The significance of pulsatility indices in the middle cerebral, internal carotid, and common carotid arteries for small vessel disease in the brain: A retrospective cross-sectional study

By Al Rasyid

https://medscience.center/journals/

TYPE OF ARTICLE: Original Article

The significance of pulsatility indices in the middle cerebral, internal carotid, and common carotid arteries for small vessel disease in the brain: A retrospective cross-sectional study

Al Rasyid[1], Putri Widya Andini[1], Taufik Mesiano[1], Ansi Rinjani[1], Mohammad Reynalzi Yugo[2], Reyhan Eddy Yunus[2], Mohammad Kurniawan[1], Rakhmad Hidayat[1], Salim Harris[1], Elvan Wiyarta[3]

[1]Department of Neurology, Faculty of Medicine, Universitas Indonesia – "Dr. Cipto Mangunkusumo" Hospital, Jakarta, Indonesia

[2]Department of Radiology, Faculty of Medicine, Universitas Indonesia – "Dr. Cipto Mangunkusumo" Hospital, Jakarta, Indonesia

[3]Faculty of Medicine, Universitas Indonesia – "Dr. Cipto Mangunkusumo" Hospital, Jakarta, Indonesia

Al Rasyid **ORCID ID:** 0000-0002-7568-8124

Corresponding author:

Al Rasyid, MD

Email: al-rasyid@ui.ac.id

Short Running Title: Pulsatility Index in CSVD

AMPH
AMALTEA MEDICAL PUBLISHING HOUSE
https://medscience.center/journals/

ABSTRACT

Background and Objectives. The Pulsatility Index (PI) indicates the resistance in distant blood vessels and the stiffness of major arteries outside the brain. For Cerebral Small Vessel Disease (CSVD), our aim is to enhance our comprehension of the Pulsatility Index (PI) in the common carotid artery (CCA), internal carotid artery (ICA), and middle cerebral artery (MCA).

Materials and Methods. This was cross-sectional retrospective research conducted between January 2020 and June 2020 at "Dr. Cipto Mangunkusumo" National Hospital, Indonesia. Patients were divided into groups with CSVD and without CSVD. Univariate and bivariate analyses, along with Spearman correlation and multivariate regression, were conducted to assess the mean difference. The overall score for CSVD was determined based on findings from brain MRI scans.

Results. The median age of the 79 participants was 60 (49-66) years. CSVD made up 54.4% of the total. The median (interquartile range) PI values for the CCA, ICA, and MCA in cases of CSVD were 1.48 (1.3-1.68), 1.12±0.3, and 1.11 (0.95-1.38), respectively. Despite this, no significant differences in PI were observed between the groups. In cases of total stroke, the PI of the CCA showed a moderate correlation with the PI of the MCA (B 0.4, p=0.001) and the PI of the ICA (B 0.34, p=0.005). However, no correlation was found between PI and either the burden of CSVD or the total score for small vessel disease.

Conclusions. The pulsatility indices for the CCA, ICA, and MCA generally rise in cases of CSVD, indicating heightened resistance in distal blood vessels and increased stiffness in the large arteries outside the skull. This highlights the potential use of PI measurement as a promising adjunctive screening and evaluation tool in CSVD.

Keywords: cerebral small vessel disease, measurement of vascular resistance, brain vessel ultrasound imaging

Abbreviations:

CCA: common carotid artery

TCD-CD: transcranial Doppler-carotid Doppler

CI: confidence interval

CSVD: cerebral small vessel disease

CT: computed tomography

DWI: diffusion-weighted imaging

EDV: end-diastolic volume

FLAIR: fluid-attenuated inversion recovery

IBM: International Business Machines

ICA: internal carotid artery

IQR: interquartile range

MCA: middle cerebral artery

MRI: magnetic resonance imaging

PI: Pulsatility index

PSV: peak systolic velocity

SD: standard deviation

SPSS: Statistical Package for Social Sciences

WMH: white matter hyperintensity

AMPH AMALTEA MEDICAL PUBLISHING HOUSE
https://medscience.center/journals/

TITLE: The Significance of Pulsatility Indices in the Middle Cerebral, Internal Carotid, and Common Carotid Arteries for Small Vessel Disease in the Brain: A Retrospective Cross-Sectional Study

INTRODUCTION

Cerebral small vessel disease (CSVD) encompasses conditions affecting the brain's small arteries, arterioles, capillaries, and venules, presenting a diverse spectrum of clinical symptoms, imaging findings, and pathological features. For this reason, CSVD is often reported as an accidental discovery from neuroimaging assessment, especially in the elderly, and may develop for many years during the early stage of the illness when no symptoms are present [1]. The emergence of CSVD often goes unnoticed, and symptoms are typically identified only in later stages when clinical consequences like ischemic and hemorrhagic strokes, Parkinsonism, cognitive deterioration, walking difficulties, and functional impairments manifest [2,3].

White matter lesions, microbleeds, increased perivascular spaces, and brain atrophy are only few of the neuroimaging findings of CSVD that may be seen on an MRI, which have been an invaluable aid in the early diagnosis of CSVD[4]. However, since brain MRI is not routinely performed in patients with vascular risk factor, a comprehensive evaluation is required for screening and evaluation of CSVD.

Gosling's pulsatility index (PI) is a calculated flow parameter in Doppler ultrasound used in evaluating distal vascular resistance. In lacunar infarction, previous research has shown that PI of the MCA, ICA, and CCA are independent determinants of infarct magnitude and reflect distal vascular resistance and large-artery stiffness [5-7]. Recognizing the characteristics of CSVD enables prompt diagnosis and treatment that can slow or possibly halt disease progression and debilitating and costly health outcomes [8,9]. This study aims to describe the demographic features and hemodynamic parameter changes of intra- and extracranial vessels of patients with CSVD.

MATERIALS AND METHODS

Study design and population

This retrospective study utilized data from the Department of Neurology at "Dr. Cipto Mangunkusumo" National Hospital in Jakarta, Indonesia, spanning from January 2020 to June 2020 as its source. The research received approval from the Universitas Indonesia Institutional Review Board, under the protocol number KET-401/UN2.F1/ETIK/PPM.00.02/2023. Participants had to be aged 18 years or older to be included in the study, diagnosed with ischemic stroke by the neurologist and neuroradiologist, and had undergone neuroimaging (CT-scan/MRI) and transcranial Doppler and carotid duplex ultrasound or TCD-CD (within a month of having a diagnosis). For this study, ischemic strokes were divided into two groups, CSVD and nonCSVD according to the clinical assessment and neuroimaging findings of CSVD.

Meanwhile, the exclusion criteria were missing data, patients with cardiac arrhythmias; uni- or bilateral MCA, ICA, and CCA stenosis of more than 50%; neuroimaging studies revealed no infarcts, or intracerebral hemorrhage, or large infarcts extending to the cerebral cortex, or infarct lesion size of more than 20 mm.

Variables and measurements

The overall score for small vessel disease (SVD) was determined for patients who received an MRI scan. One point was given each for 1) lacunar, 2) microbleed, 3) moderate-severe perivascular space (number of lesions more than 10), and 4) white matter hyperintensities (periventricular Fazekas 3 and/or subcortical Fazekas 2-3[10]. A lacune was characterized as a circular or oval-shaped abnormality measuring between 3 and 20 millimeters in diameter, exhibiting cerebrospinal fluid signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging, without any heightened signal on diffusion-weighted imaging (DWI), located in the centrum semiovale, basal ganglia, internal capsule, or brainstem[11]. Microbleeds were identified as round hypointense lesion measuring up to 10 mm, differentiated from other possible diagnosis using the cerebral microbleeds guideline[11]. The position and quantity of microbleeds were evaluated utilizing the Microbleed Anatomical Rating Scale[12]. Perivascular or

Virchow-Robin spaces were identified as lesions that appear hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging, with a diameter of less than 3 mm[12]. Total perivascular spaces were calculated as sum of basal ganglia and centrum semiovale and were classified into 3 groups (<11, 11-20, and >20)[7, 13]. Fazekas scale (0,1,2,3) was used to assess the burden of WMH. MRI evaluation was performed by two radiologists.

Potential risk factors included were hypertension, diabetes mellitus, heart disease, dyslipidemia, and history of smoking. An increase in systolic blood pressure to at least 140 mm Hg and/or diastolic blood pressure to at least 90 mm Hg for a minimum of one week prior to the onset of stroke, or the administration of antihypertensive medication, was noted. Meanwhile, two glucose measures above 200 mg/dL, two fasting glucose measurements over 126 mg/dL, or the use of any antidiabetic medicine constitutes a diagnosis of diabetes mellitus. Dyslipidemia is indicated by cholesterol levels exceeding 200 mg/dL, triglyceride levels surpassing 150 mg/dL, low-density lipoprotein (LDL) levels above 130 mg/dL, high-density lipoprotein (HDL) levels below 40 mg/dL, or the utilization of statins, whereas arrhythmia is not classified as a cardiac condition on its own. History of smoking was defined as ever smoking or had quit smoking or was an active smoker. Pulsatility index (PI) of MCA, ICA, and CCA were extracted from the TCD-CD registry and were calculated as follows:

$$PI = \frac{Peak\ systolic\ volume\ (PSV) - End\ diastolic\ volume (EDV)}{Mean\ flow\ velocity\ (MFV)}$$

Statistical analysis

IBM SPSS 23 was used for the statistical analysis. Normally distributed data were showed as mean (SD) and abnormally distributed data were showed as median (IQR). The difference of proportion was analyzed using Chi-Square/Fisher exact test, while the mean difference was evaluated using the T-test for data following a normal distribution and the Mann-Whitney test for data not adhering to normal distribution, as determined by the Kolmogorov-Smirnov test. In the multivariate logistic regression analysis, we only included variables having a univariate p value of less than 0.25. The correlation between PI of MCA, ICA, and CCA was tested using Spearman correlation. Linear regression analysis was performed to evaluate the independent association of PI and SVD score. P value significant at <0.05.

RESULTS

Out of the 79 cases chosen for the study, 43 (54.4%) were categorized as having CSVD and 36 (45.6%) were identified as not having CSVD. Overall, the average age of stroke patients was 60 (49-66) years. The CSVD group had a greater proportion of >60 years of age than the nonCSVD group (p <0.001; 95% CI 1.03-7.45). Meanwhile, the proportion of men (p=0.04, 95% CI 0.05-0.47) was found to be greater in the nonCSVD (Table 1). In logistic regression analysis, age older than 60 years old and male gender remained statistically significant.

Table 2 shows the vascular hemodynamic parameters of MCA, ICA, and CCA in the two groups. The median and interquartile range for the PI of the CCA, ICA, and MCA within the CSVD group were 1.48 (1.3-1.68), 1.12 ± 0.3, and 1.11 (0.95-1.38), respectively. We found lower CCA PSV and EDV in CSVD than nonCSVD. Meanwhile, ICA had higher EDV and lower PSV. Despite these findings, there were no significant differences between the two groups.

In 66 patients who underwent TCD examination, we found a stronger correlation between PI of CCA and PI MCA in overall stroke (B = 0.4, p = 0.001), compared to PI of ICA and CCA (B = 0.34, p = 0.005). A total of 14 (32.6%) patients underwent brain MRI. Table 3 shows that lacunar infarction was found in 7/14 (50%) subjects, microbleed in 4/13 (30.8%), perivascular spaces ≥11 in 4 (28.6%), Fazekas ≥2 periventricular and subcortical in 7 (50%) with a median total SVD score of 1 (0.75-3). When considering age, no significant correlation was found between the PI and the burden of CSVD.

DISCUSSION

This study highlights the potential use of PI measurement as a promising adjunctive screening and evaluation tool in CSVD. Up to half of all ischemic strokes in this research were caused by CSVD. This finding is consistent with Indonesian multicenter study which showed lacunar infarction prevalence of 45.07%[4]. Other studies in China and Japan also reported similar prevalence rate of 30-50% of all ischemic strokes [14,15]. The increased presence of males in the group without CSVD further corroborates earlier studies that have pointed to being male, aged over 55, having high blood pressure, abnormal lipid levels, and diabetes as contributing factors to the occurrence of lacunar stroke[4].

Pulsatility index reflects the distal vascular resistance and is used as an index for the presence of CSVD [5-7]. Our observations indicated a pattern of rising PI values moving towards more central arteries, with median values for the CCA, ICA, and MCA at 1.48 (1.3-1.68), 1.12 ± 0.3, and 1.11 (0.95-1.38) within the CSVD cohort, respectively. These results are consistent with previous study which showed similar trends in lacunar stroke (PI CCA: 1.57 (0.29), PI ICA: 1.28 (0.27), PI MCA: 1.08 (0.24)) [7]. Cruz et al., also showed similar PI of ICA in CSVD (1.46)[6]. Meanwhile, previous study conducted by Harris et al., which assessed the PI of MCA in patients with hypertension and cognitive impairment showed PI of 1,04 ± 0.25[9].

In contrast to earlier findings, no evidence of correlation between PI of MCA, ICA, and CCA with CSVD burden and total SVD score was detected. This discrepancy could be attributed to smaller sample size of our study, as MRI was not routinely performed in our hospital. Lau et al., found greater burden of CSVD along with increased PI of MCA, followed by ICA and CCA. A possible explanation for this is that large-artery stiffness may lead to an increase in pulsatile flow transmission along the carotid arteries to cerebral vessels which then contributes to the pathophysiology of CSVD and possible cognitive impairment [7,9].

The results of this investigation are constrained by three limitations. Initially, due to the cross-sectional nature of this study, it is not possible to establish a causal link between the pulsatility index and lacunar stroke. Second, this retrospective study relied on the completeness of the data from the available TCD-CD registry, so there was a possibility of selection bias. Third, although brain CT-scan was performed in all patients, brain MRI was not routinely performed. Thus, the number of CSVD diagnosis might be less than actual case.

CONCLUSION

In CSVD conditions, the pulsatility measures of the common carotid artery, internal carotid artery, and middle cerebral artery typically elevate, reflecting an increase in resistance within distant vascular regions and a greater rigidity of the major extracranial arteries. This highlights the potential use of PI measurement as a promising adjunctive screening and evaluation tool in CSVD.

Conflict of interest

I undersign and certificate that I do not have any financial or personal relationships that might bias the content of this work.

Author's contributions

Conceptualization, A.R, P.W.A, T.M, An.R, M.K., R.H., S.H.; methodology, A.R, P.W.A, T.M, An.R, M.R.Y., R.E.Y, M.K., R.H., E.W.; software, A.R, P.W.A, T.M, An.R, .W.; validation, A.R, P.W.A, T.M, ; formal analysis, A.R, P.W.A.; investigation, A.R, P.W.A.; resources, A.R, P.W.A, T.M, An.R, M.R.Y., R.E.Y, M.K., R.H., S.H., E.W. ;data curation, A.R, P.W.A, E.W.; writing—original draft preparation, A.R, P.W.A..; writing—review and editing, all authors; visualization, A.R, P.W.A, E.W.; supervision, A.R.; project administration, E.W.; funding acquisition, A.R, T.M, M.K., R.H., S.H. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Valdés Hernández MdC, Maconick LC, Muñoz Maniega S, Wang X, Wiseman S, Armitage PA, et al. A comparison of location of acute symptomatic vs. 'silent' small vessel lesions. Int J Stroke. 2015;10(7):1044-50.

2. Staszewski J, Piusińska-Macoch R, Brodacki B, Skrobowska E, Macek K, Stępień A. Risk of vascular events in different manifestations of cerebral small vessel disease: A 2-year follow-up study with a control group. Heliyon. 2017;3(11):e00455.

3. Jiménez-Balado J, Riba-Llena I, Abril O, Garde E, Penalba A, Ostos E, et al. Cognitive Impact of Cerebral Small Vessel Disease Changes in Patients With Hypertension. Hypertension. 2019;73(2):342-9.

4. Harris S, Kurniawan M, Rasyid A, Mesiano T, Hidayat R. Cerebral small vessel disease in Indonesia: Lacunar infarction study from Indonesian Stroke Registry 2012-2014. SAGE Open Med. 2018;6:2050312118784312.

5. Kim Y, Lee H, An SA, Yim B, Kim J, Kim OJ, et al. The Effect of Pulsatility Index on Infarct Volume in Acute Lacunar Stroke. Yonsei Med J. 2016;57(4):950-5.

6. de la Cruz-Cosme C, Dawid-Milner MS, Ojeda-Burgos G, Gallardo-Tur A, Segura T. Doppler Resistivity and Cerebral Small Vessel Disease: Hemodynamic Structural Correlation and Usefulness for the Etiological Classification of Acute Ischemic Stroke. J Stroke Cerebrovasc Dis. 2018;27(12):3425-35.

7. Lau KK, Pego P, Mazzucco S, Li L, Howard DP, Küker W, et al. Age and sex-specific associations of carotid pulsatility with small vessel disease burden in transient ischemic attack and ischemic stroke. Int J Stroke. 2018;13(8):832-9.

8. Makin SD, Turpin S, Dennis MS, Wardlaw JM. Cognitive impairment after lacunar stroke: systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes. J Neurol Neurosurg Psychiatry. 2013;84(8):893-900.

9. Harris S, Reyhan T, Ramli Y, Prihartono J, Kurniawan M. Middle Cerebral Artery Pulsatility Index as Predictor of Cognitive Impairment in Hypertensive Patients. Frontiers in Neurology. 2018;9.

10. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. Neurology. 2014;83(14):1228-34.

11. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol. 2009;8(2):165-74.

12. Gregoire SM, Chaudhary UJ, Brown MM, Yousry TA, Kallis C, Jäger HR, et al. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. Neurology. 2009;73(21):1759-66.

13. Potter GM, Chappell FM, Morris Z, Wardlaw JM. Cerebral perivascular spaces visible on magnetic resonance imaging: development of a qualitative rating scale and its observer reliability. Cerebrovasc Dis. 2015;39(3-4):224-31.

14. Turin TC, Kita Y, Rumana N, Nakamura Y, Takashima N, Ichikawa M, et al. Ischemic stroke subtypes in a Japanese population: Takashima Stroke Registry, 1988-2004. Stroke. 2010;41(9):1871-6.

15. Tsai CF, Thomas B, Sudlow CL. Epidemiology of stroke and its subtypes in Chinese vs white populations: a systematic review. Neurology. 2013;81(3):264-72.

AMALTEA MEDICAL PUBLISHING HOUSE

https://medscience.center/journals/

TABLES

Table 1. Demographic characteristics

Characteristics	CSVD (N= 43)	nonCSVD (N= 36)	p	95%CI
Age >60 years, n (%)	22 (51.2)	5 (13.9)	0.001*	1.03-7.45
Male, n (%)	24 (55.8)	28 (77.8)	0.04*	0.05-0.47
Risk factors >2, n (%)	31 (72.1)	27 (75)	0.77	0.42-3.18
Heart disease, n (%)	9 (20.9)	10 (27.8)	0.48	0.52-4.09
Hypertension, n (%)	38 (88.4)	34(94.4)	0.34	0.41-12.29
Diabetes mellitus, n (%)	23 (53.5)	14 (38.9)	0.2	0.23-1.36
Dyslipidemia, n (%)	7 (16.3)	5 (13.9)	0.77	0.24-2.88
History of smoking, n (%)	9 (24.3)	15 (45.5)	0.06	0.94-7.17

Abbreviation: CSVD, Cerebral small vessel disease

*p<0.05

Table 2. Hemodynamic parameters of middle cerebral artery, internal carotid artery, and common carotid artery

Parameters	CSVD (N= 43)	nonCSVD (N= 36)	p	95% CI
Common carotid artery	**n = 37**	**n = 36**		
PSV, cm/s	52.65 (42.85-67.79)	62.72 (48.34-73.39)	0.28	0.97-1.1
EDV, cm/s	14.18 ± 5.69	15.74 ± 6.18	0.64	0.85-1.30
MFV, cm/s	28.39 ± 8.74	29.83 ± 7.45	0.3	0.82-1.06
PI	1.48 (1.3-1.68)	1.49 (1.37-1.84)	0.92	0.1-12.04
Internal carotid artery	**n= 38**	**n = 36**		
PSV, cm/s	51.78 (43.15-64.51)	55.75 (42.16-68.52)	0.83	0.97-1.02
EDV, cm/s	19.37 (15.86-25.57)	16.43 (13.83-22.83)	0.32	0.91-1.03
MFV cm/s	28.82 (24.91-39.31)	29.79 (24.55-37.39)	0.73	0.95-1.04
PI	1.12 ± 0.3	1.22 ± 0.37	0.26	0.55-0.87
Middle cerebral artery	**n =36**	**n = 30**		
PI	1.11 (0.95-1.38)	1.09 (0.91-1.46)	0.24	0.69-4.48

Abbreviation: EDV, end-diastolic volume; MFV, Mean flow velocity, PI, pulsatility index; PSV, *peak systolic velocity*

*p<0.05

Table 3. Pulsatility index based on MRI findings in CSVD

Parameters	Lacunar infarcts (N=7)	*Microbleeds* (N=2)	*Perivascular spaces* ≥11 (N=3)	Fazekas grade ≥2 (N=6)
PI MCA	134 (1.06-1.97)	1.89 ± 0.94	1.13 ± 0.3	1.5 (0.6)
PI ICA	1.35 ± 0.3	1.1 ± 0.31	1.34 ± 0.29	1.35 (0.3)
PI CCA	1.4 ± 0.35	1.33 ± 0.41	1.58 ± 0.24	1.57 (0.39)

Abbreviation: PI, pulsatility index; CCA, common carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery