96 ml。有学者对枕骨大孔或中脑导水管每搏量与脑白质高信号进展的关系进行研究，但结论不尽一致[20]。而脑脊液搏动与腔隙性梗死或脑微出血进展的关系尚未见报道。

综上所述，脑血流动力学损害是小动脉硬化型脑小血管病发病机制的重要环节，病程中表现出血压变异性增加、血管搏动性改变、脑血流量降低等脑血流动力学损害，这些变化可能具有部位异质性，且与脑小血管病病理学特征的部位特异性相关，此外，脑血流动力学改变与类淋巴系统动力学改变的相互作用也可加剧疾病进展。尽管已有诸多横断面研究提示脑血流动力学损害与小动脉硬化型脑小血管病病理改变存在关联性，但尚缺乏更多的纵向研究进一步证实。

利益冲突　无

参 考 文 献

[1] Ter Telgte A, van Leijsen EMC, Wiegertjes K, Klijn CJM, Tuladhar AM, de Leeuw FE. Cerebral small vessel disease: from a focal to a global perspective[J]. Nat Rev Neurol, 2018, 14:387-398.

[2] Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease: a clinical review[J]. Neurology, 2019, 92:1146-1156.

[3] Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications[J]. Lancet Neurol, 2019, 18:684-696.

[4] de Heus RAA, Reumers SFI, van der Have A, Tumelaire M, Tully PJ, Claassen JAHR. Day-to-day home blood pressure variability is associated with cerebral small vessel disease burden in a memory clinic population[J]. J Alzheimers Dis, 2020, 74:463-472.

[5] Tully PJ, Yano Y, Launer LJ, Kario K, Nagai M, Mooijaart SP, Claassen JAHR, Lattanzi S, Vincent AD, Tzourio C; the Variability in Blood Pressure and Brain Health Consortium. Association between blood pressure variability and cerebral small-vessel disease: a systematic review and Meta-analysis[J]. J Am Heart Assoc, 2020, 9:e013841.

[6] Filomena J, Riba-Llena I, Vinyoles E, Tovar JL, Mundet X, Castañé X, Vilar A, López-Rueda A, Jiménez-Baladó J, Cartanyà A, Montaner J, Delgado P; ISSYS Investigators. Short-term blood pressure variability relates to the presence of subclinical brain small vessel disease in primary hypertension[J]. Hypertension, 2015, 66:634-640.

[7] Yang S, Qin W, Yang L, Fan H, Li Y, Yin J, Hu W. The relationship between ambulatory blood pressure variability and enlarged perivascular spaces: a cross-sectional study[J]. BMJ Open, 2017, 7:e015719.

[8] Liu W, Liu R, Sun W, Peng Q, Zhang W, Xu E, Cheng Y, Ding M, Li Y, Hong Z, Wu J, Zeng J, Yao C, Huang Y; CASISP Study Group. Different impacts of blood pressure variability on the progression of cerebral microbleeds and white matter lesions[J]. Stroke, 2012, 43:2916-2922.

[9] Palatini P. Day-by-day blood pressure variability: cause or consequence of vascular brain injury[J]? Hypertension, 2014, 63:1163-1165.

[10] Liu N, Xue Y, Tang J, Zhang M, Ren X, Fu J. The dynamic change of phenotypic markers of smooth muscle cells in an animal model of cerebral small vessel disease[J]. Microvasc Res, 2021, 133:104061.

[11] Tang J, Xiao W, Li Q, Deng Q, Chu X, Chen Y, Pan D, Fu J. A cyclooxygenase-2 inhibitor reduces vascular wall thickness and ameliorates cognitive impairment in a cerebral small vessel diseases rat model[J]. Curr Alzheimer Res, 2015, 12:704-710.

[12] Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage[J]. J Appl Physiol (1985), 2008, 105:1652-1660.

[13] Jolly TA, Bateman GA, Levi CR, Parsons MW, Michie PT, Karayanidis F. Early detection of microstructural white matter changes associated with arterial pulsatility[J]. Front Hum Neurosci, 2013, 7:782.

[14] Zhang K, Jiang Y, Wang Y, Suo C, Xu K, Zhu Z, Zhu C, Zhao G, Jin L, Ye W, Cui M, Chen X. Associations of arterial stiffness and carotid atherosclerosis with cerebral small vessel disease in a rural community-based population[J]. J Atheroscler Thromb, 2020, 27:922-933.

[15] Mok V, Ding D, Fu J, Xiong Y, Chu WW, Wang D, Abrigo JM, Yang J, Wong A, Zhao Q, Guo Q, Hong Z, Wong KS. Transcranial doppler ultrasound for screening cerebral small vessel disease: a community study[J]. Stroke, 2012, 43:2791-2793.

[16] Nam KW, Kwon HM, Lee YS. Distinct association between cerebral arterial pulsatility and subtypes of cerebral small vessel disease[J]. PLoS One, 2020, 15:e0236049.

[17] Lee KJ, Jung KH, Park CY, Kim JM, Lee ST, Chu K, Kim M, Lee SK, Roh JK. Increased arterial pulsatility and progression of single subcortical infarction[J]. Eur Radiol, 2017, 27:899-906.

[18] Chou KH, Wang PN, Peng LN, Liu LK, Lee WJ, Chen LK, Lin CP, Chung CP. Location-specific association between cerebral microbleeds and arterial pulsatility[J]. Front Neurol, 2019, 10:1012.

[19] Rosano C, Watson N, Chang Y, Newman AB, Aizenstein HJ, Du Y, Venkatraman V, Harris TB, Barinas-Mitchell E, Sutton-Tyrrell K. Aortic pulse wave velocity predicts focal white matter hyperintensities in a biracial cohort of older adults[J]. Hypertension, 2013, 61:160-165.

[20] Shi Y, Thrippleton MJ, Blair GW, Dickie DA, Marshall I, Hamilton I, Doubal FN, Chappell F, Wardlaw JM. Small vessel disease is associated with altered cerebrovascular pulsatility but not resting cerebral blood flow[J]. J Cereb Blood Flow Metab, 2020, 40:85-99.

[21] Birnefeld J, Wåhlin A, Eklund A, Malm J. Cerebral arterial pulsatility is associated with features of small vessel disease in patients with acute stroke and TIA: a 4D flow MRI study[J]. J Neurol, 2020, 267:721-730.

[22] Schnerr RS, Jansen JFA, Uludag K, Hofman PAM, Wildberger JE, van Oostenbrugge RJ, Backes WH. Pulsatility of lenticulostriate arteries assessed by 7 Tesla Flow MRI-measurement, reproducibility, and applicability to aging effect[J]. Front Physiol, 2017, 8:961.

[23] Geurts LJ, Zwanenburg JJM, Klijn CJM, Luijten PR, Biessels

GJ. Higher pulsatility in cerebral perforating arteries in patients with small vessel disease related stroke, a 7T MRI study[J]. Stroke, 2018, 50:STROKEAHA118022516.

[24] Shi Y, Thrippleton MJ, Makin SD, Marshall I, Geerlings MI, de Craen AJM, van Buchem MA, Wardlaw JM. Cerebral blood flow in small vessel disease: a systematic review and meta-analysis[J]. J Cereb Blood Flow Metab, 2016, 36:1653-1667.

[25] Mochizuki Y, Oishi M, Takasu T. Cerebral blood flow in single and multiple lacunar infarctions[J]. Stroke, 1997, 28:1458-1460.

[26] Wang H, Nie ZY, Liu M, Li RR, Huang LH, Lu Z, Jin LJ, Li YX. Clinical characteristics of perivascular space and brain CT perfusion in stroke-free patients with intracranial and extracranial atherosclerosis of different extents[J]. Ann Transl Med, 2020, 8:215.

[27] Gregg NM, Kim AE, Gurol ME, Lopez OL, Aizenstein HJ, Price JC, Mathis CA, James JA, Snitz BE, Cohen AD, Kamboh MI, Minhas D, Weissfeld LA, Tamburo EL, Klunk WE. Incidental cerebral microbleeds and cerebral blood flow in elderly individuals[J]. JAMA Neurol, 2015, 72:1021-1028.

[28] Yu C, Lu W, Qiu J, Wang F, Li J, Wang L. Alterations of the whole cerebral blood flow in patients with different total cerebral small vessel disease burden[J]. Front Aging Neurosci, 2020, 12:175.

[29] Wong SM, Jansen JFA, Zhang CE, Hoff EI, Staals J, van Oostenbrugge RJ, Backes WH. Blood-brain barrier impairment and hypoperfusion are linked in cerebral small vessel disease[J]. Neurology, 2019, 92:e1669-1677.

[30] Blair GW, Doubal FN, Thrippleton MJ, Marshall I, Wardlaw JM. Magnetic resonance imaging for assessment of cerebrovascular reactivity in cerebral small vessel disease: a systematic review[J]. J Cereb Blood Flow Metab, 2016, 36:833-841.

[31] Deplanque D, Lavallee PC, Labreuche J, Gongora-Rivera F, Jaramillo A, Brenner D, Abboud H, Klein IF, Touboul PJ, Vicaut E, Amarenco P; Lacunar-BICHAT Investigators. Cerebral and extracerebral vasoreactivity in symptomatic lacunar stroke patients: a case-control study[J]. Int J Stroke, 2013, 8:413-421.

[32] Staszewski J, Skrobowska E, Piusińska-Macoch R, Brodacki B, Stępień A. Cerebral and extracerebral vasoreactivity in patients with different clinical manifestations of cerebral small-vessel disease: data from the significance of hemodynamic and hemostatic factors in the course of different manifestations of cerebral small-vessel disease study[J]. J Ultrasound Med, 2019, 38:975-987.

[33] Blair GW, Thrippleton MJ, Shi Y, Hamilton I, Stringer M, Chappell F, Dickie DA, Andrews P, Marshall I, Doubal FN, Wardlaw JM. Intracranial hemodynamic relationships in patients with cerebral small vessel disease[J]. Neurology, 2020, 94:e2258-2269.

[34] Fu JH, Lu CZ, Hong Z, Dong Q, Ding D, Wong KS. Relationship between cerebral vasomotor reactivity and white matter lesions in elderly subjects without large artery occlusive disease[J]. J Neuroimaging, 2006, 16:120-125.

[35] Kozera GM, Dubaniewicz M, Zdrojewski T, Madej-Dmochowska A, Mielczarek M, Wojczal J, Chwojnicki K, Swierblewska E, Schminke U, Wyrzykowski B, Nyka WM; SOPKARD Study Group. Cerebral vasomotor reactivity and extent of white matter lesions in middle-aged men with arterial hypertension: a pilot study[J]. Am J Hypertens, 2010, 23:1198-1203.

[36] Sam K, Crawley AP, Conklin J, Poublanc J, Sobczyk O, Mandell DM, Venkatraghavan L, Duffin J, Fisher JA, Black SE, Mikulis DJ. Development of white matter hyperintensity is preceded by reduced cerebrovascular reactivity[J]. Ann Neurol, 2016, 80:277-285.

[37] Poels MM, Vernooij MW, Ikram MA, Hofman A, Krestin GP, van der Lugt A, Breteler MM. Prevalence and risk factors of cerebral microbleeds: an update of the rotterdam scan study[J]. Stroke, 2010, 41(10 Suppl):103-106.

[38] Sachdev P, Wen W, Chen X, Brodaty H. Progression of white matter hyperintensities in elderly individuals over 3 years[J]. Neurology, 2007, 68:214-222.

[39] Blanco PJ, Müller LO, Spence JD. Blood pressure gradients in cerebral arteries: a clue to pathogenesis of cerebral small vessel disease[J]. Stroke Vasc Neurol, 2017, 2:108-117.

[40] Spence JD. Blood pressure gradients in the brain: their importance to understanding pathogenesis of cerebral small vessel disease[J]. Brain Sci, 2019, 9:21.

[41] Plog BA, Nedergaard M. The glymphatic system in central nervous system health and disease: past, present, and future[J]. Annu Rev Pathol, 2018, 13:379-394.

[42] Mestre H, Kostrikov S, Mehta RI, Nedergaard M. Perivascular spaces, glymphatic dysfunction, and small vessel disease[J]. Clin Sci (Lond), 2017, 131:2257-2274.

[43] Brown R, Benveniste H, Black SE, Charpak S, Dichgans M, Joutel A, Nedergaard M, Smith KJ, Zlokovic BV, Wardlaw JM. Understanding the role of the perivascular space in cerebral small vessel disease[J]. Cardiovasc Res, 2018, 114:1462-1473.

[44] Xue Y, Liu N, Zhang M, Ren X, Tang J, Fu J. Concomitant enlargement of perivascular spaces and decrease in glymphatic transport in an animal model of cerebral small vessel disease[J]. Brain Res Bull, 2020, 161:78-83.

[45] Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, Xie L, Kang H, Xu Q, Liew JA, Plog BA, Ding F, Deane R, Nedergaard M. Impairment of paravascular clearance pathways in the aging brain[J]. Ann Neurol, 2014, 76:845-861.

[46] Liu Q, Yan L, Huang M, Zeng H, Satyanarayanan SK, Shi Z, Chen D, Lu JH, Pei Z, Yao X, Su H. Experimental alcoholism primes structural and functional impairment of the glymphatic pathway[J]. Brain Behav Immun, 2020, 85:106-119.

[47] Zhou Y, Cai J, Zhang W, Gong X, Yan S, Zhang K, Luo Z, Sun J, Jiang Q, Lou M. Impairment of the glymphatic pathway and putative meningeal lymphatic vessels in the aging human[J]. Ann Neurol, 2020, 87:357-369.

[48] Riba-Llena I, Jiménez-Balado J, Castañé X, Girona A, López-Rueda A, Mundet X, Jarca CI, Álvarez-Sabin J, Montaner J, Delgado P. Arterial stiffness is associated with basal ganglia enlarged perivascular spaces and cerebral small vessel disease load[J]. Stroke, 2018, 49:1279-1281.

[49] Wardlaw JM, Benveniste H, Nedergaard M, Zlokovic BV, Mestre H, Lee H, Doubal FN, Brown R, Ramirez J, MacIntosh BJ, Tannenbaum A, Ballerini L, Rungta RL, Boido D, Sweeney M, Montagne A, Charpak S, Joutel A, Smith KJ, Black SE; Colleagues from the Fondation Leducq Transatlantic Network of Excellence on the Role of the Perivascular Space in Cerebral Small Vessel Disease. Perivascular spaces in the brain: anatomy, physiology and pathology[J]. Nat Rev Neurol, 2020, 16:137-153.

[50] Ding J, Sigurðsson S, Jónsson PV, Eiriksdottir G, Charidimou A, Lopez OL, van Buchem MA, Guðnason V, Launer LJ. Large perivascular spaces visible on magnetic resonance imaging, cerebral small vessel disease progression, and risk of dementia: the age, gene/environment susceptibility-reykjavik study[J]. JAMA Neurol, 2017, 74:1105-1112.

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