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

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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 study is a cross-sectional retrospective research, which was conducted between January 2020 and June 2020 at the 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 years (49-66). 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 (in alphabetical order):

CCA – common carotid artery
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
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].

Neuroimaging abnormalities such as white matter lesions, microbleeds, enlarged perivascular spaces, and brain atrophy can be observed on an MRI scan and have proven to be extremely helpful in the early detection of cerebral small vessel disease (CSVD) [4]. However, since brain MRI is not routinely performed in patients with vascular risk factors, 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 as well as 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.

This study is the initial comprehensive investigation of the Indonesian population, taking into account their unique epidemiological and healthcare characteristics, despite the fact that previous research and a systematic review have already explored PI in various groups [10,11]. Indonesia, being a developing country, faces specific challenges in providing healthcare services and managing illnesses. CSVD is frequently associated with both stroke and cognitive impairment in this particular group. Therefore, by tailoring our research findings to the specific circumstances of each locality, we address a crucial deficiency in the development of targeted interventions and the provision of information for national stroke prevention and management initiatives.

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. This retrospective study enrolled participants aged 18 years and older, diagnosed with ischemic stroke by both a neurologist and a neuroradiologist, and who had undergone neuroimaging (CT-scan/MRI) and transcranial Doppler and carotid duplex ultrasound (TCD-CD) within a month of diagnosis. Participants were divided into groups with CSVD and without CSVD based on clinical assessment and neuroimaging findings indicative of CSVD. Exclusion criteria included patients with transient ischemic attack (TIA), cardiac arrhythmias; uni- or bilateral MCA, ICA, and CCA stenosis of more than 50%; and those with neuroimaging findings of normal pressure hydrocephalus, multiple sclerosis, non-ischemic leukoencephalopathy, or absence of infarcts, intracerebral hemorrhage, or large infarcts extending to the cerebral cortex. Additionally, patients with bilaterally absent transtemporal windows in TCD were also excluded to ensure the reliability of the PI measurements.

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 haemorrhage, 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 each was given for: 1) lacunar, 2) microbleed, 3) moderate-severe perivascular space (number of lesions more than 10), and 4) white mat-
ter hyperintensities (periventricular Fazekas 3 and/or subcortical Fazekas 2-3) [12]. A lacune was characterized as a circular or oval-shaped abnormality measuring between 3 and 20 millimetres 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 [13]. Microbleeds were detected as circular areas of decreased signal intensity, with a size of up to 10 mm. They were distinguished from other potential diagnoses using the cerebral microbleeds guideline [13]. The position and quantity of microbleeds were evaluated utilizing the Microbleed Anatomical Topography scale [14]. 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 [14]. Total perivascular spaces were calculated as the sum of basal ganglia and centrum semiovale and were classified into 3 groups (<11, 11-20, and >20) [7,15]. 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. PI of MCA, ICA, and CCA were extracted from the TCD-CD registry. PI measurements were obtained using the Philips iU22 ultrasound system with a 2.5 MHz transducer for carotid duplex and a 2 MHz probe for transcranial Doppler. PI was calculated using the formula: PI = (PSV−EDV)/MFV, where PSV is the peak systolic volume, EDV is the end diastolic volume, and MFV is the mean flow velocity. Measurements were taken bilaterally for the ICA, and MCA and the average values were used for analysis to ensure consistency and accuracy across all subjects. Additionally, measurements of the CCA were included due to its importance in evaluating overall arterial stiffness and its role as a significant extracranial contributor to cerebral hemodynamics.

**Statistical analysis**

IBM SPSS 23 was used for the statistical analysis. Normally distributed data were shown as mean (SD), and abnormally distributed data were shown 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 the 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 years (49-66). The CSVD group had a greater proportion of >60 years of age than the non-CSVD 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 non-CSVD (Table 1). In logistic regression analysis, age above 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 non-CSVD. Meanwhile, ICA had higher EDV and lower PSV. Despite these findings, there were no significant differences between the two groups.

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

Abbreviation: CSVD, Cerebral small vessel disease *p<0.05
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 the Indonesian multicentre study which showed lacunar infarction prevalence of 45.07% [4]. Other studies in China and Japan also reported a similar prevalence rate of 30-50% of all ischemic strokes [16,17]. 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 a 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, a 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 the smaller sample size of our study, as MRI was not routinely performed in our hospital. Lau et al. found a 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].

An examination of the association between PI values and certain clinical outcomes in CSVD can provide further insights into the pathophysiological mechanisms. Research has indicated that elevated PI levels, which indicate greater arterial stiffness, may play a role in the development of white matter hyper-intensities and lacunar infarcts, which are frequently seen in individuals with CSVD [18]. The results of our research provide evidence in favor of this notion, however the specific mechanisms still need to be clarified by additional longitudinal investigations. Moreover, our research highlights the capacity of PI

| 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 | 0.1-1.12.04 |
| 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.**

| 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.**
measures as a non-intrusive instrument that may be incorporated into regular clinical evaluations to anticipate and track the advancement of CSVD, therefore assisting in early intervention and management methods. Furthermore, the correlation observed between PI of the CCA and other arteries in the brain indicates that the overall health of the systemic arteries may have a more complex relationship with the integrity of the small blood vessels in the brain than previously known. This result is consistent with recent research that suggests that the health of the blood vessels throughout the body affects the blood flow in the brain, and hence, the risk of CSVD [19]. Through the examination of these connections, our research contributes to the expanding collection of literature that emphasizes the importance of doing a thorough evaluation of blood vessels in individuals who are at risk of or displaying symptoms of CSVD.

Our study faces several limitations that are inherent to its design and scope. First, as a retrospective cross-sectional analysis, it does not allow for the observation of changes over time or the establishment of causality between pulsatility indices and cerebral small vessel disease (CSVD). Second, only a small proportion (32%) of patients underwent an MRI exam, which may limit the generalizability of our findings to all stroke patients. Additionally, our analysis did not adjust for age and other significant risk factors for CSVD, which could affect the associations observed. Lastly, our study did not differentiate between patients with lacunar strokes and those with non-lacunar strokes, which may have provided further insights into the specific vascular changes associated with different types of stroke. Finally, the non-blinding of measurements for MRI grading and TCD measuring of the PI could introduce observer bias. However, all evaluations were conducted by a highly experienced neuroradiologist, ensuring a high level of diagnostic accuracy and consistency in the assessments. While the inclusion of multiple independent readers could potentially enhance the objectivity of our findings, the expertise of our examiner provides a strong foundation for the reliability of our results.

This study’s importance goes beyond simply replicating the already recognized connections between pulsatility indices and CSVD. It also offers essential local data that is crucial for the Indonesian healthcare system. Given the increasing prevalence of stroke, namely cerebrovascular small vessel disease (CSVD), as a major health issue in Indonesia [4], the findings of this study have the potential to provide valuable guidance for the development of health policies and targeted intervention techniques that are specifically designed for the Indonesian population. The study’s results are crucial for policymakers and healthcare professionals to comprehend the hemodynamic changes linked to CSVD in Indonesia, where there has been a notable absence of such data.

CONCLUSION

In CSVD conditions, the pulsatility measures of the common carotid artery, internal carotid artery, and middle cerebral artery typically increase, 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.


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