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Elevated Pulse Pressure Is a Risk Factor for Cerebral Microbleeds. A Single Center Case-Control Study

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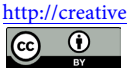

Abstract

Recent developments in brain magnetic resonance imaging using advanced Susceptibility Weighted Imaging (SWI) have significantly increased the detection and prevalence of Cerebral Microbleeds (CMBs). Here, we aimed to explore the association between Pulse Pressure (PP) and CMBs. Having been implicated in various arteriopathies, we hypothesized that elevated PP could also be a risk for CMBs. A retrospective case-control study was conducted from August 2021 to September 2022 at Zhongnan Hospital of Wuhan University China. Extracted data were analyzed in SPSS. Chi-square test, binary logistic regression, and Spearman's correlation analysis were conducted.104 patients were analyzed. Univariate analysis showed no significant association between PP and CMBs, OR 1.65 (95% CI: 0.737 - 3.694; $p > 0.05$), while DBP and alcohol consumption were significant, ORs 2.956 (95% CI: 1.249 - 6.997, $p < 0.05$) and 2.525 (95% CI: 1.062 - 6.002, $p < 0.05$) respectively. Multivariate analysis, showed that PP was significantly associated with CMBs, OR 3.194 (95% CI: 1.024 - 9.964, $p < 0.05$) in combination with SBP, DBP, gender, age, smoking and alcohol consumption. Taken together, the study showed that elevated PP is associated with CMB, but is not an independent risk factor for CMBs.

Keywords

Cerebral, Microbleeds, Pulse, Pressure, Susceptibility Weighted Imaging, MRI, CMBs

1. Introduction

The recent use of Susceptibility Weighted Imaging (SWI) in brain MRI has dramatically increased the diagnosis of petechial cerebral hemorrhagic lesions

(CMBs) among patients with stroke, cognitive impairment, dementia, hypertension and the elderly [1] [2] [3] [4]. These lesions are clinically covert, yet they are radiological markers for small vessel diseases. CMBs occur in approximately 29.4% of the elderly patients [5], and are of increasing public health concern. They are majorly associated with; Cerebral Amyloid Angiopathy (CAA), Hypertensive arteriopathy, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), and Moyamoya disease [6]-[13]. Other risk factors include; Hypertension [14] [15] [16], advanced age (>60 years) [17] [18] [19] [20], gender (male) [19], diet [21], and antithrombotic therapy [22] [23] [24].

In principle, the origin of CMBs is considered to be microvascular fragility, which then promotes micro-hemorrhage within the cerebral vasculature [25]. In this case managing CMBs should involve identifying all the clinical and subclinical parameters linked to microvascular fragility. To this effect, studies have exposed hypertension as the most common risk factor for CMBs [16] [26] [27], although cases are also seen in normotensive subjects [28]. Other than hypertension, pulse pressure (PP), a derivative of the arithmetic difference between systolic and diastolic blood pressure, has also been implicated in a number of arteriopathies [29]-[36]. One study suggested that PP-induced arteriopathy could be due to the cerebrovascular stiffness common in advanced age, and the lack of an external elastic lamina by intracranial vessels [37]. Moreover, it is also suggested that elevated PP could promote endothelial dysfunction that concurrently with accumulation of proinflammatory cells and oxidative stress, induces cerebrovascular damage [38]. So elevated PP likely promotes the development and ultimate rupture of micro-aneurysms, hastens the development of atherosclerosis, and thrombotic events, and induces CMBs.

While various studies have explored the relationship between hypertension and CMBs [26] [39] [40], the relationship between elevated PP and CMBs has not been well elucidated. Considering that PP is an easily acquirable, non-invasive, low cost parameter, establishing its association with CMBs could offer a cheap and faster mechanism for determining risks for CMBs whether alone or in combination with other parameters like patient age, gender, blood pressure and alcohol consumption. On the basis of its implication in various arteriopathies, we hypothesized that elevated PP could be associated with CMBs, and so took advantage of the use of the advanced SWI imaging technique to explore this possible association.

2. Materials and Methods

We recruited a total of 104 patients (81 males and 24 females; aged 18 - 95 years, mean age 69.73 ± 8.74 years) from August 2021 to September 2022 at Zhongnan Hospital of Wuhan University. All recruited patients underwent brain MRI scan using SWI techniques. They were then divided into two groups based on their MRI results: 54 with CMBs, and 54 without CMBs. Patients were excluded if

they had the following: Those on hormonal replacement therapy that included estrogen, (evidence suggest that these drugs induce significant PP alterations [41]; those diagnosed with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral amyloid angiopathy (CAA) or Moyamoya disease. The study was approved by the ethics committee of Zhongnan Hospital of Wuhan University, and patient consent was waived as the data were retrospectively collected. All recruited patients underwent MRI scan by MAGNETOM Avanto & Prisma 3T MRI systems (Siemens, Germany) using SWI sequence, and parameters set as follows: 800 ms repetition time, 20 - 50 ms echo time, 20 - 30 flip angles, 256 × 256 matrix, 240 × 100 vision, 7-mm scan slice thickness, and 2.5 mm spacing. MRI data were retrieved from the hospital Picture Archiving and Communication System (PACS), while other clinical information were got from the electronic medical database. Cerebral microhemorrhage was defined as loss of circular signal with a uniform diameter of 2 - 5 mm, with clear margin and no edema around the circular punctate non-sulcus area.

3. Blood Pressure Measurements and Comorbidities

Blood pressure measurements retrieved were single measurement recorded in the system for each patient. Hypertension was defined according to the International Society of Hypertension (ISH) [42] as blood pressure readings of ≥140/90 mmHg. Pulse pressure (PP) was derived as the arithmetic difference between Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) measurements. It was then divided in to three categories; low, normal and high with a threshold for normal being 40 to 60 mmHg [43] [44]. Other comorbidities collected were diabetes, hyperlipidemia, and stroke, all defined by the World Health Organization criteria for diagnosing hypertension, diabetes, and hyperlipidemia. In addition, history of smoking and alcohol consumption were also extracted. Confirmation of a stroke diagnosis was made based on definitive diagnosis and treatment from Zhongnan Hospital and image findings of obsolete cerebral lesions. Other data collected were: subject demographic information, clinical and medical characteristics, and treatment details.

4. Brain MRI Scan Results

All brain MRI results retrieved were conducted by highly qualified radiologists. When viewed on SWI, CMBs appear as small homogenous, and round foci with low signal intensity, having a diameter < 10 mm and without peripheral edema. Structures such as vascular gap, cavernous hemangioma, calcified plaque of atherosclerosis, hemosiderin deposition on the pia mater, and calcification of the globus pallidus are excluded. The number of CMBs located in the cortical region, sub cortical region, brain stem, cerebellum, and those that were diffuse were recorded. CMBs were defined as: non-CMB, (0), mild (1 - 2), moderate (3 - 10) and severe (>10) and patients grouped accordingly.

5. Statistical Analysis

Statistical analysis was conducted in SPSS version 25 software (IBM Inc. USA). Continuous variables were expressed as mean ± SD and categorical variables presented as counts and percentages. Independent student's t test was used to analyze the mean difference between groups of continuous data, while Pearson's Chi-square test was used for categorical data. Correlation analysis was conducted using the Spearman's rank test. A p-value ≤ 0.05 was considered statistically significant.

6. Results

Patient characteristics

A total of 104 patients were included in this study; 52 cases and 52 controls. Mean (± SD) age of the cases and controls were; 68.79 ± 9.104 vs 68.52 ± 9.359 years respectively ($p > 0.05$), and 69.2% were males ($p < 0.001$). Hypertension was the most frequent comorbidity accounting for 55.8% vs 44.2% ($p > 0.05$) of all comorbidities among cases and controls respectively, while limb disorders (hemiplegia, bradykinesia, limb weakness, numbness, and tremors) were the most notable primary complaints in both groups, though with a higher frequency amongst cases ($p > 0.05$). Average systolic BP and mean arterial pressure (MAP) were both higher in cases than controls (all $p < 0.05$), while average diastolic BP and pulse pressure (PP) though higher in cases than controls were not statistically different (all $p > 0.05$) (Figure 1). Detailed clinical and demographic information is presented in Table 1.

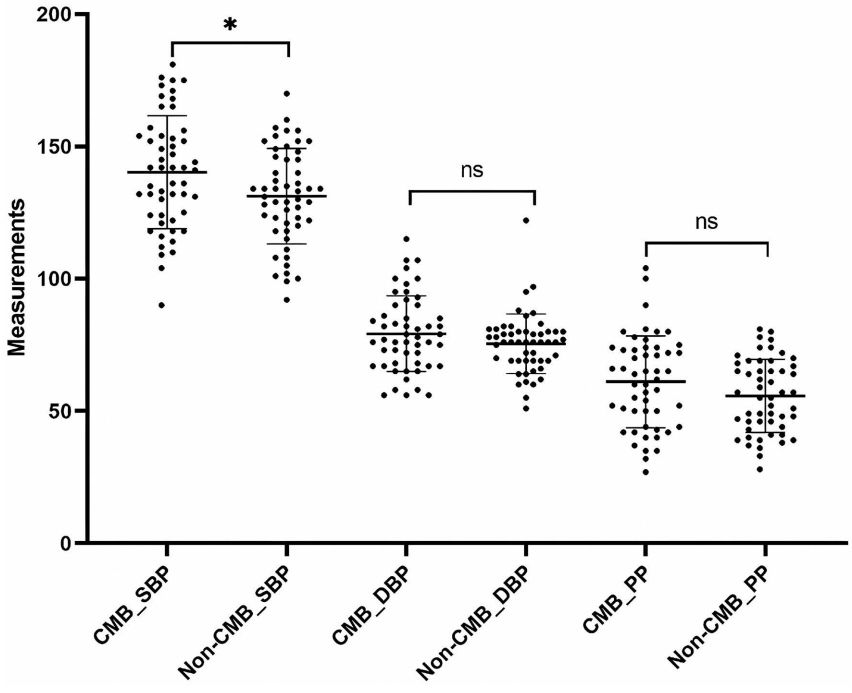

Figure 1. Mean difference in systolic BP, diastolic BP and pulse pressure among patients with CMBs and those without.

Table 1. Demographic and clinical characteristics of the patients.

Characteristic	Case, N = 52	Controls, N = 52	p
Gender (male), n %	43 (82.7)	38 (73.1)	<0.001*
Age, y (Mean ± SD)	70.6 ± 8.56	68.9 ± 8.93	0.76
SBP (mmHg)	140.0 ± 20.6	133.0 ± 19.2	0.02*
DBP (mmHg)	79.2 ± 14.2	76.8 ± 11.8	0.14
PP (mmHg)	61.0 ± 17.0	56.0 ± 14.0	0.06
MAP (mmHg)	99.4 ± 14.5	95.4 ± 13.1	0.04*
Co-morbidities			
Stroke n, %	4 (7.7)	2 (1.9)	0.16
Diabetes mellitus n, %	1 (1.9)	0 (0)	0.31
Hyperlipidemia n, %	4 (5.8)	3 (5.8)	0.98
Smoking, n (%)	22 (44.2)	31 (57.7)	0.18
Alcohol, n (%)	11 (21.2)	21 (40.4)	0.03*

SBP: Systolic blood pressure. DBP: diastolic blood pressure. PP: Pulse pressure. MAP: Mean arterial pressure. *Significant result.

Association between pulse pressure and CMBs

Univariate and multivariate analyses were conducted to determine the association between PP and CMBs. SBP, DBP, age, smoking history and alcohol consumption history were also included in the multivariate analysis. Preliminary multicollinearity analysis showed no significant association between PP and the other blood pressure parameters. Univariate analysis revealed that PP was not significantly associated with CMBs, OR 1.65 (95% CI: 0.737 - 3.694; $p > 0.05$), while DBP and alcohol consumption were significant, ORs 2.956 (95% CI: 1.249 - 6.997, $p = 0.014$) and 2.525 (95% CI: 1.062 - 6.002, $p = 0.044$) respectively (Table 2). However, when PP was included in the multivariate analysis, it was significantly associated with the occurrence of CMBs, OR 3.194 (95% CI: 1.024 - 9.964, $p = 0.045$) (Table 3). These results suggest that PP is not an independent risk factor for CMBs but rather acts in combination with other risk factors to promote CMBs.

Correlations between pulse pressure and severity of CMBs

Pulse pressure (PP) was then divided into three categories; low, normal and high, while CMBs were ranked in severity according to number of micro bleeds (severity) as described by Ibrahim *et al.* [5], and the number of micro bleeds counted in each rank and the corresponding PP quartile, Table 4. Correlation among the CMBs ranks (CMBs severity) and the PP quartiles was then determined using Spearman's rank test, to ascertain whether severity of CMBs increased with increase in PP. The results showed a weak correlation, $r = 0.188$; and $p = 0.057$.

Correlation between pulse pressure and location of CMBs

The distribution of micro bleed lesions was not uniform across the brain,

Table 2. Univariate analysis of the association between pulse pressure and CMBs.

	B	SE	Wald	df	Sig	OR	95% CI
SBP	0.336	0.476	5.000	1	0.479	1.400	0.551 - 3.557
DBP	1.084	0.440	6.079	1	0.014*	2.956	1.249 - 6.997
PP	0.501	0.411	1.483	1	0.223	1.650	0.737 - 3.694
Gender	0.92	0.429	0.046	1	0.830	1.096	0.473 - 2.541
Age	0.217	0.467	0.216	1	0.642	1.242	0.498 - 3.102
Smoking	0.542	0.396	1,874	1	0.171	1.719	0.791 - 3.736
Alcohol	0.926	0.442	4.395	1	0.044*	2.525	1.062 - 6.002

SBP: Systolic blood pressure. DBP: diastolic blood pressure. PP: Pulse pressure. *Significant result.

Table 3. Multivariate analysis of the association between pulse pressure and CMBs.

	B	SE	Wald	df	Sig	OR	95% CI
SBP	−1.115	0.724	2.375	1	0.123	0.328	0.079 - 1.354
DBP	1.604	0.563	8.109	1	0.004*	4.971	1.648 - 14.989
PP	1.161	0.580	4.002	1	0.045*	3.194	1.024 - 9.964
Gender	0.313	0.488	0.411	1	0.521	1.368	0.525 - 3.562
Age	−0.093	0.523	0.032	1	0.859	0.911	0.327 - 2.539
Smoking	0.134	0.469	0.082	1	0.774	1.144	0.456 - 2.867
Alcohol	1.086	0.529	4.212	1	0.040*	2.962	1.050 - 8.356

SBP: Systolic blood pressure. DBP: diastolic blood pressure. PP: Pulse pressure. *Significant result.

Table 4. Correlation between pulse pressure and severity of CMBs.

CMB grade	Pulse pressure quartiles				N
	Q1	Q2	Q3	Q4	
0 (0)	13	16	16	7	52
1 (1 - 2) Mild	7	2	3	7	19
2 (3 - 10) Moderate	4	5	7	7	23
3 (>10) Severe	1	3	2	4	10
N	25	26	28	25	104

Spearman r = 0.188; p = 0.057.

Figure 2. 34.6% (18/52) were in the cortical region, 32.7% (17/52) in the sub cortical region, 19.2% (10/52) in the brain stem, 7.7% (4/52) in the cerebellum, and 5.7% (3/52) were diffuse. We used Spearman's rank test to determine the correlation among the CMBs distribution and PP quartiles. The result showed that no correlation existed (Spearman's r = −0.01; p > 0.05) (Table 5).

Table 5. Correlation between pulse pressure and location of CMBs.

Brain location	Pulse pressure quartiles				N
	Q1	Q2	Q3	Q4	
Cortical Region	6	2	3	7	18
Subcortical Region	4	4	3	6	17
Brainstem	2	3	4	1	10
Cerebellum	0	1	1	2	4
Diffuse	1	1	0	1	3
N	13	11	11	17	52

Spearman r = −0.01; p = 0.992.

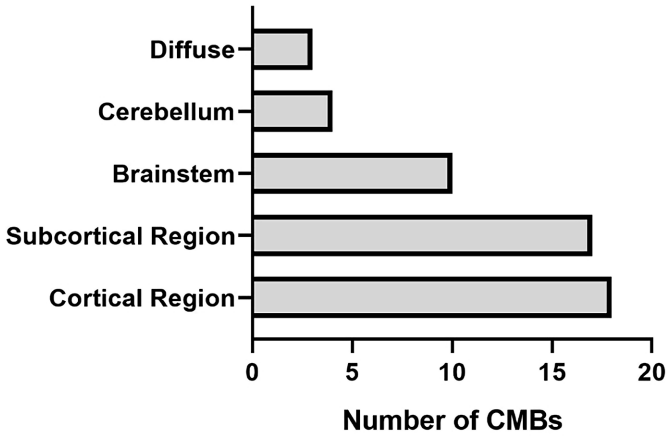

Figure 2. Brain distribution of CMBs.

7. Discussion

This study was conducted to mainly examine the association between pulse pressure (PP) and the occurrence of cerebral microbleeds (CMBs) in patients who underwent brain MRI using Susceptibility Weighting techniques. Blood pressure, gender, age, smoking and alcohol consumption were the other factors assessed. PP is often an overlooked parameter in clinical practice yet studies have demonstrated that it is involved in a number of arteriopathies [29]-[36]. Moreover, it is a rapidly acquirable, non-invasive, and economically cheap parameter that could be used as a predictor of vascular disease.

Our results revealed that PP is associated with the occurrence of cerebral microbleeds among the patients analyzed, ($p < 0.05$). However, the association occurred in combination with other risk factors *i.e.* SBP, DBP, age, gender, smoking and alcohol consumption, suggesting that PP is not an independent risk factors for CMBs. This result is consistent with those of Park *et al.*, [45] who found that long-term elevated PP in conjunction with high systolic blood pressure increased the risk of hemorrhagic stroke among stroke patients with cerebral microbleeds. Furthermore, like Emstahl *et al.*, [39], and Ding *et al.*, [46], we also showed that diastolic blood pressure and alcohol consumption are independent

risk factors for CMBs respectively, (all $p < 0.05$). Taken together, our results highlight the need to also consider elevated PP when assessing possible risk factors for CMBs in clinical practice.

In assessing how PP relates to the severity and brain location of CMBs, we considered the number of CMBs to show severity, and then mapped the brain location of the identified CMBs. The results revealed no distinct association between PP and the severity of CMBs or their location within the brain. This finding is in agreement with that of Lyu *et al.*, [40] who showed that there was no association between hypertension and the location of CMBs in the brain.

Evaluation of the patients' clinical characteristics revealed that limb disorder—which included hemiplegia, bradykinesia, limb weakness, numbness, and tremors—was the commonest primary complaint amongst the groups. Previously, White Matter hyper-intensities (WMHs), lacunas, and brain atrophy were confirmed to be associated with gait disorders. In general motor coordination relies on interrelated activity by distinct parts of the brain and injury to any of these parts may clinically manifest as limb disorder. CMBs are a manifestation of ongoing cerebral vascular disease which ultimately leads to injury of parts of the brain [47] [48]. In particular, the motor cortex plays the primary role in the motor activity of the body. Our results show that most CMBs amongst the cases were frequently noted in the cortical and subcortical regions, and this may explain the primary clinical observation of limb disorder. Indeed, Hou *et al.* [49] recently confirmed that CMBs are associated with lower gait velocity, wider stride width, longer Time-up-and-Go (TUG) test times, and other upper and lower extremity dysfunctions amongst patients with CMBs.

The results of our study offer significant insight into improved understanding of the risk factors for CMBs with the hope that early detection and subsequent intervention may prevent progression to worse outcomes such as stroke, cognitive impairment and dementia. Furthermore, our results offer grounds for possible consideration of PP as one of the risk factors, when assessing the risk of CMBs in clinical practice. Being a non-invasive, and easy to obtain parameter, its utilization could prevent CMBs and spare patients the need for invasive tests including cerebral angiography or brain biopsy.

This study had a few major limitations; first, we utilized only single blood pressure measurements extracted from the electronic database to determine PP, and yet a 24-hour ambulatory blood pressure could be a more reliable measurement to use. Second, the study was limited by sample size which affected the power. Third, being a retrospective study, it has inherent biases and limited parameters to analyze. We therefore think that a more robust, well designed, prospective cohort study is needed to validate our results.

8. Conclusion

In summary, this study revealed that there is an association between pulse pressure (PP) and cerebral microbleeds (CMBs). However, according to our analysis,

PP is not an independent risk factor for CMBs. The study also revealed that increased diastolic BP and alcohol consumption are independent risk factors for CMBs. The study limitations notwithstanding, including the assessment of PP among the other risk factors for CMBs could offer a cheap, non-invasive parameter that improves CMBs risk assessment and hence prevention of CMBs in patients at risk. To validate these results, a larger, well designed prospective cohort study is warranted.

Author Contributions

CN and HX conceived the study. CN: Conducted data collection. CN: conducted data curation and analysis. CN: Wrote the draft manuscript. HX reviewed the manuscript. HX: Supervised the study. Both authors have read and approved the final manuscript.

Ethical Approval

This study was approved by the Zhongnan Hospital of Wuhan University Research Ethics committee. Patients' permission was waived by the committee since the data were retrospectively collected.

Conflicts of Interest

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] Nighoghossian, N., Hermier, M., Adeleine, P., Blanc-Lasserre, K., Derex, L., Honnorat, J., *et al.* (2002) Old Microbleeds Are a Potential Risk Factor for Cerebral Bleeding After Ischemic Stroke: A Gradient-Echo T2*-Weighted Brain MRI Study. *Stroke*, **33**, 735-742. https://doi.org/10.1161/hs0302.104615

[2] Vernooij, M.W., van der Lugt, A., Ikram, M.A., Wielopolski, P.A., Niessen, W.J., Hofman, A., *et al.* (2008) Prevalence and Risk Factors of Cerebral Microbleeds: The Rotterdam Scan Study. *Neurology*, **70**, 1208-1214. https://doi.org/10.1212/01.wnl.0000307750.41970.d9

[3] Haller, S., Vernooij, M.W., Kuijer, J.P.A., Larsson, E.M., Jäger, H.R. and Barkhof, F. (2018) Cerebral Microbleeds: Imaging and Clinical Significance. *Radiology*, **287**, 11-28. https://doi.org/10.1148/radiol.2018170803

[4] Sepehry, A.A., Lang, D., Hsiung, G.Y. and Rauscher, A. (2016) Prevalence of Brain Microbleeds in Alzheimer Disease: A Systematic Review and Meta-Analysis on the Influence of Neuroimaging Techniques. *American Journal of Neuroradiology*, **37**, 215-222. https://doi.org/10.3174/ajnr.A4525

[5] Ibrahim, A.A., Ibrahim, Y.A., Darwish, E.A. and Khater, N.H. (2019) Prevalence of Cerebral Microbleeds and Other Cardiovascular Risk Factors in Elderly Patients with Acute Ischemic Stroke. *Egyptian Journal of Radiology and Nuclear Medicine*, **50**, Article No. 38. https://doi.org/10.1186/s43055-019-0034-7

[6] Graff-Radford, J., Lesnick, T.G., Mielke, M.M., Constantopoulos, E., Rabinstein,

A.A., Przybelski, S.A., *et al.* (2021) Cerebral Amyloid Angiopathy Burden and Cerebral Microbleeds: Pathological Evidence for Distinct Phenotypes. *Journal of Alzheimer's Disease*, **81**, 113-122. https://doi.org/10.3233/JAD-201536

[7] Renard, D., Tatu, L. and Thouvenot, E. (2018) Infratentorial Cerebral Microbleeds in Patients with Cerebral Amyloid Angiopathy. *Journal of Stroke and Cerebrovascular Diseases*, **27**, 2534-2537. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.05.015

[8] Werring, D.J. (2011) Cerebral Microbleeds: Pathophysiology to Clinical Practice. Cambridge University Press, Cambridge. http://libgen.rs/book/bibtex.php?md5=6e6009954c7515822490f845c3c7b582

[9] Alistair, D.G. (2006) Hypertensive Cerebral Small Vessel Disease and Stroke. *Brain Pathology*, **12**, 358-370. https://doi.org/10.1111/j.1750-3639.2002.tb00450.x

[10] Munoz, D.G. (2003) Small Vessel Disease: Neuropathology. *International Psychogeriatrics*, **15**, 67-69. https://doi.org/10.1017/S1041610203008986

[11] Lesnik Oberstein, S.A.J., van den Boom, R., van Buchem, M.A., van Houwelingen, H.C., Bakker, E., Vollebregt, E., *et al.* (2001) Cerebral Microbleeds in CADASIL. *Neurology*, **57**, 1066-1070. https://doi.org/10.1212/WNL.57.6.1066

[12] Ishikawa, T., Kuroda, S., Nakayama, N., Terae, S., Kudou, K. and Iwasaki, Y. (2005) Prevalence of Asymptomatic Microbleeds in Patients with Moyamoya Disease. *Neurologia Medico-Chirurgica*, **45**, 495-500. https://doi.org/10.2176/nmc.45.495

[13] Kikuta, K.-I., Takagi, Y., Nozaki, K., Hanakawa, T., Okada, T., *et al.* (2005) Asymptomatic Microbleeds in Moyamoya Disease: T2*-Weighted Gradient-Echo Magnetic Resonance Imaging Study. *Journal of Neurosurgery*, **102**, 470-475. https://doi.org/10.3171/jns.2005.102.3.0470

[14] Tsushima, Y., Tanizaki, Y., Aoki, J. and Endo, K. (2002) MR Detection of Microhemorrhages in Neurologically Healthy Adults. *Neuroradiology*, **44**, 31-36. https://doi.org/10.1007/s002340100649

[15] Liu, P.-F., Cui, Y.-Z., Na, J. and Gao, P.-Y. (2010) Cerebral Microbleeds-Prevalence, Distribution and Risk Factors in Northeast Population without Preceding Large-Area Stroke. *Chinese Medical Journal*, **123**, 286-290.

[16] Staals, J., van Oostenbrugge, R.J., Knottnerus, I.L.H., Rouhl, R.P.W., Henskens, L.H.G. and Lodder, J. (2009) Brain Microbleeds Relate to Higher Ambulatory Blood Pressure Levels in First-Ever Lacunar Stroke Patients. *Stroke*, **40**, 3264-3268. https://doi.org/10.1161/STROKEAHA.109.558049

[17] van Es, A.C.G.M., van der Grond, J., de Craen, A.J.M., Admiraal-Behloul, F., Blauw, G.J. and van Buchem, M.A. (2008) Risk Factors for Cerebral Microbleeds in the Elderly. *Cerebrovascular Diseases*, **26**, 397-403. https://doi.org/10.1159/000151680

[18] Roob, G., Schmidt, R., Kapeller, P., Lechner, A., Hartung, H.P. and Fazekas, F. (1999) MRI Evidence of Past Cerebral Microbleeds in a Healthy Elderly Population. *Neurology*, **52**, 991-991. https://doi.org/10.1212/WNL.52.5.991

[19] Sveinbjornsdottir, S., Sigurdsson, S., Aspelund, T., Kjartansson, O., Eiriksdottir, G., Valtysdottir, B., *et al.* (2008) Cerebral Microbleeds in the Population Based AGES-Reykjavik Study: Prevalence and Location. *Journal of Neurology, Neurosurgery & Psychiatry*, **79**, 1002-1006. https://doi.org/10.1136/jnnp.2007.121913

[20] Poels, M.M.F., Vernooij, M.W., Ikram, M.A., Hofman, A., Krestin, G.P., van der Lugt, A., *et al.* (2010) Prevalence and Risk Factors of Cerebral Microbleeds. *Stroke*, **41**, S103-S106. https://doi.org/10.1161/STROKEAHA.110.595181

[21] Lee, S.-H., Bae, H.-J., Yoon, B.-W., Kim, H., Kim, D.-E. and Roh, J.-K. (2002) Low

Concentration of Serum Total Cholesterol Is Associated with Multifocal Signal Loss Lesions on Gradient-Echo Magnetic Resonance Imaging. *Stroke*, **33**, 2845-2849. https://doi.org/10.1161/01.STR.0000036092.23649.2E

[22] Darweesh, S.K.L., Leening, M.J.G., Akoudad, S., Loth, D.W., Hofman, A., Arfan Ikram, M., *et al.* (2013) Clopidogrel Use Is Associated With an Increased Prevalence of Cerebral Microbleeds in a Stroke-Free Population: The Rotterdam Study. *Journal of the American Heart Association*, **2**, e000359. https://doi.org/10.1161/JAHA.113.000359

[23] Ge, L., Niu, G., Han, X., Gao, Y., Wu, Q., Wu, H., *et al.* (2011) Aspirin Treatment Increases the Risk of Cerebral Microbleeds. C*anadian Journal of Neurological Sciences*, **38**, 863-868. https://doi.org/10.1017/S0317167100012440

[24] Vernooij, M.W., Haag, M.D.M., van der Lugt, A., Hofman, A., Krestin, G.P., Stricker, B.H., *et al.* (2009) Use of Antithrombotic Drugs and the Presence of Cerebral Microbleeds: The Rotterdam Scan Study. *Archives of Neurology*, **66**, 714-720. https://doi.org/10.1001/archneurol.2009.42

[25] Kim, B.J. and Lee, S.-H. (2013) Cerebral Microbleeds: Their Associated Factors, Radiologic Findings, and Clinical Implications. *Journal of Stroke*, **15**, 153-163. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3859003/

[26] Reddy, S.T. and Savitz, S.I. (2020) Hypertension-Related Cerebral Microbleeds. *Case Reports in Neurology*, **12**, 266-269. https://doi.org/10.1159/000508760 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7548923/

[27] Yamashiro, K., Tanaka, R., Shimo, Y., Oyama, G., Ogawa, T., Umemura, A., *et al.* (2018) Cerebral Microbleeds and Blood Pressure Abnormalities in Parkinson's Disease. *eNeurologicalSci*, **10**, 5-11. https://www.sciencedirect.com/science/article/pii/S2405650217300370

[28] Fisher, M., French, S., Ji, P. and Kim, R.C. (2010) Cerebral Microbleeds in the Elderly: A Pathological Analysis. *Stroke*, **41**, 2782-2785. https://doi.org/10.1161/STROKEAHA.110.593657

[29] Bots, M.L., Witteman, J.C.M., Hofman, A., de Jong, P.T. and Grobbe, D.E. (1996) Low Diastolic Blood Pressure and Atherosclerosis in Elderly Subjects: The Rotterdam Study. *Archives of Internal Medicine*, **156**, 843-848. https://doi.org/10.1001/archinte.1996.00440080029004

[30] Franklin, S.S., Sutton-Tyrrell, K., Belle, S.H., Weber, M.A. and Kuller, L.H. (1997) The Importance of Pulsatile Components of Hypertension in Predicting Carotid Stenosis in Older Adults. *Journal of Hypertension*, **15**, 1143-1150. https://doi.org/10.1097/00004872-199715100-00012

[31] James, M.A., Watt, P.A.C., Potter, J.F., Thurston, H. and Swales, J.D. (1995) Pulse Pressure and Resistance Artery Structure in the Elderly. *Hypertension*, **26**, 301-306. https://doi.org/10.1161/01.HYP.26.2.301

[32] Khattar, R.S., Acharya, D.U., Kinsey, C., Senior, R. and Lahiri, A. (1997) Longitudinal Association of Ambulatory Pulse Pressure with Left Ventricular Mass and Vascular Hypertrophy in Essential Hypertension. *Journal of Hypertension*, **15**, 737-743. https://journals.lww.com/jhypertension/Fulltext/1997/15070/Longitudinal_association_of_ambulatory_pulse.5.aspx

[33] Lassila, H.C., Tyrrell, K.S., Matthews, K.A., Wolfson, S.K. and Kuller, L.H. (1997) Prevalence and Determinants of Carotid Atherosclerosis in Healthy Postmenopausal Women. *Stroke*, **28**, 513-517. https://doi.org/10.1161/01.STR.28.3.513

[34] Matthews, K.A., Owens, J.F., Kuller, L.H., Sutton-Tyrrell, K., Lassila, H.C. and

Wolfson, S.K. (1998) Stress-Induced Pulse Pressure Change Predicts Women's Carotid Atherosclerosis. *Stroke*, **29**, 1525-1530. https://doi.org/10.1161/01.STR.29.8.1525

[35] Nielsen, W.B., Lindenstrøm, E., Vestbo, J. and Jensen, G.B. (1997) Is Diastolic Hypertension an Independent Risk Factor for Stroke in the Presence of Normal Systolic Blood Pressure in the Middle-aged and Elderly? *American Journal of Hypertension*, **10**, 634-639. https://doi.org/10.1016/S0895-7061(96)00505-5

[36] Suurküla, M., Agewall, S., Fagerberg, B., Wendelhag, I., Widgren, B. and Wikstrand, J. (1994) Ultrasound Evaluation of Atherosclerotic Manifestations in the Carotid Artery in High-Risk Hypertensive Patients. Risk Intervention Study (RIS) Group. *Arteriosclerosis and Thrombosis: A Journal of Vascular Biology*, **14**, 1297-1304. https://doi.org/10.1161/01.ATV.14.8.1297

[37] Thorin-Trescases, N., de Montgolfier, O., Pinçon, A., Raignault, A., Caland, L., Labbé, P., *et al.* (2018) Impact of Pulse Pressure on Cerebrovascular Events Leading to Age-Related Cognitive Decline. *American Journal of Physiology-Heart and Circulatory Physiology*, **314**, H1214-H1224. https://doi.org/10.1152/ajpheart.00637.2017

[38] Heistad, D.D. (2001) What's New in the Cerebral Microcirculation? *Microcirculation*, **8**, 66-75. https://doi.org/10.1111/j.1549-8719.2001.tb00184.x

[39] Elmståhl, S., Ellström, K., Siennicki-Lantz, A. and Abul-Kasim, K. (2019) Association between Cerebral Microbleeds and Hypertension in the Swedish General Population "Good Aging in Skåne" Study. *The Journal of Clinical Hypertension*, **21**, 1099-1107. https://onlinelibrary.wiley.com/doi/abs/10.1111/jch.13606

[40] Lyu, L., Shen, J., Zeng, C., Ji, J., Hu, W., Wei, T., *et al.* (2020) Cerebral Microbleeds Are Associated with Blood Pressure Levels in Individuals with Hypertension. *Clinical and Experimental Hypertension*, **42**, 328-334. https://doi.org/10.1080/10641963.2019.1665673

[41] Van Bortel, L.M.A.B., Struijker-Boudier, H.A.J. and Safar, M.E. (2001) Pulse Pressure, Arterial Stiffness, and Drug Treatment of Hypertension. *Hypertension*, **38**, 914-921. https://doi.org/10.1161/hy1001.095773

[42] Unger, T., Borghi, C., Charchar, F., Khan, N.A., Poulter, N.R., Prabhakaran, D., *et al.* (2020) 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*, **75**, 1334-1357. https://www.ahajournals.org/doi/full/10.1161/HYPERTENSIONAHA.120.15026

[43] Safar, M.E., St Laurent, S., Safavian, A.L., Pannier, B.M. and London, G.M. (1987) Pulse Pressure in Sustained Essential Hypertension: A Haemodynamic Study. *Journal of Hypertension*, **5**, 213-218. https://doi.org/10.1097/00004872-198704000-00013

[44] Asmar, R., Vol, S., Brisac, A.M., Tichet, J. and Topouchian, J. (2001) Reference Values for Clinic Pulse Pressure in a Nonselected Population. *American Journal of Hypertension*, **14**, 415-418. https://doi.org/10.1016/S0895-7061(01)01284-5

[45] Park, J.-H., Lee, J., Kwon, S.U., Kwon, H.S., Lee, M.H. and Kang, D.-W. (2022) Elevated Pulse Pressure and Recurrent Hemorrhagic Stroke Risk in Stroke with Cerebral Microbleeds or Intracerebral Hemorrhage. *Journal of the American Heart Association*, **11**, e022317. https://doi.org/10.1161/JAHA.121.022317

[46] Ding, J., Sigurdsson, S., Garcia, M., Phillips, C.L., Eiriksdottir, G., *et al.* (2015) Risk Factors Associated with Incident Cerebral Microbleeds According to Location in Older People: The Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study. *JAMA Neurology*, **72**, 682-688.

https://doi.org/10.1001/jamaneurol.2015.0174

[47] Su, N., Zhai, F.-F., Zhou, L.-X., Ni, J., Yao, M., Li, M.-L., *et al.* (2017) Cerebral Small Vessel Disease Burden Is Associated with Motor Performance of Lower and Upper Extremities in Community-Dwelling Populations. *Frontiers in Aging Neuroscience*, **9**, Article 313. https://doi.org/10.3389/fnagi.2017.00313

[48] Hou, Y., Li, Y., Yang, S., Qin, W., Yang, L. and Hu, W. (2021) Gait Impairment and Upper Extremity Disturbance Are Associated with Total Magnetic Resonance Imaging Cerebral Small Vessel Disease Burden. *Frontiers in Aging Neuroscience*, **13**, Article 640844. https://doi.org/10.3389/fnagi.2021.640844

[49] Hou, Y., Yang, S., Li, Y., Qin, W., Yang, L. and Hu, W. (2022) Impact of Cerebral Microbleeds on Lower and Upper Extremities Function in Cerebral Small Vessel Disease. Preprint. https://www.researchsquare.com/article/rs-1868697/v1