Pulsatility index in the middle cerebral artery- associated with cognitive impairment in lacunar stroke?

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Key words: Pulsatility index, Lacunar stroke, Lacunar infarct, Cognitive impairment

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Abstract

Background and Purpose-- Pulsatility index (PI) of the middle cerebral artery is postulated to reflect the vascular resistance in the artery distal of the probe, and has been reported to increase in small vessel disease, diabetes mellitus, ageing and dementia. Lacunar infarcts are considered to be related to cognitive impairment. We therefor conducted a study to assess the association between cognitive impairment and PI in patients with a lacunar infarct.

Methods-- Consecutive patients presenting with an acute lacunar syndrome who were admitted to the stroke unit were enrolled. The patients were examined with Doppler ultrasonography of the intracranial arteries, and the pulsatility index of the middle cerebral artery was recorded. Cognitive function was evaluated by Mini Mental State Examination (MMSE), Clock Drawing Test and Trail Making Test (TMT) A and B.

Results-- Among the 113 patients included, 85 patients had an acute lacunar infarct and 28 had one or more non-lacunar infarcts. The mean pulsatility index was 1.46 (SD=0.33). PI was significantly ($P < 0.05$) associated with MMSE, TMT A and TMT B in patients with lacunar infarct, even after adjustment for multiple patient characteristics (Age, Sex, Prestroke Hypertension, Smoking, Previous stroke and Diabetes).

Conclusions-- Pulsatility index was associated with the cognitive performance in patients with lacunar infarcts and a lacunar syndrome. An elevated PI may be related to impairment in several cognitive domains. These findings suggest that TCD may be a useful supplement to other cognitive investigations in clinical practice.

Introduction

Lacunar infarcts are typically located in the basal ganglia and the subcortical white matter. The clinical syndromes are characterized by motor, sensory or sensorimotor hemisymptoms without cortical deficits. Lacunar infarcts have been related to cerebral small vessel disease, pathologically characterized by lipohyalinosis in end arteries deep in the brain,¹ and both lacunar infarcts and small vessel disease are associated with cognitive impairment and dementia.²⁻⁴ Studies have documented cognitive impairment in the acute phase^{3, 5, 6} as well as in long term follow up.^{2, 7, 8} Cognitive impairment in patients with lacunar infarcts may be just as frequent and important as motor and sensory sequelae, but may be overlooked.⁹ A systematic review by Edwards et al. documented that all major cognitive domains were affected in lacunar infarcts.¹⁰ Some reports show that executive functions and working memory are particularly affected in small vessel disease.¹¹

Transcranial Doppler Ultrasonography (TCD) is a non-invasive method which is easy to apply, and which provides information about intracranial hemodynamics and structural changes in the large intracranial vessels. It is used to detect stenosis and occlusions, and to evaluate revascularization after thrombolysis, as well as facilitate thrombolysis. Ultrasound may also be used to measure the variability of blood velocity in a vessel, the pulsatility index (PI). The index is derived from TCD, and was first described by Gosling and King.¹² PI characterizes the shape of the spectral waveform and is independent of probe angle to vessel. It is postulated to reflect the vascular resistance in the artery distal of the probe, and has been reported to increase in small vessel disease, diabetes mellitus, ageing and dementia.¹³⁻¹⁸ In a metaanalysis of TCD-studies in Alzheimer's disease (AD) and vascular dementia (VaD),¹⁹ the authors found significantly higher PI in patients with VaD compared to those with AD. Lopez-Oloriz and colleagues^{20, 21} have found that PI of the medial cerebral artery is independently associated with cognitive impairment in community-dwelling asymptomatic

participants. TCD may provide crucial information on the relation between cognitive impairment and vascular risk factors.²²

As increased PI is seen in VaD, and since lacunar infarcts are related to cognitive impairment, we hypothesized a relation between lacunar infarcts, PI and reduced mental capacity. Hence, we conducted a study to assess the association between cognitive impairment and PI in patients with a lacunar infarct, and differences in association between patients with lacunar and non-lacunar infarct. The primary aim was to investigate whether increased PI in patients with lacunar infarcts, is associated with impairment in different cognitive domains, notably executive functioning.

Methods

Patients presenting with an acute clinical lacunar syndrome, admitted to the stroke unit of Akershus University Hospital from February 2011 to January 2013, were prospectively included and screened for a lacunar infarct. The methods have been described in detail elsewhere.²³

The diagnosis of a lacunar syndrome was based upon the patients' history and neurological examination, i.e. clinical findings compatible with a lacunar syndrome. Patients who were treated with intravenous thrombolysis were included, even when their symptoms lasted less than 24 hours. Exclusion criteria were intracerebral hemorrhage and transient ischemic attack (TIA, symptoms lasting <24 h). Patients who had no visible acute infarct on radiological examination were excluded.

Assessments

The patients underwent standard examination at our stroke unit including blood samples, electrocardiogram records (ECG) and cerebral computed tomography (CT) at admittance. We registered cerebrovascular risk factors (i.e. hypertension, smoking, atrial fibrillation, hypercholesterolemia, ischemic heart disease, diabetes, large vessel disease and previous stroke or TIA), and defined prestroke hypertension as on-treatment at admittance. Patients were examined with Doppler ultrasonography of precerebral and intracranial arteries within three days of admittance. The examination was performed by one neurologist (M.A.) using GE Vivid 7 Dimension, 4 MHz probe (GE Vingmed Ultrasound AS, Horten, Norway). The middle cerebral arteries (MCAs) were insonated through the transtemporal window at a depth of 50 to 60 mm. The vascular peak systolic velocity, pulsatility index (PI), spectrum shape and direction of blood flow in the proximal MCA (M1) were observed and recorded. The PI value was automatically calculated by the Doppler machine using the mean of 5 cycles (according to the formula $PI = (\text{systolic flow velocity} - \text{diastolic flow velocity}) / \text{mean flow velocity}$). A mean MCA PI was calculated by averaging the MCA PI from both hemispheres. If the patient only had good temporal window on one side, unilateral MCA PI was considered as mean PI. Findings of symptomatic carotid or middle cerebral artery stenosis $\geq 50\%$ were registered. Patients underwent magnetic resonance imaging (MRI) with diffusion-weighted images (DWI) within a week after admittance to hospital. The brain imaging was done on Philips Achieva (Royal Philips, Amsterdam, The Netherlands) 1.5T or 3T MRI scanners employing standard sequences, using T1 weighted sagittal, T2 weighted axial, T2/FLAIR weighted coronal and diffusion weighted (DWI) axial imaging. Isolated acute ischemic lesions on DWI or CT were defined as lacunar infarcts (LI) if <15 mm and located subcortically or in the brainstem,²⁴ whereas all other acute ischemic lesions were defined as

non-lacunar infarcts (NLI). All included patients were examined clinically by an experienced stroke neurologist (M.A.).

Neurological impairment was assessed by using the 11-items version of the National Institutes of Health Stroke Scale (NIHSS)²⁵ on day one after admittance to hospital and at discharge. Global function was evaluated using the modified Rankin Scale (mRS)^{26, 27} at discharge. Cognitive function was evaluated by Mini Mental State Examination (MMSE),^{28, 29} Clock Drawing Test³⁰ and Trail Making Test A and B,³¹ and all assessments were performed between day 2 and day 5. The cognitive assessments evaluate different cognitive domains. The MMSE is used for global cognitive screening. The TMT B measures executive functioning, while the Clock Drawing Test primarily measures visuospatial functions in addition to executive functioning. The TMT A is considered to be a test of psychomotor speed. The Clock Drawing Test was dichotomized into correct or incorrect answers (5 vs. ≤ 4) according to Shulman.^{30, 32} TMT A and B were measured in seconds, and the tests were interrupted after 6 minutes if not completed.

Statistical Analyses and ethical aspects

Data were analyzed using SPSS version 22 (SPSS Inc., Chicago IL). All significance tests were two-tailed and performed at the 5% level. Continuous variables were presented as means and standard deviations (SD) or medians and the interval between first (Q1) and third (Q3) quartiles. Normality of continuous variables was assessed by inspecting the histograms. Between-group (LI vs. NLI) differences of the characteristics and stroke risk factors were compared using independent samples t-test for normally distributed continuous data, Mann-Whitney test for skewed continuous data, and χ^2 -test for categorical variables. The associations between performances on cognitive tests and PI were assessed by linear

regression models for continuous outcomes (MMSE, TMT A and B) and a logistic regression model for dichotomous outcome (Clock Drawing Test). First models containing PI and group indicator (LI vs. NLI) as well as interaction between the two were estimated. The interaction terms quantify possible differences in association in two groups of infarcts. The models were further adjusted for age, gender, prestroke hypertension, diabetes and previous stroke. Due to interaction terms in the models, the results were presented as regression coefficients with standard errors and corresponding p-values. For easier interpretation of modeling results, estimated means with corresponding 95% confidence intervals (CI) were presented graphically for a number of PI values. We then excluded the NLI-group and did further analyses on the association between PI and cognitive tests performance in the lacunar group, using a linear and logistic multivariate regression model where appropriate. These results were presented as regression coefficients or ORs with standard errors and corresponding p-values.

Oral and written informed consent was obtained from all included patients. The study was approved by The Regional Committee for Ethics in Medical Research.

Results

We recruited 147 patients presenting with symptoms compatible with a lacunar syndrome. Of these, 34 patients had no sign of acute ischemic lesion on CT or DWI and were excluded from the analyses due to uncertainty about stroke subtype. Among the remaining 113 patients, 85 (75.2%) patients had an acute lacunar infarct, and 28 (24.8%) had one or more non-lacunar infarcts. The lacunar infarcts were localized in the basal ganglia (44%), the periventricular white matter (21%), the thalamus (14%) or in the brainstem (21%). The non-lacunar infarcts

were localized in the cortex or subcortically, but none were due to occlusion of a major vessel.

The mean age was 70.1 years (SD=11.5), and 69% were men. The median mRS at discharge was 2 (1-3) and NIHSS 1 (0.5-3). The mean MMSE score was 26.1 (SD=3.6), and 43% scored ≤ 26 . The mean TMT A time was 72.6 seconds (SD=43.8) and the mean TMT B time was 195.1 seconds (SD=107.8). 47% had a TMT B age adjusted score $\geq 2SD$.³³ 68.1% of the patients had a normal Clock Drawing Test score. Adequate Transtemporal window for Doppler data was achieved in 84% of the patients. The mean PI was 1.46 (SD=0.33). Characteristics and stroke risk factors are presented in Table 1. We found no statistically significant difference in PI between patients with lacunar and non-lacunar infarcts.

Estimated means of unadjusted MMSE and TMTB score with corresponding 95% CIs are presented graphically for a number of PI values, see figure 1. There were no statistically significant differences between lacunar and non-lacunar infarct groups with respect to the association between PI and the different outcome variables. The results from the multiple and logistic regression model for the LI group are presented in Table 2. PI was significantly ($P < 0.05$) associated with MMSE, TMT A and TMT B in the LI group, even after adjustment for a number of patient characteristics. The Clock Drawing Test was not significantly associated with PI (unadjusted $P=0.057$, adjusted $P=0.348$).

Discussion

Our study demonstrates that TCD PI values were significantly associated with MMSE, TMT A and TMT B performances in patients with a lacunar infarct. To the best of our knowledge, our study is the first to identify this association in patients with ischemic strokes. The results are however in accordance with those found by Lopez-Oloriz et al.²⁰ in a study of asymptomatic participants between 50-65 years. We found no statistically significant

differences between LI and NLI groups with respect to the association between PI and cognitive tests. In a review by Sabyan and colleagues,¹⁹ the authors found disturbances in cerebrovascular hemodynamics in patients with Alzheimer's disease and vascular dementia compared to healthy controls. PI was significantly higher in patients with vascular dementia compared to patients with Alzheimer's disease. PI is believed to reflect the resistance in the arteries deep in the brain, and may be an indicator of small vessel disease.¹⁴ The lack of stronger association between the cognitive tests and PI in the LI group compared with the NLI group in our study may be due to a too small NLI group. The NLI group in the present study is a highly selected group in which all patients presented with a lacunar syndrome. As they therefore may not represent a typical NLI group among patients with stroke, small vessel disease may have been prevalent in this particular NLI group. Well known risk factors for small vessel disease such as hypertension, diabetes and other cerebrovascular risk factors were present in both groups.

The association between PI and MMSE was significant in both groups, and was not affected when we adjusted for age, previous stroke, hypertension and diabetes. Adjustment for previous stroke is important, as repeated strokes may result in progressive cognitive impairment. Both age and prior stroke are well recognized predictors of cognitive impairment, and hypertension and diabetes are closely linked to small vessel disease.⁸ Ihle-Hansen and colleagues³⁴ found that impaired executive functioning and memory were associated with white matter lesions on MRI. Kidwell et al.¹⁴ showed a strong correlation between PI and MRI changes compatible with small vessel disease.

MMSE is frequently used for global cognitive screening, but may lack sensitivity in patients with stroke.³⁵ Nevertheless, there is a strong association between MMSE and PI values in our study, where an elevated PI predicts a low score on MMSE. The association between PI and TMT A also remained significant in both groups after adjustment. TMT A

measures psychomotor speed and TMT B measures visual attention, information processing and executive functioning. These are cognitive impairments traditionally associated with lacunar infarcts. Such cognitive dysfunctions occur in the domains most susceptible to disruptions in subcortical grey and white matter. The finding of an association between PI and TMT B after adjustment was only present in analyses performed after excluding the NLIs. This may suggest a stronger association between PI and TMT B in lacunar infarcts, but further studies with higher sample size are needed to confirm this finding. We did not find any association between the Clock Drawing test and PI values in our study. In a quantitative systematic review by Edwards and colleagues,¹⁰ the authors provided evidence for a cognitive impairment profile in patients with lacunar stroke that involves several domains, including information processing speed, attention/working memory, executive function, language, memory and visuospatial processing. They found no evidence for change in domain-specific cognitive function over time after lacunar stroke, and assumed that the longer-term rate of cognitive decline is due to stroke recurrence. The Secondary Prevention of Small Subcortical Strokes (SPS3) clinical trial³⁶ examined domain-specific cognitive outcomes in patients with symptomatic lacunar infarcts.⁹ In this study, they found episodic memory deficits in patients in addition to the typical impairment pattern for small vessel disease. Mild cognitive impairment was present in almost half of their participants, and was more prevalent than physical disability defined by mRS ≥ 2 . This is in accordance with the findings in our study, although we did the testing in the acute phase after stroke. More than 40 % of the patients in the LI group in our study had a MMS score ≤ 26 , while 39% had mRS ≥ 2 . Cognitive impairment after lacunar stroke is common, and may have a major impact on the patient's quality of life.

Diabetes was also a strong predictor of low MMSE score in the multivariate analyses. Patients with diabetes are more likely to develop dementia than those without diabetes.³⁷

Diabetes is an independent risk factor for lacunar infarction,⁸ and has previously been found to be independently associated with a high PI.³⁸ In an autopsy study of patients with stroke, cerebral small vessel disease was 2.5 times more frequent among patients with diabetes than patients without diabetes.³⁹ Widespread atherosclerosis may as well affect the ostium of the perforating arteries and lead to lacunar infarcts.

We screened consecutive patients presenting with a lacunar syndrome to identify lacunar infarcts. A limitation of our study comparing lacunar and non-lacunar infarcts were few patients in the non-lacunar infarct group, which may entail too little power to discover between-group differences. Further studies will be required to look at the association between PI and cognitive impairment in different subgroups of stroke.

Conclusions

In conclusion, pulsatility index was associated with the cognitive performance in patients with lacunar infarcts and a lacunar syndrome. An elevated PI may be related to impairment in several cognitive domains. These findings suggest that TCD may be a useful supplement to other cognitive investigations in clinical practice.

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Table 1 Characteristics and stroke risk factors

	All patients	Lacunar infarct	Non-lacunar infarct	P value
n (%)	113	85 (75.2)	28 (24.8)	
Age, mean (SD)	70.1 (11.5)	69 (11.6)	74.0 (10.0)	0.068*
Males	78 (69.0)	60 (70.6)	19 (67.9)	0.532 [†]
Current smokers	39 (34.5)	34 (40.0)	5 (17.9)	0.033 [†]
Prestroke hypertension	62 (54.9)	44 (51.8)	18 (64.3)	0.248 [†]
Diabetes	28 (24.8)	19 (22.4)	9 (32.1)	0.298 [†]
Use of statins	42 (37.2)	30 (35.3)	12 (42.9)	0.473 [†]
Coronary disease [§]	21 (18.6)	17 (20)	4 (14.3)	0.500 [†]
Large vessel disease [‡]	17 (15.0)	11 (12.9)	6 (21.4)	0.276 [†]
Atrial fibrillation	16 (14.2)	11 (12.9)	6 (21.4)	0.518 [†]
Previous stroke [‡]	20 (17.7)	14 (16.5)	6 (21.4)	0.551 [†]
NIHSS at admission, median, (Q ₁ -Q ₃)	3 (2-4)	3 (2-4)	2 (1.25-3.75)	0.218 [‡]
NIHSS at discharge, median, (Q ₁ -Q ₃)	1 (0.5-3)	2 (1-3)	1 (0-2)	0.112 [‡]
Barthel ADL index day 2-4, median, (Q ₁ -Q ₃)	20 (16-20)	20 (15-20)	20 (17.25-20)	0.738 [‡]
mRS at discharge, median, (Q ₁ -Q ₃)	2 (1-3)	2 (1-3)	2 (1.25-2)	0.458 [‡]
MMSE score, mean (SD)	26.1 (3.6)	26.3 (3.5)	25.3 (4.0)	0.227 [‡]
TMT A sec, mean (SD)	72.6 (43.8)	68.7 (41.1)	85.9 (50.8)	0.075 [‡]
TMT B sec, mean (SD)	195.1(107.8)	188.5 (111.8)	217.4 (92.2)	0.107 [‡]
Correct Clock drawing test	77 (68.1)	61 (75.3)	16 (66.7)	0.400 [†]
Transtemporal window TCD	95 (84.1)	73 (85.9)	22 (78.6)	0.359 [†]
Pulsatility index MCA, mean (SD)	1.46 (0.33)	1.45 (0.34)	1.49 (0.28)	0.636*
Intima - Media Thickness, mean (SD)	0.87 (0.23)	0.86 (0.19)	0.89 (0.32)	0.545*

ADL, Activities of Daily Living; MCA, middle cerebral artery; MMSE, Mini-Mental state examination; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, Standard deviation; TCD, Transcranial Doppler ultrasonography; TMT, Trail Making Test.

Results are n and (%) unless indicated otherwise

* Independent samples t-test

[†] χ^2 -test

[‡] Mann-Whitney test

[§] Previous myocardial infarction and/or angina pectoris

[‡] >50% stenosis in the internal carotid artery or middle cerebral artery

Table 2 The association between PI and cognitive tests in the lacunar infarct group

Variables	Bivariate analyses		Multivariate analyses*	
	Regr coeff (95 % CI)	P value	Adjusted Regr coeff (95 % CI)	P value
MMSE	-4.00 (-6.19- -1.81)	0.001	-2.98 (-5.48- -0.49)	0.020
TMT A	51.03 (24.08-78.00)	<0.001	44.26 (9.52-78.99)	0.013
TMT B	115.2 (40.9-189.5)	0.003	100.13 (1.15-199.11)	0.047
	OR (95 % CI)	P value	Adjusted OR (95 % CI)	P value
Clock Drawing Test	0,21 (0.04-1.02)	0.053	0.34 (0.04-2.68)	0.341

* adjusted for Age, Sex, Prestroke hypertension, Smoking, Previous stroke and Diabetes

PI, Pulsatility Index; MMSE, Mini-Mental state examination; TMT, Trail Making Test.

Figure 1 Graphically presentation of estimated means with corresponding 95% confidence intervals (CI) for a number of PI values.