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Associations between variation of systolic blood pressure and neurological deterioration of ischemic stroke patients

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Abstract

Objectives: To assess the relationship of variation of blood pressure and neurological deterioration (ND) in ischemic stroke patients. *Methods:* We recruited patients with the first-ever ischemic stroke at a teaching hospital. The National Institutes of Health Stoke Score (NIHSS) of each patient was monitored for 2 months. ND was defined as an increase of ≥ 2 points in NIHSS during the first 7 days after stroke. Blood pressure was measured every 6 hours for first 7 days. We analyzed blood pressure data in the first 36 hours to study the relationship between variation of blood pressure and ND. Successive variation of systolic (svSBP) and diastolic (svDBP) blood pressure was calculated as svSBP= $|SBP_{n+1} - SBP_n|$ and svDBP= $|DBP_{n+1} - DBP_n|$ respectively. The largest svSBP in the first 36 hours of hospitalization or before ND was defined as maximum variation of systolic blood pressure (maxvSBP). Then, the mean variation of systolic (mvSBP) and diastolic (mvDBP) blood pressure was calculated as mvSBP= svSBP/N and mvDBP= svDBP/N respectively. *Results:* A total of 121 patients were included in this study, and 38 of them had ND. The mvSBP was higher in the ND Group (17.9±8.4 mmHg vs. 13.7±4.4 mmHg, p=0.006) but the difference in mvDBP did not reach statistical significance (9.8±3.5mmHg vs. 8.6±3.0 mmHg p=0.06). The ND Group had a larger maxvSBP (35.2±17.2 vs. 27.6±11.6 mmHg, p =0.01), which was more frequently over 30mmHg than that in the stable group (P=0.02).
Conclusions: A large svSBP is associated with an increased risk for ND. The study highlights the importance of close monitoring of blood pressure in ischemic stroke patients.

INTROUDUCTION

Neurological deterioration (ND) is a common event in the first hours or days of cerebral infarction. Stroke patients with ND stay longer at the hospital, are more disabled, and need more institutional care than patients without ND. The incidence of ND in cerebral infarction ranges from 9.8% to 40%.[1-4] Over the past several decades, many studies have been conducted on the causes of ND in acute stroke patients. Although several variables have been found to be associated with ND, little is known about the etiology. Theories regarding the etiology of ND include extension of brain edema, absence of recanalization, thrombous propagation, recurrent embolism, and various system diseases.[5,6]

The reported indicators of ND in acute ischemic stroke patients include neuroimaging, ultrasonographic, and biochemical parameters.[6,7] The presence of mass effect on brain computed tomography (CT) has been suggested to be a predictor of ND[8], and transcranial Doppler has been shown to be a useful technique in the identification of patients at risk of developing ND. During the first 6 hours of stroke, absence of blood flow in the middle cerebral artery was found in 40% of patients with ND, but in only 22% of patients without ND.[9] High plasma levels of glucose, fibrinogen, and glutamate were found to be associated with ND.[5,10]

It is well known that blood pressure (BP) control can reduce the risk of stroke recurrence. However, during the acute phase of stroke or in a transient ischemic attack (TIA), BP reduction may worsen an already compromised perfusion

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in pneumobra. Therefore, some researchers do not recommend lowering BP during the acute phase of stroke.[11] It has been reported that a decrease in nocturnal BP is associated with an increase in the regional cerebral blood flow of patients with stroke in the territory of carotid artery.[12] Whereas circadian BP reduction in the first 24 hours of stroke onset is not related to a patient's outcome[13], the morning pressure surge and nocturnal BP decline are common and associated with the development of stroke.[14] It has been shown that a BP reduction in the first 24 hours of stroke is associated with poor outcome.[15] Blood pressure variation had been reported to relate to circadian onset of cardiovascular disease and cerebrovascular disease.[16] Because of the different results in previous reports, the question as to whether BP variation is associated with ND remains unanswered, and the degree of variation that will affect the clinical course of stroke is yet to be determined. The purposes of this study were to assess the relationship between variation of systolic blood pressure and ND in patients with ischemic stroke.

METHODS

We recruited consecutive patients of stroke who were admitted to the neurological ward of a teaching hospital in Chia-Yi, Taiwan from July 2003 to June 2005. The inclusion criteria were: (1) initial evaluation within 24 hours after the onset symptoms, (2) persistence of neurological symptoms at the time of initial evaluation, (3) no ongoing anticoagulant treatment and no clinical indication of thrombolytic therapy, (4) no history of previous TIA or stroke, and (5) brain CT showed normal finding or only ischemic infarction consistent with the presented neurological findings. Accordingly, all recruited participants were admitted to the Neurological ward through the Emergency Department, because those who were admitted through the outpatient department could not meet the first criterion.

BP, blood sugar, biochemistries, cell count, chest X-ray, electrocardiogram (ECG), and non-contrast CT were obtained from each patient at the Emergency Department before the intravenous injection of normal saline, and all the diagnoses of stroke were confirmed by a Neurologist. The National Institutes of Health Stroke Scale (NIHSS) was determined immediately after the patient was included in the study. Patients were re-evaluated daily during the first week. In the morning after admission to the neurological ward, serum levels of cholesterol, triglyceride, and fasting sugar were measured, and carotid sonography and intracranial Doppler were performed on the second day of hospitalization. During the hospitalization, patients were treated with aspirin 100 mg/day, pentoxifylline 400 mg twice a day, and 0.9% normal saline 40 cc/hr. Aspirin was changed to ticlopidine 250 mg/day or clopidogrel 75 mg/day if the patient showed symptoms or signs of gastric ulcer. Normal saline was not given to patients with congestive heart failure or end stage renal disease. The same dosages of hypoglycemic agents were prescribed for patients who had used those drugs before the event. Antihypertensive agents were not given except patient's BP over 220/120 mmHg. When the patient's BP was over 220/120 mmHg, nifedipine (5 mg) oral administration or labetalol (25 mg) intravenous injection was given. ND was defined as an increase of ≥ 2 points in the NIHSS in the first seven days of stroke in comparison to the initial neurological examination at Emergency Department[6,17], and a Neurologist evaluated all of the patients and assessed the risk factors. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg at the time of admission and lasted longer than 2 weeks after stroke onset, or the use of antihypertensive drugs. Diabetes mellitus was defined as fasting blood sugar ≥ 126 mg/dl lasted for at least 3 days or the use of oral hypoglycemic agents or insulin. Hypercholesterolemia was defined as serum cholesterol ≥ 200 mg/dl or the use of antilipidemic drugs. Information regarding smoking and alcohol intake, as well as history of myocardial infarction and coronary artery disease were recorded.

After initial neurological evaluation at emergency department, BP was measured three times on the right arm of the patient with a supine position using mercury sphygmomanometer every 6 hours. Noninvasive cuff BP, pulse rate, and body temperature were also measured. The mean of the three measurements was calculated and used for analysis. In the patients whose ND occurred before 36 hours of stroke onset, BP before ND was included in the analysis. In the other patients, BP of the first 36 hours was included in the analysis. The mean SBP and DBP were taken as the means of all the SBP and DBP recording in the first 36 hours of hospitalization or before ND. Successive variation of systolic (svSBP) and diastolic (svDBP) blood pressure was calculated as $svSBP = |SBP_{n+1} - SBP_n|$ and $svDBP = |DBP_{n+1} - DBP_n|$ respectively, where n indicates the nth measurement of BP. The largest svSBP in the first 36 hours of hospitalization or before ND was

defined as maximum variation of systolic blood pressure (maxvSBP). Then, the mean variation of systolic (mvSBP) and diastolic (mvDBP) blood pressure was calculated as mvSBP= svSBP/N and mvDBP= svDBP/N respectively, where N is the total number of measurements of SBP or DBP. Mean artery pressure (MAP) was calculated as (SBP + DBP×2)÷3.

We compared the age, sex, risk factors, the time of arrival at the hospital, SBP, DBP, MAP, maxvSBP, svSBP, and svDBP between patients with and without ND. We used the t test to evaluate differences in continuous variables and the chi-square or Fisher's exact test to evaluate differences in categorical variables. All statistical analyses were performed using the Prism 5 software at the two-tailed significance level of 0.05. This study was approved by the Ethics Committee of the Hospital, and a written informed consent was obtained from each patient.

RESULTS

Of the stroke patients who admitted to the Neurology ward during the study period, 121, including 55 women and 66 men, fit the including criteria, and their mean age was 68.7±10.4 years. The main reasons for exclusion were initial evaluation being performed after 24 hours (38 patients), symptoms disappearing before the initial neurological evaluation (20 patients), and brain CT showed silent infarcts (SIs) (44 patients). We excluded the patients with SIs, because SIs may affect the outcome of stroke patients.[18] Among the patients included in the analysis, 38 (31.4%) showed early clinical ND and were thus assigned to the ND Group. In all these 38 patients, ND occurred in motor function or facial palsy, and all associated with dysarthria, dysphagia, or sensory impairment. Of them, 25 (65.8%) showed symptoms of ND within the first 48 hours, 8 (21.1%) between 48 and 72 hours, and 4 (10.5%) between 73 and 122 hours.

At the time of admission, the mean SBP and DBP pressures were 162.4±26.9 and 89.1±12.8 mmHg, respectively, for the ND Group, and 156.1±24.6 and 85.5±14.1 mmHg for the Stable Group. In the first36 hours or before ND, the mean SBP, DBP and MAP were not significantly different between the two groups. (Table 1, Fig 1) The mvSBP was higher in the ND Group (17.9±8.4 mmHg vs. 13.7±4.4 mmHg, p=0.006) (Figure 2), but the difference in mvDBP did not reach statistical significance (9.8±3.5mmHg vs. 8.6±3.0 mmHg p=0.06) (Table 1). The ND Group had a larger maxvSBP (35.2±17.2 vs. 27.6±11.6 mmHg, p=0.01), which was more frequently over 30mmHg than that in the stable group (p=0.02).

DISCUSSION

In this study, the frequency of ND in patients with the first-ever stroke was found to be 31.4%, which is similar to those observed in previous studies.[1-4] Hypertension has been shown to be a modifiable risk factor for stroke, and it is well known that BP control may decrease the recurrence of stroke.[19,20] Whereas a previous study found that BP levels were lower in hypertensive patients with stroke than in hypertensive patients without stroke[21], it may be due to the higher awareness of BP control as a measure of secondary prevention of stroke among patients with stroke.

Previous studies provided evidence that BP is initially high and spontaneously fall within 7 days after hospitalization in ischemic stroke patients. They suggest that reduction of BP is unnecessary and dangerous in acute ischemic stroke patients.[22,23] However, a study found that SBP on admission directly predicted ND in ischemic stroke patients, with an OR of 1.01 for each 1-mmHg raise in SBP.[24] Carlberg *et al*. also found that the increase of BP in stroke patients with impaired consciousness was associated with higher rates of ND and mortality.[25] Our study is different from the previous studies in that we evaluated all the BP within first 7 days and the relationship between BP variation and ND. Our study had three new findings. First, we evaluated the relationship between vSBP and ND in acute ischemic stroke patients and found that severe vSBP was associated with ND. We also found that the degree of maxvSBP appeared to be related to the highest BP, and the highest SBP was not always present on the first day of stroke. In some cases, it appeared on the second or the third day of stroke and even after antihypertensive medications had been given to patients (58%) who had used antihypertensive medication before the stroke attack. Second, we found that a maxvSBP > 30 mmHg increases the risk of developing ND in ischemic stroke patients. Third, higher svSBP in first 36 hours of stroke was associated with ND.

SBP and mean BP have been reported to be predictors of stroke[26], and BP variation is common in normal subjects. Circadian BP variation has been classified as dipping (mean nocturnal SBP is 10-20% lower than daytime SBP), extreme

Table1: Characteristics of patient in the Neurological Deterioration and Stable Group

	Neurological Deterioration Group N=38	Stable Group N=83	*p value
Age (year)	69.8±8.2	67.8±11.6	0.19
Sex (male/female)	21/17	45/38	>0.95
Myocardial infarction	1 (2.6%)	1 (1.2%)	>0.95
Arrhythmia	5 (13.1%)	11 (13.4%)	>0.95
Hypertension	24 (63.2%)	52 (62.7%)	>0.95
Diabetes mellitus	18 (47.4%)	29 (33.7%)	0.16
Smoking	8 (21.0%)	25 (30.1%)	0.38
Hypercholesterolemia	15 (39.5%)	32 (38.6%)	>0.95
Alcohol consumption	4 (10.5%)	5 (6.0%)	0.46
Hypertriglyceridemia	8 (21.0%)	24 (28.9%)	0.51
Interval before arrival (hr)	9:09	7:35	0.34
Admission NIHSS	5.9	4.4	0.25
Admission SBP (mean±SD)(mmHg)	162.4±26.9	156.1±24.6	0.22
Admission DBP (mean±SD)(mmHg)	89.1±12.8	85.5±14.1	0.16
maxvSBP (mean±SD)	35.2±17.2	27.6±11.6	<0.01
Mean SBP (mmHg)	150.1±18.6	146.9±17.7	0.38
Mean DBP (mmHg)	83.3±10.6	81.9±9.8	0.49
Mean MAP (mmHg)	105.6±12.6	103.7±11.6	0.42
mvSBP (mmHg) (mean±SD)	17.9±8.4	13.8±5.6	< 0.01
mvDBP (mmHg) (mean±SD)	9.8±3.5	8.9±3.9	0.16
maxvSBP (mmHg)			
≤ 30 mmHg	16 (42.1%)	51 (61.4%)	
31-50 mmHg	16 (42.1%)	29 (34.9%)	
> 50 mmHg	6 (15.8%)	3 (3.7%)	0.02

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean artery pressure
maxvSBP: maximum variation of systolic blood pressure
mvSBP: mean variation of systolic blood pressure
mvDBP: mean variation of diastolic blood pressure
*for χ^2test or t test

dipper (reduction ≥ 20%), non-dipper (reduction < 10%), and reverse dipper.[27] A previous study of acute stroke patients found that patients who were extreme dippers or reverse dippers had higher mortality and disable rates at 3 months.[13] Another study showed that a reduction of BP in the first 24 hours of stroke onset was associated with a poor outcome.[15] Furthermore, Metoki *et al.* found that inhibition of morning pressure surge by antihypertensive medications could reduce the risk of intracranial hemorrhage and that the lowering of nocturnal BP could reduce the risk of cerebral infarction.[14] In addition, a study of patients with ischemic stroke observed a negative correlation between the percent of change in nocturnal BP and the regional cerebral blood flow in cerebrum.[12]

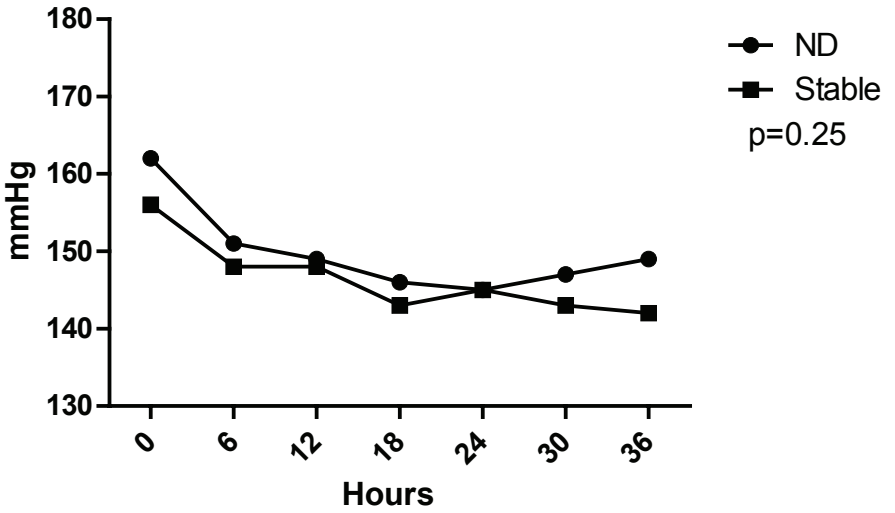

Figure 1: Change in systolic blood pressure during the first 36 hours of hospitalization

Kario *et al*. found a J-shape relationship between the nocturnal dipping state and stroke and suggested that attacks of stroke may be due to exaggerated rise of BP in the morning or due to cerebral hypoperfusion at night.[24] In the current study, we also found most of the highest SBP present in the morning, while they may present in any time of a day. Besides morning surge in BP, emotional effect on BP variation is possible.

The current study showed that higher svSBP and maxvSBP > 30 mmHg was related to the development of ND and that patients with lower svSBP and maxvSBP ≤ 30 mmHg was less likely to develop ND, which support the findings in previous studies, including (1) High variability of SBP is associated with less favorable outcome[28], (2) moderate changes in SBP do not influence the early clinical course[29], and (3) high SBP increases the risk of early ND.[30] These observations are important in the treatment of ischemic stroke patients, and accordingly we suggest monitoring BP in patients with ischemic stroke closely. Monitoring of BP, preferably ambulatory BP monitor[16], should start early after stroke onset and continue during the first seven days. Severe BP variation may increase the risk for developing ND, which may be due to cerebral hypoperfusion during lower BP or due to severe hypertension,

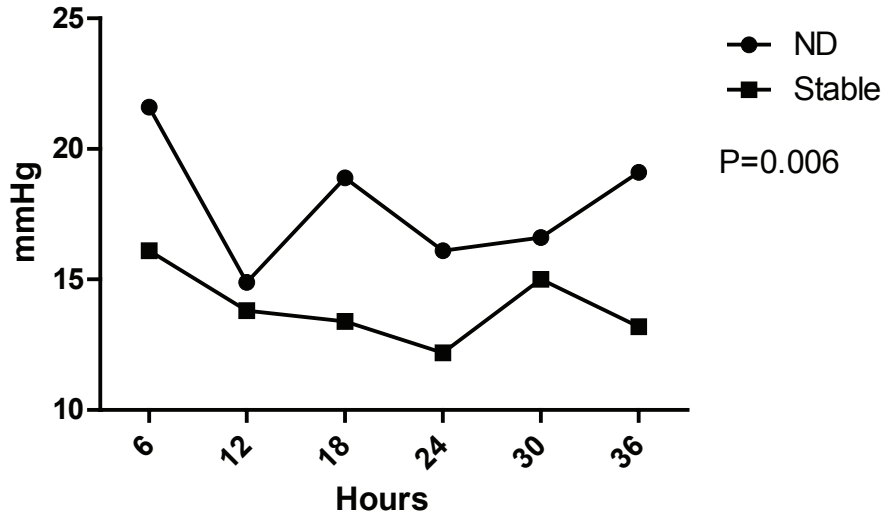

Figure 2: Change in variation of systolic blood pressure during the first 36 hours

and controlling of BP within the safe levels may prevent the development of ND. Our results also show that the high SBP was related to ND. In order to control high BP in morning and to reduce its effect on end organs, it has been suggested that in addition to strict BP control, antihypertensive agents combined with statin, perioxisome proliferator-activated receptor-γ agonist, and inhibitors of the rennin-angiotensin system can be more beneficial for prevention cardiovascular disease.[31] Whereas further studies are need to support the recommendation. These results suggest that in order to control high BP in stroke patients, physicians should exercise caution and in addition to using antihypertensive medication to treat stoke patients with hypertension, the control of patient's emotion may be beneficial. The main limitations of this study include (1) We did not use ambulatory BP monitor to measure blood pressure and white-coat hypertension was possible, (2) there was no intervention on blood pressure variation, (3) the patients were from only one center, a further multi-center study is necessary.

In conclusion, our study showed that a substantial proportion of patients with first-ever stroke may develop ND. We also found that a high degree of svSBP and extreme SBP variation were risk factors for ND in patients with mild to moderate stroke. Therefore, close monitoring and control of BP within safe levels are important to patients with ischemic stroke. In the current study, the NIHSS was evaluated once daily only, and therefore further studies which evaluate NIHSS more frequently in the first 48 hours are warranted.

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