Original Research Report

HbA1c AND PULSATILITY INDEX IN MIDDLE CEREBRAL ARTERY OF PATIENTS WITH ACUTE THROMBOTIC STROKE

Rio Tasti Surpa Rahmat Bintan[1], Sita Setyowati[1], Yudhi Adrianto[1,2*]

[1]Department of Neurology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[2]Indonesian Neurological Association

ABSTRACT

Stroke is the second leading cause of death and disability in the world. Diabetes mellitus is a risk factor for stroke due to an increase in blood viscosity associated with hyperglycemia, with HbA1c being a well-established biomarker for the long-term glycemic control in patients with diabetes mellitus. The Pulsatility Index (PI) parameter of Transcranial Doppler (TCD) measures blood vessel resistance. This study aims to investigate the correlation between HbA1c and PI in the Middle Cerebral Artery (MCA) of acute thrombotic stroke patients. A cross-sectional study was conducted on thrombotic stroke patients treated at the neurological ward of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from March 2019 to April 2020, who met the inclusion and exclusion criteria. Data were obtained from medical records and analyzed using the Spearman's test for numerical data and chi-squared test for categorical data with a p-value of less than 0.05. A total of 32 subjects met the inclusion and exclusion criteria, comprising 24 males (75%) and eight females (25%), with a mean age of 56.41±13.22 years. Abnormal PI MCA results were observed in 14 subjects (43.75%) with an average of 1.8±0.97, while normal PI MCA results were observed in 18 subjects (56.25%) with an average of 0.87±0.15. The average HbA1c was 6.55 ± 1.9%. No statistically significant correlation was observed between HbA1c and PI in the MCA examination (r=0.07; p=0.73). In conclusion, this study found no correlation between pulsatility index and HbA1c in patients with acute ischemic stroke. This underscores the importance of comprehensive cerebrovascular evaluation regardless of HbA1c status.

Keywords: Acute thrombotic stroke; HbA1c; Trans Cranial Doppler; Pulsatility Index; blood viscosity; diabetes mellitus

***Correspondence:** Yudhi Adrianto, Department of Neurology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Email: yudhi_neuro@yahoo.com

Article history
●Submitted 05/01/2023 ● Revised 18/04/2023 ● Accepted 27/05/2024 ● Published 10/06/2024

How to cite: Bintan RTSR, Setyowati S, Adrianto Y (2024). HbA1c and Pulsatility Index in Middle Cerebral Artery of Patients with Acute Thrombotic Stroke. Folia Medica Indonesiana 60 (2), 141-146. doi: https://doi.org/10.20473/fmi.v60i2.26698

Copyright: © 2024 Folia Medica Indonesiana.
This is an open-access article distributed under the terms of the Creative Commons Attribution License as stated in https://creativecommons.org/licenses/by-nc-sa/4.0/deed.id.
pISSN:2355-8393, eISSN: 2599-056x

Highlights:
1. This study's findings indicate that clinicians should remain vigilant, as effective glycemic control, reflected by optimal HbA1c levels, does not necessarily correlate with favourable distal cerebrovascular resistance, as measured by pulsatility index (PI).
2. This study recommends that patients with acute thrombotic stroke undergo a comprehensive examination to ensure an accurate diagnosis and appropriate treatment.

INTRODUCTION

Stroke is the second cause of death and the third cause of disability in the world (World Health Organization 2012). Stroke is classified into ischemic and bleeding stroke. Mostly, 60-80% are ischemic stroke (Chugh 2019). The incidences of stroke in low and middle-income countries has more than doubled in the past four decades (Feigin et al. 2014).

The prevalence of stroke in Indonesia has increased from 7% in 2013 to 10.9% in 2018 (Minister of Health of the Republic of Indonesia 2018). Risk factors for stroke incidence in Indonesia include hypertension, diabetes mellitus and dyslipidemia (Kusuima et al. 2009). More than 60% of incidence are ischemic stroke (Harris et al. 2018). The main causes of ischemic stroke include thrombosis and embolism (Kanyal 2015).

The main mechanism that causes thrombotic stroke is the formation of atherosclerotic plaques which is influenced by several risk factors, such as diabetes mellitus, hypertension and dyslipidemia. There was an increase in blood viscosity in patients with type 2 diabetes mellitus who had a metabolic syndrome (Minato et al. 2017). Blood viscosity (BV) is related to glucose levels (Irace et al. 2014).

One main instrument for assessing cerebral vascular function is the Transcranial Doppler (TCD). It is a noninvasive, rapid examination and provides real-time data on cerebral vascular function. One of the TCD parameters is the Pulsatility Index (PI) which can measure the resistance of blood vessels. PI is able as an indicator of cerebrovascular resistance; it can assess cerebral autoregulation and risk stratification in neurological disorders. However, the use of PI in TCD has some limitations. Some of the disadvantages include its lack of specificity because various factors, including arterial compliance, distal vascular resistance, and proximal arterial stiffness, influence it. Interpreting PI values can also be challenging due to differences in normal values across age groups, vascular territories, and individual patient characteristics. There is also the influence of extracranial factors such as cardiac output, systemic vascular resistance, and arterial blood pressure that complicate the interpretation of TCD findings (Lau & Arntfield 2017).

The risk factor of stroke among diabetics is the increase in blood viscosity associated with hyperglycemia. HbA1c (glycated hemoglobin) is primarily utilized for long-term monitoring of glycemic control in patients with diabetes mellitus. Elevated blood glucose levels during the acute phase of stroke are associated with worsened outcomes and increased risk of mortality. It also identifies the stroke etiology and risk factors. Evaluation of stroke etiology and identification of underlying risk factors, such as hypertension, atrial fibrillation, hyperlipidemia, and diabetes mellitus, are crucial for determining appropriate treatment strategies and secondary prevention measures (Lerstad et al. 2014). Therefore, in view of the limitations present in PI applied in TCD, the use of HbA1c in middle cerebral artery for patients with acute thrombotic stroke may be potential as it reflects average blood glucose levels over the past 2-3 months, indicates poorer long-term glycemic control, and could predict outcomes or provide additional prognostic information beyond acute blood glucose levels (Wang et al. 2019).

This study, therefore, aimed to prove the correlation between HbA1c and pulsatility index in patients with acute thrombotic stroke.

MATERIALS AND METHODS

This was an observational study using cross-sectional design in acute thrombotic stroke patients. Data were obtained from medical records of patients treated at the neurological ward of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from March 2019 to April 2020. The inclusion criteria included age over 18 years, and having undergone a TCD examination to assess the hemodynamics of the Middle Cerebral Artery (MCA) (Farhoudi et al. 2011). Patients who experienced an embolic stroke, bleeding stroke, or had incomplete medical records were excluded. In total, 32 patients who met the criteria were included in the study. We collected demographic data from the patients, including age, sex, smoking history, statin use, and history of hypertension, as these are recognized risk factors for both stroke and diabetes clinical data in the form of clinical manifestations of hemiparesis and facial-lingual palsy; data on the results of TCD examination to measure the pulsatility index of the MCA; as well as laboratory data on HbA1c (Bill et al. 2020).

Statistical analysis

Statistical analysis was performed to determine the correlation of HbA1c with PI in patients with acute thrombotic stroke using the Spearman correlation test for numerical data and the Chi-square test for categorical data with a significant value of $p < 0.05$. The data were analyzed using the IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA).

Ethical clearance

Research ethics were obtained from the health research ethics committee of the Faculty of Medicine, Universitas Airlangga; Dr. Soetomo General Academic Hospital. This research had been carried out based on a certificate of ethical eligibility number 0285/LOE/301.4.2/I/2021, issued on 2 January 2021. Confidentiality of research subjects was well maintained by not mentioning names, but written based on initials. The data from this research are only used for research purposes.

RESULTS

A total of 32 acute thrombotic stroke patients who were included in the study consisted of 24 subjects (75%) males and 8 (25%) females. The mean age of the subjects was 56.41±13.22 years with a mean age of 56.83±13.77 years for males and 55.13±12.19 years for females. In this study, all patients with acute thrombotic stroke were found with clinical manifestations of hemiparesis. The results of the TCD examination showed that the MCA PI was abnormal in 14 subjects (43.75%) with an average

of 1.8±0.97 and a normal MCA PI in 18 subjects (56.25%) with an average of 0.87±0.15. From the results of the HbA1c examination, it was found normal in 7 subjects (21.87%) with an average of 5.66±0.54% and abnormal in 25 subjects (78.13%) with an average of 9.75±1.66 %. There were 3 subjects (9.38%) using statin drugs and 29 subjects (90.62%) without statin drug use. Smoking history was found in 15 subjects (46.87%) and 17 subjects (53.13%) had no smoking experience. Hypertension was found in 14 subjects (43.75%) and 18 subjects (56.25%) had no hypertension (Table 1).

Table 1. Characteristics of study subjects.

Variable	n (%)	mean±SD
Sex		
Male	24 (75)	
Female	8 (25)	
Age		56.41 ± 13.22 years
Male		56.83 ± 13.77 years
Female		55.13 ± 12.19 years
Clinical manifestations		
Left hemiparesis	17 (53.13)	
Right hemiparesis	15 (46.8)	
PI MCA (*Cut off* = 1.10)		1.29 ± 0.80
Normal	18 (56.25)	0.87 ± 0.15
Abnormal	14 (43.75)	1.8 ± 0.97
HbA1c (*Cut off* = 6.5%)		6.55 ± 1.9%
Normal	7 (21.87)	5.66 ±0.54%
Abnormal	25 (78.13)	9.75 ±1.66%
Smoking		
Yes	15 (46.87)	
No	17 (53.13)	
Use of statins		
Yes	3 (9.38)	
No	29 (90.62)	
Hypertension		
Yes	14 (43.75%)	
No	18 (56.25%)	

In this study, the mean PI MCA examination results were 1.29±0.80. It was 1.33±0.84 in male subjects and 1.20±0.74 in female subjects. There was no significant difference in the results of PI MCA examination between the sexes with p=0.714. The mean result of MCA PI examination in elderly subjects was 1.54±1.02 and before elderly subjects was 1.18±0.68. There was no significant difference in the results of PI MCA examination based on age with p 0.224 (Table 2).

Table 2. Pulsatility index middle cerebral artery based on sex and age

PI MCA	Mean ± SD	p
Sex		
Male	1.33 ± 0.84	0.714
Female	1.20 ± 0.74	
Age		
Elderly	1.54 ±1.02	0.224
Before elderly	1.18 ±0.68	

In this study, several factors were analyzed that could affect the results of the PI MCA examination, including: sex, age, history of statin use, smoking and hypertension. There were no significant differences in sex, age, history of statin use, smoking and hypertension on the results of normal and abnormal PI MCA examination with p 0.217; p 0.212, p 0.702, p 0.067 and p 0.119, respectively (Table 3). In this study, there was a very weak but not significant correlation between HbA1c and PI MCA in acute thrombotic stroke patients with p 0.73 which was analyzed using the Spearman correlation test.

Table 3. Factors affecting pulsatility index middle cerebral artery.

	Normal PI MCA	Abnormal PI MCA	Total	p
Sex				
Male	15	9	24	0.217
Female	3	5	8	
Age				
Elderly	4	6	10	0.212
Before Elderly	14	8	22	
Use of Statins				
Yes	2	1	3	0.702
No	16	13	29	
Smoking				
Yes	11	4	15	0.067
No	7	10	17	
Hypertension				
Yes	6	8	14	0.119
No	13	5	18	

DISCUSSION

The subjects of this study were dominated by males, as many as 24 patients (75%). This was in contrast to several studies that have linked PI to several metabolic factors, such as a study by Farhoudi et al. (2011) in Iran, which used a case-control design in hypercholesterolemic patients. In that study, the comparison between male and female patients was 14:16. A study by Han et al. (2019) regarding the correlation between PI MCA and BV in stroke patients showed that male patients were as much as 57% of a total of 125 patients. The mean age of the

subjects in this study was 56.41 ± 13.22 years.

PI MCA in all subjects with symptoms of hemiparesis and mild facial-lingual palsy was 1.29 ± 0.80. There were no significant differences in PI examination results based on sex (p = 0.714) or age (p = 0.224). An abnormal PI of 1.1 was obtained at 14 (43.75%) with an average of 1.8 ± 0.97. This aligned with Fu et al. (2019) study on the relationship between PI and severe white matter lesions (WMLs). Severe white matter lesions were significantly linked with a mean PI of 1.15 ± 0.23 (p <0.001). The study indicated that a PI 1.04 cut-off might be used to diagnose severe WMLs (Fu et al. 2019).

In addition, it was found that the average HbA1c level in the sample was 6.55 ± 1.9%. Most of the samples had abnormal HbA1c levels with a cut-off of 6.5%, as many as 25 (78.13%) subjects. This was much bigger than the sample of Han et al. (2019), with a diagnosis of diabetes mellitus of 26.4% and 15% in the study of Farhoudi et al. (2011). This study also found no difference in the results of the PI MCA examination based on age (p 0.212). This finding was different from the results of a previous study by Han et al. (2019) in Seoul, South Korea, which showed an association between PI in MCA with older age, diabetes status, and elevated BV.

We also found no difference in the results of the PI MCA examination based on sex (p 0.217). Filatova et al. (2015) conducted a study on the influence of age and sex on blood rheological properties. It was found that BV decreased in elderly males but increased in females with age. They observed a rise in blood viscosity from childhood to adulthood. BV was reduced in elderly males but grew gradually with age in women. Three age categories have been identified: (1) infancy to childhood (3.6 ± 0.07 mPa s); (2) adolescence to adulthood (5.1 ± 0.06 mPa s in males and 4.3 ± 0.05 mPa s in women); (3) elderly and old age (4.7 ± 0.13 mPa s in men and 4.4 ± 0.09 mPa s in women).

In this study, there was no difference in the results of the PI MCA examination based on smoking history (p 0.067). This was different from Almarshad & Hassan (2016) study which evaluated the effect of smoking on hematological parameters. It was found that the average BV in smokers was higher, 3.72 ± 0.4 mPa.s compared to non-smokers 3.25 ± 0.21 mPa.s. Another study by Shimada et al. (2011), concerning the correlation of BV by smoking status, showed that smoking every day is associated with an increase in BV (r = 0.326, p = 0.045), but this condition will improve with smoking cessation for 3 months. In this study, there was no complete data on whether the patients smoked every day or whether they had quit smoking.

In this study, there was no difference in the results of the PI MCA examination based on statin use (p 0.702). A study by Jung et al. (2016) regarding statins that can reduce BV stated that blood viscosity is significantly lower one month after statin treatment (p = 0.044). Statins also have rheological effects in addition to their blood lipid lowering effect. In this study, there was no difference in the results of the PI MCA examination based on a history of hypertension (p 0.119). This was similar to a study by Çekici et al. (2019) regarding the correlation of blood pressure to BV, which stated that BV in hypertensive subjects was not higher than normotension. Another study by Taco-Vasquez et al. (2019) concerning the correlation of hypertension as a risk factor for cardiovascular disease with BV stated that systolic and diastolic blood pressure was not related to BV with p 0.24 and p 0.27.

In this study, there was a very weak but not significant correlation between HbA1c and PI MCA in acute thrombotic stroke patients with p 0.73. Doppler study from Farhoudi et al. (2011) showed no significant correlation between dyslipidemia and PI MCA. Hypercholesterolemic condition (LDL> 160 mg/dl) is not a factor that affects the changes in hemodynamic conditions in the intracranial arteries. This study did not obtain a significant difference in the value of PI MCA between the hypercholesterolemia group and the control group, even when the cut-off value of LDL levels was raised to 180 mg/dl (Farhoudi et al. 2011).

HbA1c measurement provides an indirect estimate of blood sugar levels for the previous three months. A study by Mushtaq et al. (2019) on the correlation between hyperglycemia and increased BV showed that uncontrolled diabetes was able to increase BV. The viscosity measurement increased slightly in diabetics over the past 5 years compared to just one year. An increase in viscosity was found in subjects who had diabetes for 10 years or more. Shen et al. (2020) study regarding the correlation of HbA1c with stroke risk in people with type 2 diabetes showed that the risk of stroke increased along with the increase in HbA1c. The risk of stroke was 1.43 (1.19-1.72) times higher in people with type 2 diabetes aged <60 years with HbA1c > 10 (Shen et al. 2020).

Strength and limitations

The findings of this study indicate the absence of a correlation between pulsatility index and HbA1c in patients with acute ischemic stroke. These results suggest that clinicians should remain vigilant, as effective glycemic control, reflected by optimal HbA1c levels, does not necessarily correlate with favorable distal cerebrovascular resistance, as measured by pulsatility index. Despite that, a

thorough examination remains crucial for improving the accuracy of diagnosis and enhancing treatment outcomes. However, the data obtained were in the form of secondary data, so that data collection was limited according to what recorded in medical records. Another limitation of this study was that it did not differentiate the type of stroke based on TOAST classification, i.e. large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology.

CONCLUSION

This study found no correlation between pulsatility index and HbA1c in patients with acute ischemic stroke. This underscores the importance of comprehensive cerebrovascular evaluation regardless of HbA1c status.

Acknowledgment

We express our gratitute to those who had contributed to the implementation of this research and the writing of this manuscript, particularly to the medical records unit of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from where the data used in this research were obtained.

Conflict of interest

None.

Ethical consideration

Research ethics were obtained from the health research ethics committee of Dr. Soetomo General Academic Hospital. This research had been carried out based on a certificate of ethical eligibility number 0285/LOE/301.4.2/I/2021, issued on 2/1/2021.

Funding disclosure

None.

Author contribution

RTS contributed in developing and designing the study, analyzing and interpreting the data, writing the article, reviewing it critically for significant intellectual contributions, and collecting and organizing the data. SS and YA provided final approval for the article, study materials, and other forms of support including administrative, technical, and logistic assistance.

REFERENCES

Almarshad HA, Hassan FM (2016). Alterations in blood coagulation and viscosity among young male cigarette smokers of Al-Jouf Region in Saudi Arabia. Clinical and Applied Thrombosis/ Hemostasis22**,** 386–389. doi: 10.1177/1076029614561319.

Bill O, Lambrou D, Sotomayor GT, et al (2020). Predictors of the pulsatility index in the middle cerebral artery of acute stroke patients. Scientific Reports 10, 17110. doi: 10.1038/s41598-020-74056-2.

Çekici Y, Kılıç S, Saraçoğlu E, et al (2019). The relationship between blood viscosity and isolated coronary artery ectasia. Acta Cardiologica Sinica 35**,** 20–26. doi: 10.6515/ACS.201901_35(1).20180701A.

Chugh C (2019). Acute ischemic stroke: Management approach. Indian Journal of Critical Care Medicine 23**,** 140–146. doi: 10.5005/jp-journals-10071-23192.

Farhoudi M, Mehrvar K, Aslanabadi N, et al (2011). Doppler study of cerebral arteries in hypercholesterolemia. Vascular Health and Risk Management 2011**,** 203–207. doi: 10.2147/VHRM.S18663.

Feigin VL, Forouzanfar MH, Krishnamurthi R, et al (2014). Global and regional burden of stroke during 1990–2010: Findings from the Global Burden of Disease Study 2010. The Lancet 383**,** 245–255. doi: 10.1016/S0140-6736(13)61953-4.

Filatova O V., Sidorenko AA, Agarkova SA (2015). Effects of age and sex on rheological properties of blood. Human Physiology 41**,** 437–443. doi: 10.1134/S0362119715030044.

Fu S, Zhang J, Zhang H, et al (2019). Predictive value of transcranial doppler ultrasound for cerebral small vessel disease in elderly patients. Arquivos de Neuro-Psiquiatria 77**,** 310–314. doi: 10.1590/0004-282x20190050.

Han JE, Kim T, Park JH, et al (2019). Middle cerebral artery pulsatility is highly associated with systemic blood viscosity in acute ischemic stroke within 24 hours of symptom onset. Journal of Neurosonology and Neuroimaging 11**,** 126–131. doi: 10.31728/jnn.2019.00050.

Harris S, Kurniawan M, Rasyid A, et al (2018). Cerebral small vessel disease in Indonesia: Lacunar infarction study from Indonesian Stroke Registry 2012–2014. SAGE Open Medicine 6**.** doi: 10.1177/2050312118784312.

IBM Corp. 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Available at: https://www.ibm.com/support/pages/downloading-ibm-spss-statistics-25.

Irace C, Carallo C, Scavelli F, et al (2014). Blood viscosity in subjects with normoglycemia and prediabetes. Diabetes Care 37**,** 488–492. doi: 10.2337/dc13-1374.

Jung LY, Lee SR, Jung JM, et al (2016). Rosuvastatin reduces blood viscosity in patients with acute coronary syndrome. Korean Circulation Journal 46**,** 147. doi: 10.4070/kcj.2016.46.2.147.

Kanyal N (2015). The science of ischemic stroke: Pathophysiology & pharmacological treatment. International Journal of Pharma Research & Review 4**,** 65–84. Available at: https://www.rroij.com/open-access/the-science-of-ischemic-stroke-pathophysiology--pharmacological-treatment-.pdf.

Kusuima Y, Venketasubramanian N, Kiemas LS, et al (2009). Burden of stroke in Indonesia. International Journal of Stroke 4**,** 379–380. doi: 10.1111/j.1747-4949.2009.00326.x.

Lau VI, Arntfield RT (2017). Point of care transcranial doppler by intensivists. Critical Ultrasound Journal 9**,** 21. doi: 10.1186/s13089-017-0077-9.

Lerstad G, Brodin EE, Enga KF, et al (2014). Hyperglycemia, assessed according to HbA1c, and future risk of venous thromboembolism: the Tromsø study. Journal of Thrombosis and Haemostasis 12**,** 313–319. doi: 10.1111/jth.12498.

Minato S, Takenouchi A, Uchida J, et al (2017). Association of whole blood viscosity with metabolic syndrome in type 2 diabetic patients: Independent association with post-breakfast triglyceridemia. Journal of Clinical Medicine Research 9**,** 332–338. doi: 10.14740/jocmr2885w.

Minister of Health of the Republic of Indonesia (2018). Report on result of national basic health research (RISKSDAS) 2018. Minist Heal Repub Indones. Available at: https://kesmas.kemkes.go.id/assets/upload/dir_519d41d8cd98f00/files/Hasil-riskesdas-2018_1274.pdf.

Mushtaq M, Abdul Mateen M, Kim UH (2019). Hyperglycemia associated blood viscosity can be a nexus stimuli. Clinical Hemorheology and Microcirculation 71**,** 103–112. doi: 10.3233/CH-180426.

Shen Y, Shi L, Nauman E, et al (2020). Association between hemoglobin A1c and stroke risk in patients with type 2 diabetes. Journal of Stroke 22**,** 87–98. doi: 10.5853/jos.2019.01704.

Shimada S, Hasegawa K, Wada H, et al (2011). High blood viscosity is closely associated with cigarette smoking and markedly reduced by smoking cessation. Circulation Journal 75**,** 185–189. doi: 10.1253/circj.CJ-10-0335.

Taco-Vasquez ED, Barrera F, Serrano-Duenas M, et al (2019). Association between blood viscosity and cardiovascular risk factors in patients with arterial hypertension in a high altitude setting. Cureus. doi: 10.7759/cureus.3925.

Wang H, Cheng Y, Chen S, et al (2019). Impact of elevated hemoglobin A1c levels on functional outcome in patients with acute ischemic stroke. Journal of Stroke and Cerebrovascular Diseases 28**,** 470–476. doi: 10.1016/j.jstrokecerebrovasdis.2018.10.026.

World Health Organization (2012). Global health estimates. WHO. Available at: https://www.who.int/data/global-health-estimates.