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## ASSOCIATION BETWEEN BLOOD PRESSURE VARIABILITY AND EARLY NEUROLOGICAL DETERIORATION IN ACUTE ISCHEMIC STROKE PATIENTS

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**Keywords:** ischemic stroke, blood pressure variability, END and NIHSS.

### Abstract

**Background:** Variability in blood pressure is a predictor of stroke severity and causes of poor functional outcome. Blood pressure variability is one of the main predictor of the prognosis acute ischemic stroke. Blood pressure variability were independently and linearly associated with the development of early neurologic deterioration (END) in acute ischemic stroke

**Objective:** To determine the association between blood pressure variability and END in acute ischemic stroke patients.

**Method:** This study uses a cross sectional design. Sampling was conducted at H. Adam Malik General Hospital Medan. Samples were taken as many as 40 subjects consecutively. Blood pressure checks were perform every hour for 72 hours then an assessment of the National Institute of Health Stroke Scale (NIHSS) score at admission and the third day of treatment. Data analysis used fisher's exact test.

**Results:** The demographic characteristics of the study subjects were an average age of 56-<71 years, high school education level, housewife occupation and Batak ethnicity. The mean of maximum systolic blood pressure (SBP) was 151±12.16 mmHg, minimum SBP 123.15±18 mmHg, delta SBP 25.35±10.66 mmHg, maximum diastolic blood pressure (DBP) 79.7±6.01 mmHg, minimum DBP 61.77±7.32 mmHg and delta DBP 17.97±8.48 mmHg. The NIHSS day 1 score had an average of 9.55±6.73, the NIHSS day 3 score was 11.25±7.93. Most subjects experienced END. There is a significant relationship between blood pressure variability and END with a p of 0.03 (p<0.05).

**Conclusion:** There is a significant relationship between blood pressure variability and END in patients with acute ischemic stroke.

### Introduction

Ischemic stroke is the leading cause of death worldwide and the leading cause of disability or long-term disability in developing countries.<sup>1</sup> More than 8% of all deaths are associated with ischemic stroke.<sup>2</sup> The worsening that occurs in the acute phase of stroke, usually occurs within the first 48 - 72 hours of the onset of the incident and can cause serious complications both short and long term.<sup>3</sup> Neurological deterioration that occurs within the first two to three days after stroke onset is defined as Early Neurological Deterioration (END), and is associated with poor outcome in acute ischemic stroke patients.<sup>4</sup> Early neurological deterioration is a frequent complication of ischemic stroke, although the incidence has varied across studies due to differences in the population studied and the definition of END used. Incidence rates range from 13-37 percent of all ischemic stroke incidence.<sup>5</sup>

Blood pressure can contribute to the development of early neurological damage and adverse outcomes by affecting brain perfusion. Reduced cerebral hemodynamic reserves and an absence of collateral blood supply appear to be associated with early neurological decline, whereas the presence of collateral blood flow appears to be associated with early spontaneous neurological improvement in acute ischemic stroke. Not only blood pressure but also blood pressure variability is mentioned to be an independent negative prognostic variable<sup>6</sup>. In a study conducted by Kang et al. in 2012, it was stated that fluctuation or variability in blood pressure is a predictor of stroke severity and causes of poor functional outcomes.<sup>7</sup> Post hoc analysis of several clinical trials in acute stroke showed that in addition to an increase in systolic blood pressure, other hemodynamic variables including higher peak systolic blood pressure, mean arterial pressure (MAP), pulse frequency and increased systolic blood pressure variability, were respectively associated with poor functional outcomes, END, recurrent stroke and death.<sup>8</sup>

A recent systematic study of seven studies on the effect of blood pressure variability shows that systolic blood pressure variability is significantly associated with poor functional outcome.<sup>9</sup> Deaths from ischemic heart disease and stroke increase with each increase of 20 mmHg and 10 mmHg in systolic and diastolic blood pressure. The



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initial hypothesis was further corroborated by clinical studies in hypertensive subjects suggesting that the assessment and quantification of blood pressure variability is both physiopathologically and prognostically important.<sup>10</sup>

### Method

#### Study sample

The study sample was taken from patients with acute ischemic stroke in H. Adam Malik General Hospital Medan with consecutive sampling techniques. The research subjects consisted of 40 acute ischemic stroke patients who willing to take part in this study by signing a research informed consent sheet.

#### Study design

This study is a analytic descriptive with cross sectional design with the source data obtained is primary data from all ischemic stroke patients who are hospitalized in H. Adam Malik General Hospital Medan. The diagnosis of acute ischemic stroke is based on history, physical and neurologic examination and head computed tomography scan (CT scan).

#### Statistical analysis

Data from the research were analyzed statistically using the SPSS Windows computer program (Statistical Product and Science Service) version 22.0. To analyze the relationship between research variables, in this case to determine the association between blood pressure variability and END with fisher's exact test.

### Result

Patients with acute ischemic stroke at H. Adam Malik Hospital Medan in March until June 2020, there were 40 patients with acute ischemic stroke who participated in the study.

Based on the characteristics of 40 research subjects, the age of all research subjects had a mean of  $60,97 \pm 9,77$  years with the largest age range was at the age of 56-<71 years, as many as 20 subjects (50%). The research subjects were 22 female subjects (55%) and 18 male subjects (45%). The education level of the most research subjects was Senior High School, as many as 23 subjects (57,5%) and at least are primary school and bachelor degree each with 5 subjects (12,5%). Respondents occupations were mostly housewife with 14 subjects (35%) and at least 1 retired (2,5%). Most of the ethnic groups of the research subjects were the Batak ethnic groups as many as 26 subjects (65%). For complete data about the characteristics of the subject of this study are presented in table 1 below.

*Table 1. Demographic Characteristics of Research Subjects (n = 40)*

Characteristics	Frequency n=40	Percentage (%)
Age, average $\pm$ SD (years)	$60,97 \pm 9,77$	
Age group		
- 41 - <56 years old	12	30
- 56 - <71 years old	20	50
- 71 - <86 years old	8	20
Sex		
- Female	22	55
- Male	18	45
Education		
- Primary School	5	12,5
- Junior High School	7	17,5
- Senior High School	23	57,5
- Bachelor Degree	5	12,5
Occupations		
- Housewife	14	35
- Entrepreneur	12	30
- Farmer	6	15
- Government Employees	4	10



- Private Employees	3	7,5
- Retired	1	2,5
Ethnic Group		
- Batak	26	65
- Malay	7	17,5
- Java	6	15
- Karo	1	2,5

Based on the results of descriptive analysis in this study, the results of the blood pressure variability characteristics were the maximum SBP mean of  $151 \pm 12.16$  mmHg, minimum SBP of  $123.15 \pm 18$  mmHg, delta SBP of  $25.35 \pm 10.66$  mmHg, maximum DBP of  $79.7 \pm 6.01$  mmHg, minimum DBP of  $61.77 \pm 7.32$  mmHg and delta DBP of  $17.97 \pm 8.48$  mmHg. This can be seen in table 2 below.

**Table 2. The Characteristics of Blood Pressure Variability**

Blood Pressure Characteristic	Mean $\pm$ SD (mmHg)
Maximum SBP	151 $\pm$ 12.16
Minimum SBP	123.15 $\pm$ 18
Delta SBP	25.35 $\pm$ 10.66
Maximum DBP	79.7 $\pm$ 6.01
Minimum DBP	61.77 $\pm$ 7.32
Delta DBP	17.97 $\pm$ 8.48

Descriptive analysis of the characteristics of the NIHSS score in this study showed that the NIHSS score on day 1 had a mean of  $9.55 \pm 6.73$  with the most characteristic neurological deficit was in the moderate category as many as 18 subjects (45%). The NIHSS score on day 3 has a mean value of  $11.25 \pm 7.93$  with the most characteristic neurological deficit is in the moderate category as many as 19 subjects (47.5%). Furthermore, the incidence of END in the subjects of this study was obtained as many as 25 subjects (62.5%). This can be seen in table 3 below.

**Table 3. NIHSS Score and END Characteristics**

Variable Characteristics	Mean $\pm$ SD	Frequency (n=40)	Percentage (%)
NIHSS Score day 1	9,55 $\pm$ 6,73		
- Mild		12	30
- Moderate		18	45
- Severe		9	22,5
- Very severe		1	2,5
NIHSS Score day 3	11,25 $\pm$ 7,93		
- Mild		8	20
- Moderate		19	47,5
- Severe		10	25
- Very severe		3	7,5
END			
- Yes		25	62,5
- No		15	37,5

Based on fisher's exact test on 40 research samples, it was found that there was a significant relationship between blood pressure variability and END with a p of 0.03 ( $p < 0.05$ ). This can be seen in table 4 below.

**Table 4. Association between Blood Pressure Variability and Early Neurological Deterioration**

Blood Pressure Variability	Early Neurological Deterioration		p	PR(CI 95%)
	Yes(%)	No(%)		
Fluctuation	21(75)	7(25)	0.03	2,25(0,98-5,15)
Not Fluctuation	4(33,3)	8(66,7)		



## Discussion

The age of all study subjects had a mean of  $60.97 \pm 9.77$  years with the largest age range at the age of 56 - <71 years, as many as 20 subjects (50%). The results of this study are relevant to previous research conducted by Rambe et al. in 2013 which stated that the mean age of stroke patients was 59 years (age range 20-95 years) and the highest number of subjects was at the age of 40-59 years.<sup>11</sup> In a study conducted by Lona et al. in 2019, it was found that the average age was  $56.2 \pm 6.92$  years with the most subjects found in the age group >50 - 60 years as many as 23 subjects.<sup>12</sup> The cumulative effects of aging on the cardiovascular system and the progressive development of stroke risk factors over a period of time increase the risk of developing a stroke. The risk of stroke doubles after age 55 years.<sup>13</sup> The risk of stroke increases with age where most cases occur at the age of more than 65 years. Elderly stroke survivors have a higher mortality rate and poorer quality of life compared to younger ages.<sup>14</sup>

In this study, as many as 22 women subjects (55%) were more than men as many as 18 subjects (45%). This is relevant with research conducted by Rambe et al. in 2013 showing that the demographic characteristics of women are more compared to men as many as 52.7%.<sup>11</sup> Women have several factors that are different from men, including coagulation factors, hormonal reproductive factors, pregnancy and childbirth, and social factors that can influence stroke risk and stroke outcome.<sup>15</sup> Several other risk factors including use of oral contraceptives, menopause and use of hormone replacement therapy are also associated with the risk of stroke. Although the incidence of stroke is low in women of reproductive age, the use of oral contraceptives with high levels of the hormone estrogen can increase the risk of ischemic stroke.<sup>14</sup>

The most educational level of the research subjects in this study were senior high school as many as 23 subjects (57.5%). The occupational status of the most subjects was housewife as many as 14 subjects (35%) and the lowest was retired as many as 1 subject (2.5%). The results of this study are relevant to previous research conducted by Kusumawardani (2011) at dr. Kariadi Semarang who found the most education for stroke sufferers was senior high school about 52.4%.<sup>16</sup> According to Riskesdas in 2013, the prevalence of stroke tended to be higher in people with low levels of education based on a diagnosis of health services as much as 32.8%.<sup>17</sup> According to Liao et al (2009), socioeconomic status has a relationship with stroke incidence. This is related to stroke prevention efforts, namely controlling stroke risk factors.<sup>18</sup>

Most of the respondents came from the Batak ethnic group as many as 26 subjects (65%). This is relevant to the research conducted by El harizah et al. in 2016, the highest number of people suffering from stroke was the Batak ethnic group as many as 63 subjects (63%).<sup>19</sup> In a study conducted by Lona et al. in 2019, the largest ethnic group was the Batak ethnic group, as many as 33 subjects (71.7%).<sup>12</sup> The cause of the incidence of stroke in the Batak ethnic group compared to the non-Batak group may be caused by risk factors that cannot be caused by genetics and risk factors for stroke that can be transmitted.<sup>20</sup> The Batak ethnic group has a characteristic that they eat more than other tribes so they are more likely to be obese.<sup>21</sup> Batak specialties also contain lots of cholesterol levels.<sup>22</sup> The Batak ethnic group is more temperamental and emotional than other ethnic groups, so that it can cause blood pressure to rise more easily.<sup>21</sup>

In this study, according to JNC VIII, the mean maximum SBP is classified as grade I hypertension while minimum SBP is classified as prehypertension. The average of delta SBP is  $25.35 \pm 10.66$  mmHg which is categorized as fluctuating, and the mean delta DBP was  $17.97 \pm 8.48$  mmHg also categorized as fluctuating. Research Chung et al. in 2015 reported that the risk of END increases every parameter of increased blood pressure variability. Additional analyzes were performed on the SBPmax and DBPmax values at 20 mmHg intervals which indicated that there was a linear relationship with p value <0.01.<sup>4</sup> Of the several risk factors such as behavioral, environmental, occupational, and metabolic risk factors, elevated systolic blood pressure is a major risk factor for the global disease burden that has the potential to cause death and morbidity due to long-term disability, and a substantial proportion of this burden is due to stroke. Hypertension is an important target for the prevention of recurrent strokes because it is a major risk factor in those with a history of stroke or TIA. Decreasing blood pressure has been shown to substantially reduce the risk of stroke.<sup>23</sup>

In this study, the NIHSS score on day 1 had a mean of  $9.55 \pm 6.73$  with the most characteristic neurological deficit in the moderate category. In a study conducted by Wouters et al. in 2018 reported that the initial NIHSS score <7 was identified as a predictor of good functional outcome (GFO) in acute ischemic stroke patients.<sup>24</sup> A recently published cohort study reported the NIHSS score at admission was associated with an increased risk of END in



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the acute phase of ischemic stroke.<sup>25</sup> However, Zhang et al. in 2016 found that the NIHSS score at admission was not related to END. A possible reason is not only the relatively small sample size, but also that the subjects included in the study were categorized as mild neurological disorders (mean NIHSS score at admission was 3). The NIHSS score represents the degree of neurological deficit. The NIHSS score at admission may be an important predictor of END in the acute phase of ischemic stroke.<sup>26</sup>

Based on statistical analysis of Fisher's exact test on 40 subjects, it was found that there was a significant relationship between blood pressure variability and END with  $p = 0.03$  ( $p < 0.05$ ). This suggests that blood pressure variability will increase the incidence of END in acute ischemic stroke patients. According to Chung et al. in 2015, blood pressure variability independently and linearly is associated with early neurological deterioration in the acute phase of ischemic stroke. The results of these studies also indicate that blood pressure variability can be a potentially modifiable risk factor for prevention of END incidence.<sup>4</sup> Leoncini et al. in 2013 stated that an increase in systolic blood pressure variability was associated with several signs of organ damage. The results of this study indicate that the variability in blood pressure is associated with a simultaneous effect on organ damage in the form of atherosclerotic in various organs.<sup>27</sup>

A study conducted by Havenon et al. in 2017 states that increased variability in blood pressure is associated with worse neurological clinical outcomes in acute ischemic stroke, especially in patients with large volume of lesions, proximal vessel occlusion and the presence of good collateral vessels. Several clinical trials involving more than 20,000 patients have been conducted to determine whether pharmacologically lowering blood pressure after ischemic stroke is beneficial. In contrast, there are no clinical trials regarding the effectiveness of reducing blood pressure variability after ischemic stroke.<sup>28</sup>

The association between blood pressure variability during the acute phase of ischemic stroke and outcome has been extensively investigated recently, but the relationship is not clear. One of the mechanisms that are thought to underlie this incident is related to arterial stiffness where when the systolic blood pressure increases, it is often found that the diastolic blood pressure increases slightly or even falls, giving rise to greater variability. During the acute phase of stroke, cerebral autoregulation is impaired and blood flow becomes completely dependent on systemic blood pressure. The increased stiffness of the arteries will cause an increase in excessive blood flow to the small blood vessels. The presence of hemodynamic stress, pulsatile pressure or variability in blood pressure can cause damage to the brain parenchyma. For this reason, fluctuations in blood pressure further damage the ischemic site.<sup>9</sup> In addition, other factors such as age, initial stroke severity, stroke subtype, history of diabetes mellitus, hyperglycemia, high initial blood pressure, arterial stenosis or occlusion, atrial fibrillation, and high serum urea levels were associated with the development of END.<sup>4</sup>

### Conclusion

There is a significant relationship between blood pressure variability and END in patients with acute ischemic stroke. Blood pressure variability will increase the incidence of END in acute ischemic stroke patients.

### Suggestion

Further research can be done with used more standard parameters of blood pressure variability. The use of ambulatory blood pressure monitoring needs to be done in order to get better results.

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