

Original Research Article

Correlation between pulsatility index of medial cerebri artery and cognitive function in patients with diabetes mellitus type 2

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ABSTRACT

Background: Cognitive impairment is prevalent among cerebrovascular disease (CVD). Diabetes mellitus type 2 (DMT2) is a major risk factor of CVD. Gold standard used for diagnosing vascular cognitive impairment (VCI) required a combination of neurophysiological approach and magnetic resonance imaging (MRI). The Neurosonological approach, involving measuring the pulsatility index (PI) of the middle cerebral artery (MCA) using Trans Cranial Doppler (TCD) could be applied as an affordable alternative to predict VCI. The objective of this study was to revealed the correlation between PI MCS and cognitive function among DMT2 patients.

Methods: This study was a cross-sectional survey in patients with DMT2 visiting Neurology and Endocrine Outpatient Clinics at Prof. Dr. R. D. Kandou Manado General Hospital, who meet the inclusion and exclusion criteria. Sixty (60) subjects were examined by TCD with 2 MHz to assess the hypo-perfusion level. Their cognitive were assessed with the Indonesian version of Montreal Cognitive Assessment (MoCa-Ina).

Results: Right and left MCA median PI was 1.1 (IQR 0.9-1.4) and 1.0 (IQR 0.9-1.2) consecutively. MoCa-Ina median score was approximately 25 (IQR 22-26). Boxplot graph showed left PI MCA median score was higher in patients with normal cognitive function compared with cognitive impairment. Authors could not reach any significant statistical difference between PI MCA score and its correlation with cognitive function ($p > 0.05$).

Conclusions: Majority of patients with DMT2 have PI MCA score within normal range. Cognitive function among patient with DMT2 was mostly impaired. There is no correlation between PI MCA with cognitive function of patients with DMT2.

Keywords: Cerebral blood flow, Cognitive function, Diabetes, Pulsatility index, Quality of life

INTRODUCTION

At present, the world's population is estimated to be around 7 billion, an increase from around 6.5 billion in 2006. The increase in population is followed by an increase in the population aged 60 years and over between 1970 and 2025, their number is expected to increase 223% or increase around 694 million people. In 2025 there will be around 1.2 billion people in the world aged 60 years and over.¹

One of the main problems of the elderly is the decline in cognitive function. Which affects the pattern of their interaction with the neighborhood, with other family

members, as well as the pattern of social activities, so that it will add to the burden on the family, environment and society.² The most important risk factor for cognitive impairment is cerebrovascular disease, especially Diabetes Mellitus (DM). Cognitive disorders caused by vascular disease are called Vascular Cognitive Impairment (VCI). VCI will cause Vascular Dementia (VaD), which is one of the causes of dementia in Asia. An estimated 1.5-4.8% of people aged 70 years will suffer from dementia and will increase with age.²

Diabetes mellitus, hypertension, and dyslipidemia cause atherosclerosis which will cause increased peripheral vascular resistance and cause hypoperfusion in the

affected area. Eventually this disease causes VCI. Diabetes mellitus as the highest prevalence of VCI in the world. In Indonesia the prevalence of diabetes mellitus is 8.5%, which means that 1 out of 11 adults has diabetes mellitus.

The gold standard for diagnosing VCI is a neuropsychological examination (such as the Montreal Cognitive Assessment questionnaire-Indonesia or MoCA-INA which is more sensitive in evaluating executive function than other examinations) and MRI for deciding areas of infarction. The presence of abnormalities on MRI such as hypointense on T1 and lesions on the substance of alba on T2-FLAIR, can be used as predictors for cognitive impairment caused by hypoperfusion, however MRI has its own challenges such as being less available and relatively expensive.²

Transcranial Doppler (TCD) or Transcranial Doppler (DT) can be used to evaluate hemodynamics in cranial arteries (media cerebral arteries or MCAs, anterior cerebral arteries or ACA, posterior cerebral arteries PCA, basilar arteries or BA and vertebral arteries or VA).³ One of the parameter assessed on the TCD is the Pulsatility Index (PI), which shows hypoperfusion in the area. This situation can predict that the increase in PI MCA in DM sufferers is associated with arteriosclerosis which is the main cause of VCI.

METHODS

A cross-sectional study was conducted to all DMT2 patients who had been treated at the outpatient clinics of Department of Neurology at Professor Dr. R. D. Kandou Hospital between July and October 2019.

Inclusion criteria

- Patients aged between 18 and 65 years,
- Patients with clinical diagnosis of dmt2 as stated in the american diabetes association (ada) 2010 classification with minimum duration of 5 years,
- Patients who were willing to participate in the study.

Exclusion criteria

- Who were experiencing or had a history of stroke, epilepsy, Parkinson disease, brain tumor, brain infection, chronic kidney failure, congestive heart failure, malignancy or mental disorder.

Pulsatility index (PI) was measured to predict stenosis on the blood vessel proximal to the measurement site, and measured by certified neurologists in Professor Dr. R. D. Kandou Hospital using DWL Compumedics®. PI was calculated automatically using this formula:

$$PI = \frac{PSV - EDV}{MV}$$

PSV= peak systolic velocity, EDV = end-diastolic volume, and MV = mean flow velocity during cardiac cycle (14, 15). Cognitive impairment was assessed using the Indonesian version of neuropsychological examination (MOCA-Ina).⁵ Subjects with a MOCA-Ina score <26 were classified as cognitive impairment while subjects with a score ≥26 were classified as normal.⁶ All subjects underwent TCD examination in which bilateral MCA PI was evaluated. MCA was chosen because it represent a total blood flow in the hemisphere, considering high blood volume (60-70%) flowed to MCA from ICA.² Statistical analysis was conducted using R. 3.6.1 statistics software. Normality data was tested using Saphiro-Wilk. Descriptive analysis was done using U Mann Whitney and Unpaired T-test. If data was not distributed normally, the analysis was continued using Mann Whitney or Wilcoxon. The correlative between PI MCA and cognitive function was evaluated at bivariate and multivariate analysis.

RESULTS

Sixty DMT2 patients participated in this study with almost the same composition between male and female sexes (27 vs 33 people). Their median age was around 55 years old (IQR between 49 and 60 years old), where the age of male participants was slightly older than female (56 vs 53 years, $p=0.046$) (Table 1). Body Mass Index (BMI) in average was within in the normal range, even though female participants had a mean value that is slightly higher than normal (mean 26.8 (SD 3.4) kg/m²) and significantly different from value in male participants (mean 23.9 (SD 2.9) kg/m²; $p=0.001$). Majority of patients had family history of DM, and more than one third ($n=21$) of the study subjects reported that they had or currently smoked, with striking differences in both sexes (3% women vs. 77% men smoked; $p<0.001$). There were 19 (32%) patients had hypertension and this proportion was not significantly different in men and women.

Laboratory data for blood other than Fasting Blood Sugar (GDP) is not available for all patients, but only 33 out of 46 people. For this reason, these variables are displayed descriptively in Table 1. Subsequent analysis did not involve laboratory blood parameters to prevent a significant loss of observation in statistical estimation. For available data, GDP and HbA1c values were, as predicted, very high above normal (the mean was 206.8 mg/dL and 12.6% respectively). Meanwhile other blood laboratories were still relatively within the range of normal values. None of the blood laboratory variables showed differences by sex.

Median PI of both right and left cerebral artery media did not differ greatly in the patients, which was 1.1 (IQR 0.9, 41.4) in the right media cerebral artery and 1.0 (IQR 0.9-1,2) on the left (Table 2). The PI distribution was not different in men and women. While concerning the results of cognitive function measurements, the median

MoCA-INA score was around 25 (IQR 22-26) which indicates the tendency of most patients to be in a state of cognitive impairment. On the distribution of research

subjects according to the MoCA-INA score, the majority (n=48 or 80%) had score 26 or lower, therefore the majority was categorized as cognitive impairment.

Table 1: Demographic characteristics of study participants.

Characteristics	Total		Female		Men		P ^a
	M (SD)	Med (Q1;Q3)	M (SD)	Med (Q1;Q3)	M (SD)	Med (Q1;Q3)	
Age (years)	-	55.0 (49.0-60.2)	-	53.0 (45.0-57.0)	-	56.0 (51.5-61.5)	0.046
Body Mass Index (BMI)	25.5 (3.5)	-	26.8 (3.4)	-	23.9 (2.9)	-	0.662
Duration (years)	-	5.0 (4.0-8.0)	-	4.0 (4.0-6.0)	-	7.5 (6.0-10.8)	<0.001
Family History	48 (81)	-	28 (85)	-	20(70)	-	0.511
Smoker	21 (36)	-	1 (3)	-	20(70)	-	<0.001
Hypertention	19 (32)	-	11 (33)	-	8(30)	-	0.978
Laboratory							
HbA1c (%)	*	8.1 (7.1-9.6)	*	8.1 (7.1-9.0)	*	8.3 (7.1-10.1)	0.440
Hemoglobin (g/dL)	12.6 (1.8)	*	12.5 (1.9)	*	12.6 (1.8)	*	0.820
Leukocytes ($\times 10^3$)	8.0 (3.5)	*	8.7 (3.5)	*	7.2 (3.4)	*	0.150
Hematocrit (%)	*	44.0 (39.0-46.0)	*	44.0 (40.0-46.2)	*	43.0 (36.0-45.8)	0.305
Trombocytes ($\times 10^3$)	*	200.0 (150.0-270.8)	*	210.0 (150.0-282.0)	*	187.0 (150.0-235.3)	0.372
Fasting glucose level (mg/dL)	206.8 (52.0)	*	210.3 (48.7)	*	202.5 (56.7)	*	0.571
Urea (mg/dL)	*	20.0 (13.0-33.0)	*	19.5 (11.2-26.5)	*	22.0 (15.8-48.0)	0.181
Creatinine (mg/dL)	*	1.0 (0.6-1.8)	*	1.0 (0.6-1.8)	*	1.0 (0.4-1.7)	0.587
GOT (mg/dL)	*	16.0 (11.0-13.0)	*	15.5 (10.5-21.2)	*	17.0 (11.0-24.0)	0.385
GPT (mg/dL)	*	15.0 (12.0-23.0)	*	15.5 (10.8-23.5)	*	15.0 (12.0-20.5)	0.713
Sodium (mmol/L)	*	136 (135.0-140.0)	*	139 (136.0-140.0)	*	136 (135.0-137.5)	0.031
Potassium (mmol/L)	*	37 (3.2-4.0)	*	37 (3.5-4.0)	*	37 (3.2-4.0)	0.635

Table 2: Characteristics PI MCA and cognitive function among DMT2 patients.

Characteristics	Total		Female		Men		P ^a
	M (SD)	Med (Q1;Q3)	M (SD)	Med (Q1;Q3)	M (SD)	Med (Q1;Q3)	
Pulsatility index and cognitive function							
Pulsatility Index							
Right	*	1.1 (0.9-1.4)	*	1.1 (0.9-1.5)	*	1.1 (0.9-1.3)	0.577
Left	*	1.0 (0.9-1.2)	*	1.1 (0.9-1.6)	*	0.9 (0.9-1.1)	0.141
MoCA INA score	*	25.0 (22.0-26.0)	*	24.0 (22.0-26.0)	*	25.0 (23.5-26.0)	0.135
Cognitive Function							
Normal	12 (20)	*	6 (18)	*	6 (22)	*	0.948
Impairment	48 (80)	*	27 (82)	*	21 (78)	*	

NOTE: Med: median, Q1: quartile I, Q3: quartile III; BMI body mass index; DM diabetes mellitus; Fasting blood sugar GDP. A Test or Mann-Whitney U according to the normality of distribution on numerical variables, test χ^2 on categorical variables. B Unless GDP data includes 59 patients, blood laboratory results are only available in 33 to 46 patients.

Table 3: Regresion logistic, correlation between PI MCA and cognitive function among DMT2 patients.

Variabel	Model Univariabel		Model Univariabel	
	OR (95% CL)	P	OR (95% CL)	P
Pulsatility Index				
Right	0.70 (0.25-1.97)	0.504	1.03 (0.26-4.01)	0.967
Left	0.70 (0.37-1.31)	0.260	0.69 (0.31-1.58)	0.384

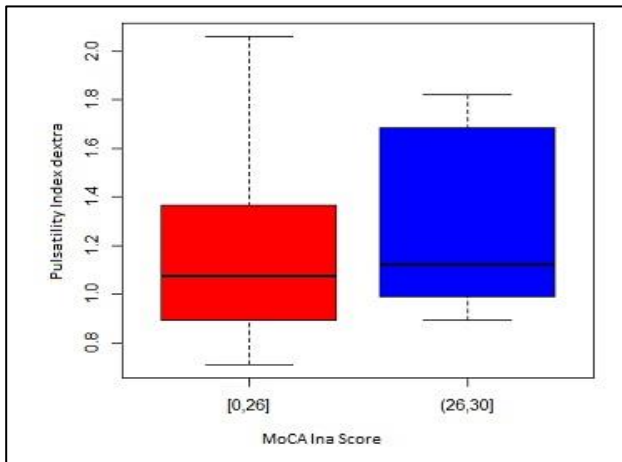


Figure 1: Density curve of right cerebral arterial artery pulsatility index according to cognitive function status.

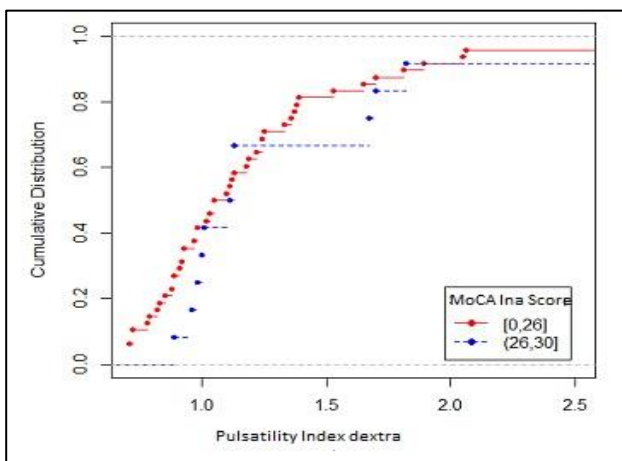


Figure 2: Boxplot of left cerebral artery pulsatility index according to cognitive function status.

As with the PI, no significant differences were found according to gender in the status of cognitive function (Table 3).

The relationships between the media cerebral artery PI with cognitive function according to the MoCA-INA score were shown in Figure 1 and 4. Overall PI distribution in patients with (MoCA-INA score ≤ 26) and without (MoCA-INA score >26) cognitive disorders overlap, which indicated the absence of significant differences in the PI distribution in the two categories of cognitive function status. These were applied to both the right and left cerebral media arteries. But even though the distribution overlaps, the graphs still helped in illustrating the distribution trends between the two groups of patients (Figure 2 and 5).

The density curves of patients with cognitive impairment appeared to accumulate at lower PI values compared to

patients with normal cognitive function. This result was seen quite clearly in the right media cerebral artery (Figure 1) and more clearly in the left media cerebral artery (Figure 4). The cumulative distribution of PI of the two groups of patients according to cognitive function showed their tendency for cognitive impairment to have an increased distribution earlier than patients with normal cognitive function; as did the density curve, inclination such distribution was more evident in the left middle cerebral artery.

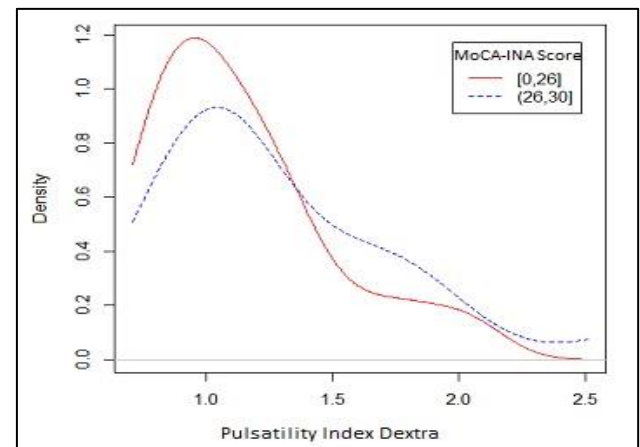


Figure 3: Cumulative distribution of left cerebral artery pulsatility index according to cognitive function status.

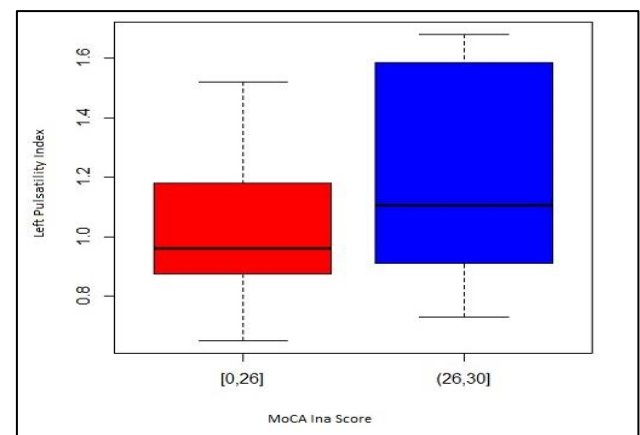


Figure 4: Density curve of left cerebral artery pulsatility index according to cognitive function status.

The interpretation was in line with the description on the density curve, namely that patients with cognitive impairment had a slightly lower PI value than those whose cognitive function was normal according to the MoCA-INA results. Finally, the boxplot chart showed the median value of left media cerebral artery PI (Figure 5 and 6) which was higher in patients with normal cognitive function than the median in those with cognitive impairment. The differences were not too significant in the right middle cerebral artery (Figure 2

and 3). However, the PI distribution of normal patients in both arteries seemed clearly to include higher values than patients with cognitive impairment. Logistic regression analysis of the odds or opportunities for cognitive impairment among type 2 diabetes mellitus patients and their relationship to the right and left MCA PI were shown in Table 3.

The results were sufficient to confirm the findings shown in Figures 1 and 4 the results of this regression modeling table showed that each unit of increase in the PI, both right and left cerebral artery media, seemed to reduce the odds of cognitive impairment by up to 30%. This value did not change much in the left MCA in multivariable analysis (with the right MCA PI as a co-factor), but in the right the relative odds ratio was equal to one and indicated the absence of an association between the PI and cognitive impairment. Apart from the association shown in the regression analysis estimation, none of the results were statistically significant.

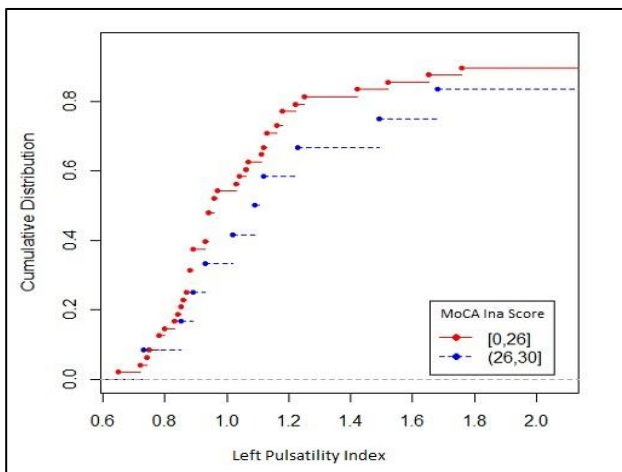


Figure 5: Boxplot of left cerebral artery artery pulsatility index according to cognitive function status.

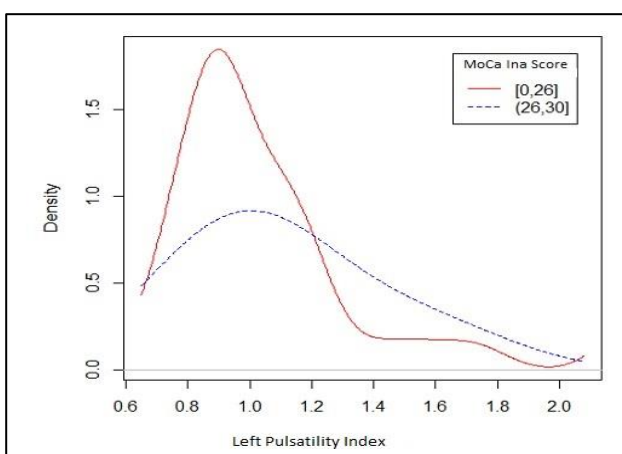


Figure 6: Cumulative distribution of left cerebral artery artery pulsatility index according to cognitive function status.

DISCUSSION

This study showed that most of DMT2 patients experience cognitive impairment. Impaired cognitive function in patients with diabetes mellitus was first put forward by Miles and Root in 1922. They suggested that people with DM had impaired memory and attention in their cognitive examinations compared to healthy population. Since then, several studies have been carried out to obtain a clear picture of the extent and degree of cognitive dysfunction in diabetes.³³ Several studies have concluded that cognitive deficits are often identified in people with type 2 diabetes, shown in the research of Kurniawan et al, who found that there was a correlation among cognitive function with glycemic control in patients DMT2.⁷ Another study by Elham et al, found that DMT2 increase the risk of cognitive impairment and dementia.⁸

Impaired cognitive function first manifest as mild symptoms, but can already interfere with daily activities, which cause depression and therefore worsens cognitive function. To a more severe extent, cognitive impairment in people with T2DM can be in the form of vascular dementia and Alzheimer's disease.⁹

Cerebral hemodynamic disorders are one of the mechanisms that cause cognitive impairment. The relationship between T2DM and cognitive function with hemodynamic disorders is related to hypoperfusion. Impaired glucose transfer and insulin transfer across the blood-brain barrier resulting in changes in metabolism and microcirculation is believed as the underlying postulated mechanism. In addition, another factor that possibly has an important role in the pathophysiology of cognitive dysfunction in people with diabetes mellitus is chronic hyperglycemia. Chronic hyperglycemia is hypothesized to contribute in impaired cognitive function through endothelial damage mechanisms and disorders of neurotransmitters. However, not all studies can prove the role of chronic hyperglycemia assessed through glycemic control associated with impaired cognitive function.⁷ Blood vessels in the brain have many adrenergic innervation that regulate vascular tone in response to various stimulations, whereas in diabetic patients, there is an impaired vasodilatation response due to exposure to beta adrenergic or sympathetic neuron dysfunction. A study in rats with DM shown reduced number of beta adrenergic receptors in small blood vessels, resulting in impaired vasodilatation response in patients with DM which leads to increased PI.¹⁰

In this study, it was found that the MCA PI tends to be high at an average of 1.1. The results of this study are similar to those of Indrasari et al, (Mean 1.17; SD 0.25) 33 and research by vicenzini et al, 1.19; SD 0.06.¹¹ The present study seveled, the median PI was higher in samples with normal cognitive function. On multivariate results, with each increase in PI, it decreases the risk of impaired cognitive function by 30%. Research conducted by Laleh et al, found that PI is increased in elderly people

(average 71 years) with normal cognitive function.¹² An increase in PI is caused by changes in the arterial system caused by aging or pathology from the disease. Pulsatility blood flow starts from the heart, then moves to the aorta and proximal branches where there are many elastin fibers that suppresses the pulsation. In older population, there is a complex relationship between large and small blood vessels so that increased blood vessel stiffness leads to increased pulsatility in vascular blood vessels.¹² Increased aortic stiffness causes pulsatile stress to the organs, thereby providing adequate pulsatile pressure on the blood vessels of the brain causing an increase of MCA blood flow causing vasodilation in small blood vessels of the MCA. Vasodilation can anticipate negative effects and maintain cognitive function.¹³

The present is similar to the study by Jacobus et al, in which patients with CBF disorders in type 2 DM patients (mean MMSE 28.6) had hypoperfusion in the brain especially in the cerebral cortex, specifically the parietal and subcortical sections.¹⁴ However, from the results of statistical processing there is no relationship between hypoperfusion and cognitive function.¹⁵ There lack of relationship is due to different areas affected as hypoperfusion or ischemic disorders occurs in the subcortical region, where cognitive function occurs in cortical areas. The study did not assess the atrophy of the brain with hypoperfused areas that might causes cognitive impairment.¹⁴ This study explore the association between MCA PI and cognitive function in T2DM. The MCA PI was assessed using TCD with a 2 Hz probe placed in the temporal window.¹⁶ A high PI will cause hemodynamic stress in the brain which will cause impaired cognitive function through damage to small cerebral vessels.¹⁷ Hypoperfusion associated with cognitive impairment.¹⁸ In DMT2, oxidative stress occurs, in which it causes inflammation and microvascular damage, atherosclerosis, vasoconstriction and stiffness of blood vessels, causing a decrease in blood vessel diameter and hypoperfusion.¹⁹ PI is derived from flow velocity and has been shown to reflect stenosis of distal insonance.²⁰

Research on PI with cognitive function obtained inconsistent results. Previous studies by Haris et al, found an association between MCA PI and cognitive function in hypertensive patients.² In this study, it was estimated that an increase in peripheral resistance causes impaired blood flow resulting in disturbances in the distal area of the blood vessels that are vascularized by MCA. This process is a part of a small vessel disease that will cause VCI.⁹ There are some studies that do not find the relationship between PI MCA and cognitive function. Research conducted by Beishon L, found that a low MFV (high PI) is not a predictor for cognitive impairment, but only reflects the disruption of cerebral hemodynamic.²¹ Research conducted by YongSoo Shim et al, shown that there is no cognitive relationship with cerebral vasoreactivity in the elderly and MCA PI among MCI, AD patients and healthy subjects.²²

This study found no relationship between MCA PI and cognitive function. Factors that cause no association in this study were relatively low risk factors for atherosclerosis such as relatively normal BMI, high percentage of hypertension and smoking in the samples of this study. The number of male and female samples was not equally balanced (27 vs 33). Type 2 DM duration and glycemic control are worse in men but cognitive impairment was found more in women. PI values and ranges were lower in men in both the left and right MCA. This study also found that in patients with type 2 DM with cognitive impairment tends to have increased PI earlier than patients with type 2 DM with normal cognitive. This is similar to research conducted by Thomas et al, stating that the average duration of T2DM is 4.6 years in one-sided blood vessel abnormalities and 5.4 years in bilateral cerebral artery blood vessel abnormalities.²³

A limitation of this study were the small sample size, relatively older age in men then female samples. Also, unbalanced sex and determined confounding factors were not able to be controlled by randomization.

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