Clinical predictors of increased middle cerebral artery pulsatility

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Abstract

Background: Transcranial Doppler Pulsatility Index (PI) has traditionally been interpreted as a descriptor of distal cerebrovascular resistance. Many authors have investigated its usefulness in the context of traumatic brain injury (TBI), subarachnoid hemorrhage (SAH) and hydrocephalus. Nonetheless, many doubts remain about its interpretation in cerebrovascular prevention. The aim of our study is to identify the clinical predictors of increased PI.

Methods: We conducted an analysis of a prospective database including all patients undergoing cerebrovascular ultrasonographic evaluation during 2011. We excluded patients with ≥70% stenosis or occlusion in any intra or extracranial artery, stenosis in middle cerebral artery (MCA), atrial fibrillation, patients without transtemporal sonographic window and all evaluations performed in context of TBI, SAH, acute ischemic stroke or intracranial hypertension. The mean PI of both MCA, measured in its middle third after a minimum of 10 minutes of rest in the supine position, was registered. Vascular risk factors and clinical conditions were analyzed.

Results: Of the 947 patients analyzed, 446 were included, of which 287 (64.3%) were male. The mean age was 62.7 years (SD = 14.92) and the mean PI was 0.995 (SD = 0.240). In multivariate analysis, age (regression coefficient Beta (B):0.007, 95% CI: 0.005-0.009, p<0.001), hypertension (B:0.056, 95% CI: 0.003-0.108, p=0.037) and diabetes mellitus (B:0.064, 95% CI: 0.006-0.121, p=0.030) were identified as predictors of increased PI.

Conclusion: These results suggest that PI is associated with vascular risk factors classically responsible for small vessel disease. We discuss the pathophysiology of elevation of PI and its possible usefulness in cerebrovascular prevention.

Keywords: Pulsatility Index, Transcranial Doppler, Cerebrovascular resistance, Small vessel disease, Cerebrovascular prevention.
Introduction

Gosling’s Pulsatility Index (PI) and Pourcelot’s Resistance Index, as derived from transcranial Doppler ultrasound (TCD), have long been proposed to reflect the degree of downstream vascular resistance caused by small vessel ischemic disease [1, 2]. PI characterizes the shape of a TCD spectral waveform and is calculated as the ratio of the difference between peak systolic and end diastolic velocities and the mean velocity (Figure 1). The index, being a ratio of velocities, does not rely on the knowledge of the diameter nor insonation angle of the vessel and thus can be directly compared between patients.

Its usefulness has been investigated for the last decades in the noninvasive assessment of intracranial pressure and cerebral perfusion pressure in the context of traumatic brain injury (TBI) [3], hydrocephalus [3] and subarachnoid hemorrhage (SAH) [4]. In cerebrovascular disease research, PI, measured in middle cerebral artery (MCA), was found to be associated with the presence and the severity of white matter lesions in magnetic resonance imaging (MRI), suggesting a role as a screening tool for cerebral small vessel disease [5, 6]. Nonetheless, the value of PI in these fields remains controversial.

The aim of our study was to identify the clinical predictors of increased MCA PI.

Methods

We performed a cross-sectional study including all patients undergoing cerebrovascular ultrasonographic evaluation in our hospital’s neurosonology laboratory during 2011. We excluded subjects with ≥70% stenosis or occlusion in any intra or extracranial artery, stenosis in MCA, atrial fibrillation, patients without transtemporal sonographic window and all evaluations performed in context of TBI, SAH, acute ischemic stroke or intracranial hypertension.

We analyzed a prospective database including mean MCA PI and presence of several vascular risk factors. PI was measured by two neurosonologists using transcranial color-coded Doppler with a handheld 3-MHz probe (General Electrics Logiq 7©). After a minimum of 10 minutes of rest in the supine position, both MCAs were insonated through transtemporal window using color Doppler technique and PI was measured in its middle third.

Vascular risk factors and clinical conditions registered were age, gender, hypertension, diabetes, dyslipidemia, hyperuricaemia, obesity, smoking, congestive heart failure (CHF), and history of stroke.

For univariate analysis of nominal variables we performed independent-samples t-tests and for age Pearson’s correlation coefficient. Considering the high number of patients included and the potential for confounding regarding the pathological relationship between the variables analyzed we decided to perform a multivariate analysis using a linear regression model that included all clinical factors. We present the results of the multivariate analysis as regression coefficient Beta (B) and 95% Confidence Interval (CI). Values of p<0.05 were regarded as significant.

Results

We analyzed 947 subjects. Of those, 501 were excluded for presenting ≥70% stenosis or occlusion in an intra or extracranial artery (72), stenosis in MCA (101), atrial fibrillation (169), missing transtemporal sonographic window (155), and evaluations performed in context of TBI, SAH, acute ischemic stroke or intracranial hypertension (43). Of the 446 patients included, 287 (64.3%) were male, mean age was 62.7 years (SD = 14.92) and mean MCA PI was 0.995 (SD = 0.240).

In univariate analysis, the clinical factors associated with elevated PI were male gender (0.94±0.21 vs. 1.02±0.25; p<0.001), hypertension (0.92±0.20 vs. 1.06±0.25; p<0.001), diabetes (0.98±0.24 vs. 1.07±0.22; p=0.001) and hyperuricaemia (0.99±0.23 vs. 1.06±0.22; p<0.031). Age (r=0.440; p<0.001) was correlated with elevated PI (Table 1).

In multivariate analysis the predictors of increased PI were age (B:0.007, 95% CI: 0.005-0.009, p<0.001), hypertension (B:0.056, 95% CI: 0.003-0.108, p=0.003) and diabetes (B:0.064, 95% CI: 0.006-0.121, p=0.030) (Table 2).

Discussion

In the present study, the main predictors of elevated PI were vascular risk factors classically responsible for small vessel disease: age, hypertension, and diabetes. Interestingly, dyslipidemia was not a clinical or analytical

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Hemodynamic parameters derived from Doppler spectrum analysis: (a) elevated PI; (b) normal PI.

PSV: Peak systolic velocity; EDV: End diastolic velocity
predictor of increased PI. In fact, dyslipidemia has shown a strong inverse association with white matter hyperintensities, suggesting a protective role in cerebral small vessel disease [7].

The pathophysiology of MCA PI elevation remains unclear and has been an object of discussion. It appears to be a complex function of various hemodynamics factors, namely cardiac function, vessel radius, blood viscosity, and cerebral perfusion pressure [8]. Increased cerebrovascular resistance, measured by MCA PI, has been interpreted as a direct consequence of the narrowing of small vessels due to lipohialynosis and microatherosclerosis.

Mok et al. [6] conducted a community study where PI was found to be independently associated with white matter lesions severity, evaluated by MRI. Moreover, the negative predictive value of PI was high, suggesting that TCD PI may guide the identification of subjects with subclinical small vessel disease. In a similar study, PI correlated well with a variety of MRI manifestations of small vessel disease: periventricular hyperintensity, deep white matter hyperintensity, lacunar disease, and pontine hyperintensity [9].

Two studies [10, 11] investigated TCD findings of diabetes-related cerebral hemodynamic changes. PI was correlated with the duration of diabetes and was significantly increased in complicated diabetic subjects (with retinopathy and lacunar infarction).

Meanwhile, other authors hypothesized that disproportionate stiffness of proximal aorta with advancing age and in the presence of various vascular risk factors, as compared with peripheral arteries, reduces the Windkessel function of aorta and therefore facilitates transmission of excessive pulsatile energy into cerebral microcirculation. These abnormal physical forces would trigger microvascular damage and remodelling, leading to microvascular ischaemia [12].

Supporting this theory, several studies have proved that MCA PI is strongly correlated with aortic pulsatility and stiffness, suggesting a causative pathophysiological relationship [5, 13].

There are limitations of our study that need to be considered. First, it has a single centered, cross-sectional design, and therefore it examined associations; additional work will be required to ascertain whether these associations represent causal relationships. Second, the time of evolution of each vascular risk factor was not analyzed, nor the possible ongoing treatments. Another natural limitation refers to the population analyzed, including only patients referred to a neurosonology laboratory, therefore with higher prevalence of risk factors. Nonetheless we feel that by selecting consecutive patients without stringent exclusion criteria and considering the multivariate analysis performed, this factor did not influence the results obtained.

### Table 1. Results of univariate analysis.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>N</th>
<th>Mean PI (SD)</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>287</td>
<td>0.94 (0.21)</td>
<td>1.02 (0.25)</td>
<td>–</td>
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<tr>
<td>Hypertension</td>
<td>234</td>
<td>0.92 (0.20)</td>
<td>1.06 (0.25)</td>
<td>–</td>
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<tr>
<td>Diabetes</td>
<td>90</td>
<td>0.98 (0.24)</td>
<td>1.07 (0.22)</td>
<td>–</td>
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<tr>
<td>Hyperuricaemia</td>
<td>59</td>
<td>0.99 (0.23)</td>
<td>1.06 (0.22)</td>
<td>–</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>271</td>
<td>0.99 (0.27)</td>
<td>1.00 (0.22)</td>
<td>–</td>
</tr>
<tr>
<td>Obesity</td>
<td>31</td>
<td>0.99 (0.24)</td>
<td>1.00 (0.25)</td>
<td>–</td>
</tr>
<tr>
<td>Smoking</td>
<td>40</td>
<td>1.00 (0.24)</td>
<td>0.98 (0.24)</td>
<td>–</td>
</tr>
<tr>
<td>CHF</td>
<td>16</td>
<td>0.99 (0.24)</td>
<td>1.09 (0.22)</td>
<td>–</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>30</td>
<td>0.99 (0.24)</td>
<td>1.06 (0.20)</td>
<td>–</td>
</tr>
<tr>
<td>Age</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.440</td>
</tr>
</tbody>
</table>

CHF = Congestive Heart Failure; PI = Pulsatility Index

### Table 2. Results of multivariate analysis.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>B</th>
<th>Lower</th>
<th>Upper</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.007</td>
<td>0.005</td>
<td>0.009</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.056</td>
<td>0.003</td>
<td>0.108</td>
<td>0.037</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.064</td>
<td>0.006</td>
<td>0.121</td>
<td>0.030</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>-0.091</td>
<td>-0.112</td>
<td>0.008</td>
<td>0.089</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>0.078</td>
<td>-0.16</td>
<td>0.109</td>
<td>0.148</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.021</td>
<td>-0.076</td>
<td>0.114</td>
<td>0.694</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.048</td>
<td>-0.041</td>
<td>0.112</td>
<td>0.362</td>
</tr>
<tr>
<td>CHF</td>
<td>0.024</td>
<td>-0.103</td>
<td>0.164</td>
<td>0.654</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>-0.062</td>
<td>-0.147</td>
<td>0.380</td>
<td>0.244</td>
</tr>
</tbody>
</table>

B = Regression Coefficient Beta; CHF = Congestive Heart Failure; PI = Pulsatility Index
The main strength of our study is its large sample, allowing to observe independent associations in multivariate analysis.

**Conclusion**

PI is directly related to higher age, hypertension, and diabetes mellitus. Longitudinal multicenter studies are needed to document its potential role in the development and severity of diffuse small vessel disease and as a measure of the effectiveness of therapeutic interventions.

**Abbreviations**

CHF: Congestive heart failure; MCA: Middle cerebral artery; MRI: Magnetic resonance imaging; PI: Pulsatility index; SAH: Subarachnoid hemorrhage; TBI: Traumatic brain injury; TCD: Transcranial Doppler ultrasound

**Acknowledgments**

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**Competing interests**

The authors declare no conflict of interest.

**References**