Relationship between Neurological Deterioration and Blood Pressure/Heart Rate Variability in Patients with Acute Cerebral Infarction

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Objectives: Neurological deterioration (ND) during hospitalization is an independent predictor of poor prognosis after stroke. Risk factors affecting early ND within 48 h post stroke have been intensively investigated, while few data are available on those for late ND after transfer to a wheelchair. Therefore, it was investigated whether hemodynamic factors may affect the late ND during hospitalization. *Materials and methods:* A retrospective study was conducted on 135 patients with atherothrombotic or cardiogenic cerebral infarction who were admitted to our hospital between April 1st, 2014 and July 31st, 2017. During hospitalization, average, maximum, and minimum values were determined for systolic blood pressure (sBP), diastolic BP (dBP), and heart rate (HR), respectively.135 patients were classified into two groups; ND (+) group, in which modified Barthel index score at the time of transfer to a wheelchair showed five points or more decrease between wheelchair transfer and discharge, and ND (−) group, which did not. Vital indices were compared between the two groups and subjected to ROC-curve analysis. *Results:* The ND (+) group included 32 patients, and the ND (−) 103. Significant differences were found between the groups in four items; sBPmin ($p = 0.029$), dBPmin ($p = 0.019$), HRave ($p = 0.028$), and HRmax ($p < 0.01$). The ND (+) group showed lower sBPmin and dBPmin, and higher HRave and HRmax than the ND (−) group. *Conclusions:* Late ND after transfer to a wheelchair is related to the vital indices during hospitalization and should be cautiously managed to prevent late ND

Key Words: Ischemic cerebral infarction—Atherothrombotic cerebral infarction—Cardiogenic cerebral infarction—Neurological deterioration—Blood pressure—Heart rate—Barthel index—Transfer

Introduction

Neurological deterioration (ND) during hospitalization is an independent predictor of poor prognosis, regardless of whether it occurs in the early (within 48 h post stroke) or late period (from 48 h post stroke to discharge) after stroke.[1] Therefore, it is highly recommended to reveal predisposing factors inducing ND and mitigate these factors in the early rehabilitation stage. In patients with acute stroke, cerebral autoregulation is often disturbed, and blood pressure (BP) variability may directly affect cerebral blood flow (CBF). Therefore, assuming an upright position may cause transient hypotension, which is usually compensated by increased heart rate (HR) and cerebral vasodilatation, thus maintaining cerebral perfusion in

normal brain tissue.[2] By contrast, in acute stroke, autoregulation of cerebral circulation is impaired. Therefore, early mobilization frequently induces hypotension[3] and subsequent decrease in local CBF in brain tissue with misery perfusion.[4] Alternatively, a rise in BP may induce an impairment of the blood-brain barrier, causing cerebral microhemorrhages and edema.[5]

In early mobilization protocol, the evaluation of BP is common[6] and, most important, as a dynamic parameter for the risk of ND. Additionally, heart rate (HR) is another parameter that reflects cardiac and autonomic function[7] and may also affect the risk of ND. However, there are no suggestions on the ideal control level of post stroke BP and HR to prevent ND. Indeed, there is a concern on early mobilization when sitting out of bed within 24 h of stroke because the alteration of BP and HR may cancel out the benefits of neurovascular repair and prevention of disuse syndrome.[8]

Several studies show the relationship between early ND and final activities of daily living (ADL) after a long-term period.[9–14] However, the frequency of ND differs in a broad range, probably due to stroke subtypes, comorbidities, and definition of ND.[15] For example, in a study of patients with penetrating territorial artery infarction, ND was defined as one point or more increase by National Institute of Health Stroke Scale (NIHSS) and encountered in 14% of patients, being associated with vascular risk factors including high hemoglobin A1c, body mass index, and hypertension.[12] In a study of acute ischemic stroke, ND was defined by two points or more increases by NIHSS and was found in 41.5% of stroke patients, especially with hypertension and severe neurological and radiological findings on admission.[14] Alternatively, ND was defined as four points or more increase by NIHSS and has been observed in 11.9% of patients within seven days, being associated with the history of myocardial infarction, high leukocyte count, low-density lipoprotein cholesterol, and hemoglobin.[16]

In this study, late ND after transfer to a wheelchair was focused on by comparing modified Barthel index (mBI) at the time of wheelchair transfer as a baseline and the worst mBI during the period between the baseline and discharge. The presence of late ND was judged by five points or more decrease in the mBI score. Direct comparison of ADL scores between at the baseline and after transfer to a wheelchair until discharge makes it possible to evaluate the effect of vital signs on the net change of ADL during hospitalization.

Subject and method

Subjects

Of 273 patients who visited the Mie University Hospital between April 1st, 2014, and July 31st, 2017, and received a diagnosis of cerebrovascular disease, 180 patients received a diagnosis of cerebral infarction, and five patients died during the hospitalization period. As a subdivision, 135 patients were diagnosed with atherothrombotic cerebral infarction (ACI), or cardiogenic cerebral infarction (CCI) subtypes, 12 patients having lacunar infarction, and 28 patients having non-classified by neurosurgeons or neurologists at the time of admission. For this study, 135 patients with ACI and CCI were analyzed.

Measurement method

Changes in circulatory dynamics (systolic blood pressure: sBP, diastolic blood pressure: dBP, and heart rate: HR) were measured over time from the time of admission to discharge. BP and HR were measured in the supine position on the bed. At the time of admission, the NIHSS score was evaluated either by neurosurgeons or neurologists. Additionally, the Barthel index (BI) was used to evaluate ADL during hospitalization and modified BI (mBI) was assessed daily using seven of ten items (eating, transferring, dressing, toileting, dressing, and control of defecation and urination). For the group classification, those whose mBI scores reduced by five points or more during hospitalization compared to those at the time of acquisition of wheelchair were defined as the neurological deterioration; ND (+) group; n = 32 patients, and those whose scores did not reduce were defined as the ND (−) group; n = 103 patients. All patients in the ND (+) group showed an ND exclusively after transfer to a wheelchair. The average, maximum, and minimum values of sBP, dBP, and HR were estimated over time from admission to discharge. The two groups were compared for each measurement item from admission to transfer to a wheelchair.

Statistical processing

For statistical processing, comparisons were made between the two groups using the t-test for each measurement item and the chi-square test for categorical variables. Association of general characteristics with two groups was evaluated by logistic regression analysis. Only those items that were significantly different in the receiver operating characteristic (ROC) curve and area under the curve (AUC) analysis were used to calculate the cut-off point. EZR (Easy R) (ver. 1.54) was used for statistical processing, and the difference was considered significant at a risk rate of 5%. This study was approved by the Ethical Review Committee of Mie University Hospital. (Approval No. 3237)

Results

Subjects

There was no significant difference in age between the ND (−) and ND (+) groups. (p = 0.24). In the ND (+) group, NIHSS at the onset was significantly higher in stroke severity (p < 0.01). Also, at the time of transfer to a wheelchair, mBI was significantly lower (p = 0.04), and ADL ability at the time of discharge was significantly

lower ($p < 0.01$) in the ND (+) group than in the ND (−) group. Hospitalization was significantly prolonged in the ND (+) group ($p = 0.049$). However, there was no significant difference in the time to transfer to a wheelchair ($p = 0.157$).

In ACI NIHSS at the onset, was significantly higher, and the time of transfer to a wheelchair was significantly delayed ($p = 0.01$) in the ND (+) group ($p < 0.01$) compared with in the ND (−) group. There was no significant difference between the ND (+) and ND (−) groups in the mBI at transfer to a wheelchair ($p = 0.075$). However, the mBI at discharge was significantly lower ($p = 0.047$), and the duration of hospitalization was significantly longer ($p = 0.010$) in the ND (+) group.

In the CCI, there was no significant difference in the NIHSS between the ND (+) and ND (−) groups at the onset ($p = 0.643$). Additionally, no difference was observed in the mBI at transfer to a wheelchair ($p = 0.227$), and at discharge ($p = 0.091$) as well as the term to transfer to a wheelchair ($p = 0.92$), or to discharge ($p = 0.58$) between the ND (+) and ND (−) groups (Table 1). The general characteristics of a logistic regression analysis were age (OR = 1.01; 95% CI 0.97-1.04; $p = 0.694$). NIHSS (OR = 1.07; 95% CI 1.02-1.11; $p < 0.01$) and Sex(male) (OR = 0.29; 95% CI 0.12-0.70; $p < 0.01$).

Hemodynamic changes

The sBPave was 137.3 ± 20.8-mmHg in the ND (+) group and 138.4 ± 15.8-mmHg in the ND (−) group, with no significant difference ($p = 0.76$). The sBPmax was 180.4 ± 28.3-mmHg in the ND (+) group and 171.0 ± 26.9-mmHg in the ND (−) group, with no significant difference ($p = 0.103$). However, the sBPmin was significantly lower in the ND (+) group; 94.6 ± 27.8-mmHg than in the ND (−) group; 105.8 ± 23.4-mmHg ($p = 0.029$) (Fig. 1-A).

The dBPave was 72.4 ± 9.6 mmHg in the ND (+) group and 76.1 ± 11.7-mmHg in the ND (−) group, with no significant difference ($p = 0.12$). The dBPmax was 119.38 ± 27.62-mmHg in the ND (+) group and 109.1 ± 29.3-mmHg in the ND (−) group, with no significant difference ($p = 0.087$). However, the dBP min was lower in the ND (+) group; 47.5 ± 14.2-mmHg than in the ND (−) group; 55.2 ± 16.3-mmHg ($p = 0.019$) (Fig. 1-B).

The HRmin was 60.7 ± 11.0 bpm in the ND (+) group and; 60.4 ± 13.0 bpm in the ND (−) group, with no significant difference ($p = 0.89$). However, the HRave in the ND (+) group, 79.6 ± 10.2 bpm was higher than in the ND (−) group; 73.5 ± 14.0 bpm ($p = 0.028$) and the HRmax in the ND (+) group; 119.9 ± 31.1 bpm was higher in the ND (−) group; 96.9 ± 25.4 bpm ($p < 0.01$) (Fig. 2).

Table 1. *Comparison of patient characteristics between the groups with and without ND.*

Characteristisc	Total	ND (-)	ND (+)	p-value
Number	135	103	32	
Age.y	72.6 ±12.5	72.2 ±11.4	75.2±15.5	p= 0.240
Sex, femal/male	40 / 95	24 / 79	16 / 16	p<0.01**
Atherothrombotic cerebral infarction	75	58	17	p= 0.860
Cardiogenic cerebral infarction	60	45	15	p= 0.845
Hypertension (%)	11.1	42.7	46.9	p= 0.678
Atrial fibillation (%)	11.2	26.2	50.0	p= 0.011*
Dyslipidemia (%)	23.7	26.2	15.6	p= 0.216
Diabetes mellitus (%)	23.7	21.4	18.8	p= 0.750
NIHSS at onset	10.1±9.5	8.7±6.4	14.9±11.2	p< 0.01**
Modified Barthel index (transfer to a wheelchair)	37.8±17.0	39.5 ±16.6	32.2±17.4	p= 0.040*
Modified Barthel index (discharge)	51.7±16.9	53.8±17.1	45.0±14.1	p< 0.01**
The term to transfer to a wheelchair (day)	8.1±21.9	6.4 ±20.8	13.3±24.7	p= 0.157
The term to discharge (day)	31.4±31.0	26.3±29.8	41.5±33.2	p= 0.049*
Atherothrombotic cerebral infarction				
NIHSS at onset	8.8±10.1	6.6±7.8	16.3 ±13.1	p< 0.01**
Modified Barthel index (transfer to a wheelchair)	38.4±15.9	40.2±15.2	32.4±17.5	p=0.075
Modified Barthel index (discharge)	54.3±14.5	56.1±14.3	48.2±13.6	p= 0.047*
The term to transfer to a wheelchair (day)	6.4±16.0	3.7±5.1	15.6±31.3	p< 0.01**
The term to discharge (day)	29.9±27.9	25.6±24.9	45.0±33.1	p= 0.010*
Cardiogenic cerebral infarction				
NIHSS at onset	11.9±8.5	11.3±8.5	13.5±8.6	p= 0.643
Modified Barthel index (transfer to a wheelchair)	37.0±18.4	36.7±18.5	32.0±17.8	p= 0.227
Modified Barthel index (discharge)	48.5±19.0	50.9±19.9	41.3±14.2	p= 0.091
The term to transfer to a wheelchair (day)	10.1±27.5	9.9±30.7	10.8±14.8	p= 0.920
The term to discharge (day)	33.2±34.7	31.7±35.2	37.5±34.0	p= 0.580
			*: p<0.05, **: P<0.01	

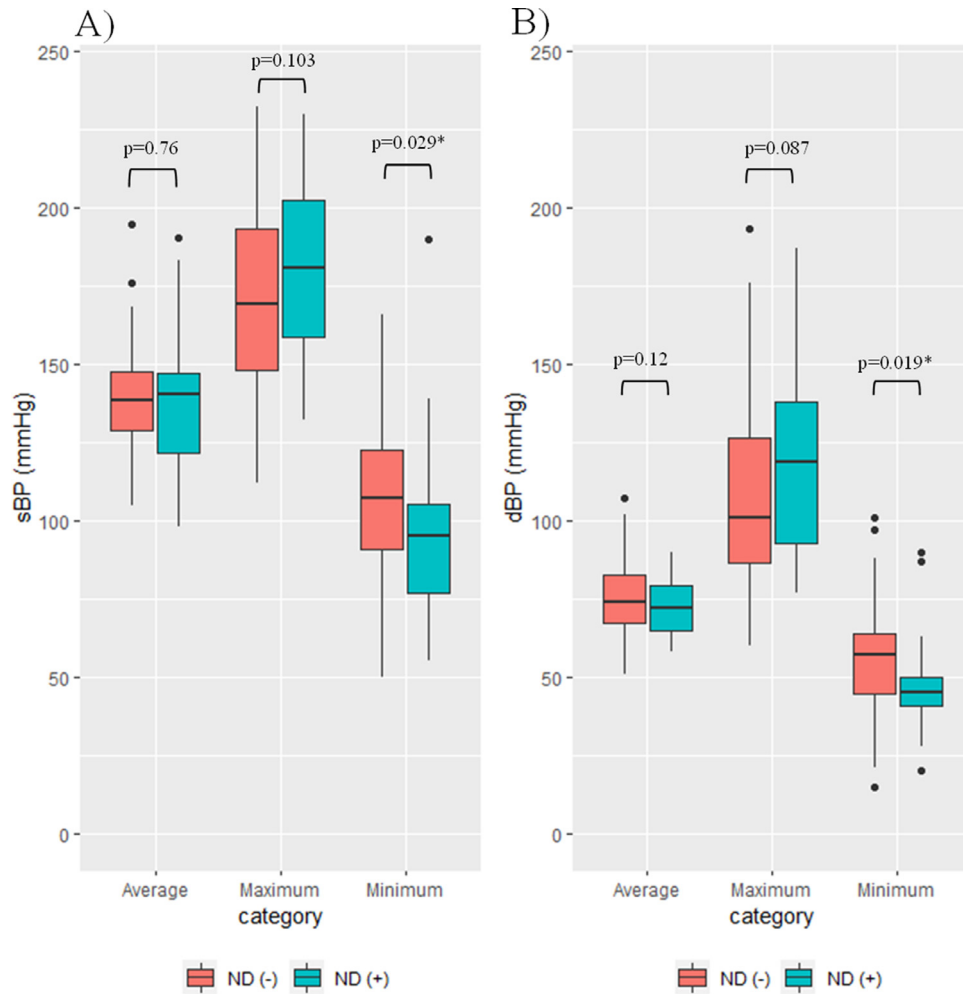ND: Neurological deterioration

Fig. 1. *systolic BP (A) and diastolic BP (B) in the whole subjects. The minimum of systolic BP and the minimum of diastolic BP were lower in the ND (+) group than in the ND (−) group (A; p = 0.029, B; p = 0.019). BP: Blood pressure, ND: Neurological deterioration ND (−): ND-negative, ND (+): ND-positive.*

ND in terms of stroke subtype

1. ACI

The sBPave was 141.2 ± 23.9-mmHg in the ND (+) group and 140.0 ± 16.5-mmHg in the ND (−) group with no significant difference ($p = 0.522$). The sBPmax was significantly higher in the ND (+) group; 184.1 ± 29.9-mmHg than in the ND (−) group; 169.2 ± 26.1-mmHg ($p = 0.036$). Additionally, the sBPmin was significantly lower in the ND (+) group: 96.8 ± 28.7-mmHg than in the ND (−) group; 113.6 ± 20.9-mmHg ($p = 0.020$) (Fig. 3-A).

The dBPave was 71.5 ± 9.2-mmHg in the ND (+) group and 75.1 ± 11.8-mmHg in the ND (−) group, with no significant difference ($p = 0.757$). The dBPmin was 47.4 ± 13.2 mmHg, in the ND (+) group and 58.9 ± 15.4-mmHg in the ND (−) group, with no significant difference ($p = 0.059$). However, the dBPmax was significantly higher in the ND (+) group 118.9 ± 26.2-mmHg than in the ND (−) group; 99.8 ± 24.2-mmHg ($p < 0.01$) (Fig. 3-B).

The HRmin was 60.9 ± 10.1 bpm in the ND (+) group and 59.0 ± 10.1 bpm in the ND (−) group, with no significant difference ($p = 0.269$). However, the HRave was significantly higher in the ND (+) group; 79.7 ± 9.6 bpm, than in the ND (−) group; 69.1 ± 9.3 bpm ($p < 0.01$). The HRmax was also significantly higher in the ND (+) group; 119.9±31.1 bpm than in the ND (−) group; 86.4 ± 19.5 bpm ($p < 0.01$) (Fig. 4).

2. CCI

Between the ND (+) and ND (−) groups, there was no significant difference in the sBPave; 133 ± 17.7-mmHg vs 136.3 ± 14.8-mmHg ($p = 0.419$), the sBPmax; 176.1 ± 26.8-mmHg vs 173.4 ± 28.1-mmHg ($p = 0.463$), and the sBPmin; 92.3 ± 27.7 vs 95.7 ± 22.8-mmHg ($p = 0.377$) (Fig. 3-A).

Also, there was no significant difference in the dBPave; 73.4 ± 10.3-mmHg vs. 77.3 ± 11.7-mmHg in the ND (−) ($p = 0.757$), the dBPmax: 119.9 ± 29.9-mmHg vs. 121.0 ±
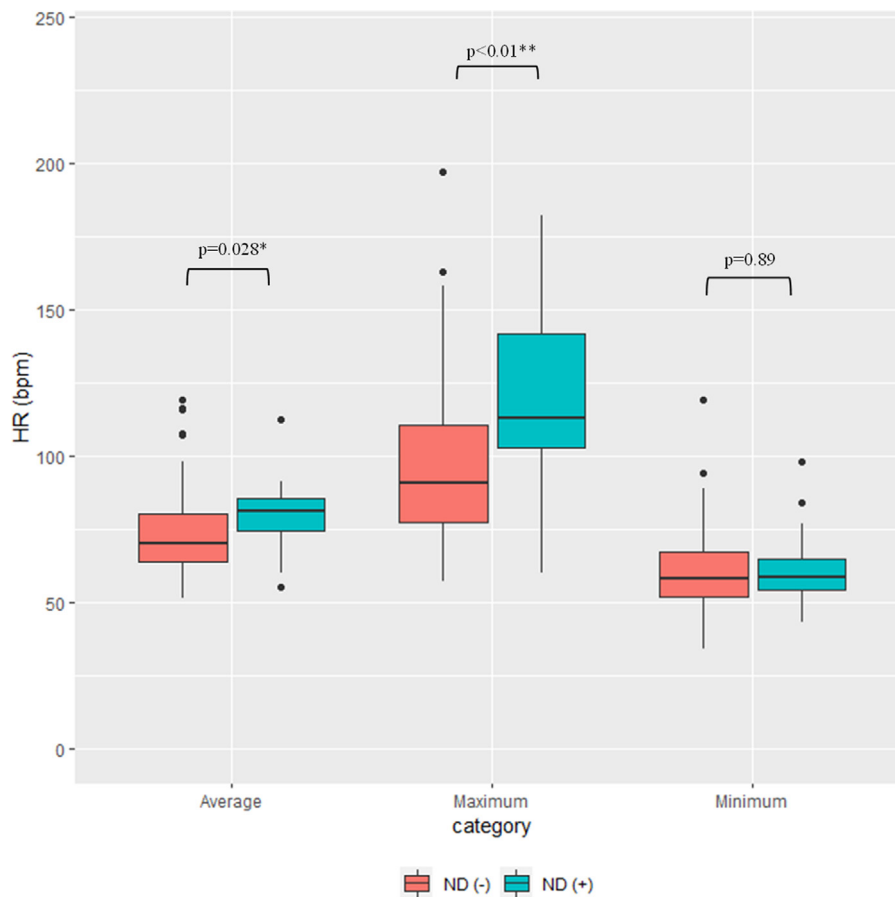
Fig. 2. *HR in the whole subjects. The average of HR and the maximum of HR were higher in the ND (+) group than in the ND (−) group (A; p = 0.028, B; p < 0.01). HR: Heart rate, ND: Neurological deterioration: ND (−): ND-negative, ND (+): ND-positive.*

31.4-mmHg (p = 0.716), and the dBPmin; 47.5 ± 15.7-mmHg vs 50.3 ± 16.3-mmHg (p = 0.165) (Fig. 3-B).

There was no significant difference in the HRave 79.6 ± 11.3 bpm vs. 79.3 ± 16.8 bpm (p = 0.605), and HRmin: 60.5 ± 12.3 bpm vs. 62.1 ± 16.1 bpm, (p = 0.788) between the ND (+) group and the ND (−) group, repetitively. However, the HRmax was significantly higher in the ND (+) group, 128.7 ± 37.7 bpm, than in the ND (−) group; 110.5 ± 25.9 bpm (p < 0.01) (Fig. 4).

ROC analysis

The measurement items with significant differences in the whole patients were found to be sBP min, dBP min, HRave, and HRmax. The cut-off point was calculated using ROC and AUC analysis. The cut-off point in the sBPmin was 104-mmHg (AUC = 0.668, 95% CI 0.558−0.777, Specificity = 56.5%, Sensitivity = 72.1%), that in the dBPmin was 49-mmHg (AUC = 0.661, 95% CI 0.579−0.783, Specificity = 64.1%, Sensitivity = 75.0%), that in the HRave was 79.3 bpm (AUC = 0.693, 95% CI 0.597−0.789, Specificity = 71.8%, Sensitivity = 65.6%) and that in the HRmax was 104 bpm (AUC = 0.738, 95% CI 0.579−0.783, Specificity = 69.9%, Sensitivity = 75.0%) (Fig. 5).

Discussion

In this study, the relationship between late ND and BP as well as HR from admission to transfer to a wheelchair has been studied. In the ND (+) group, stroke severity represented by NIHSS score was higher, fall of sBP and dBP and an increase in HR being more marked, and the time to transfer to a wheelchair was prolonged. The mean time of transfer to a wheelchair was 13.3 ± 24.7 d with no significant difference from the ND (−) group, but the mean duration of hospitalization was significantly (41.5 ± 33.2 d) longer than in the ND (−) group (26.3±29.8 d). Altogether, these results exhibit ND after transfer to a wheelchair may be predicted by the variability of the vital index until the time of transfer and may cause a prolonged hospitalization.

A recent study has revealed that early ND within 24 h post stroke is characterized by lower NIHSS score, capsular warning syndrome, ventral pontine infarct, and hypoperfusion on imaging, and was significantly associated with 3-month poor outcome.[17] High BP, the severity of neurological deficit on admission,[18,19] and radiological findings, such as stenosis of large arteries and number of DWI-positive lesions, have been reported to be independently associated with ND in patients with large artery
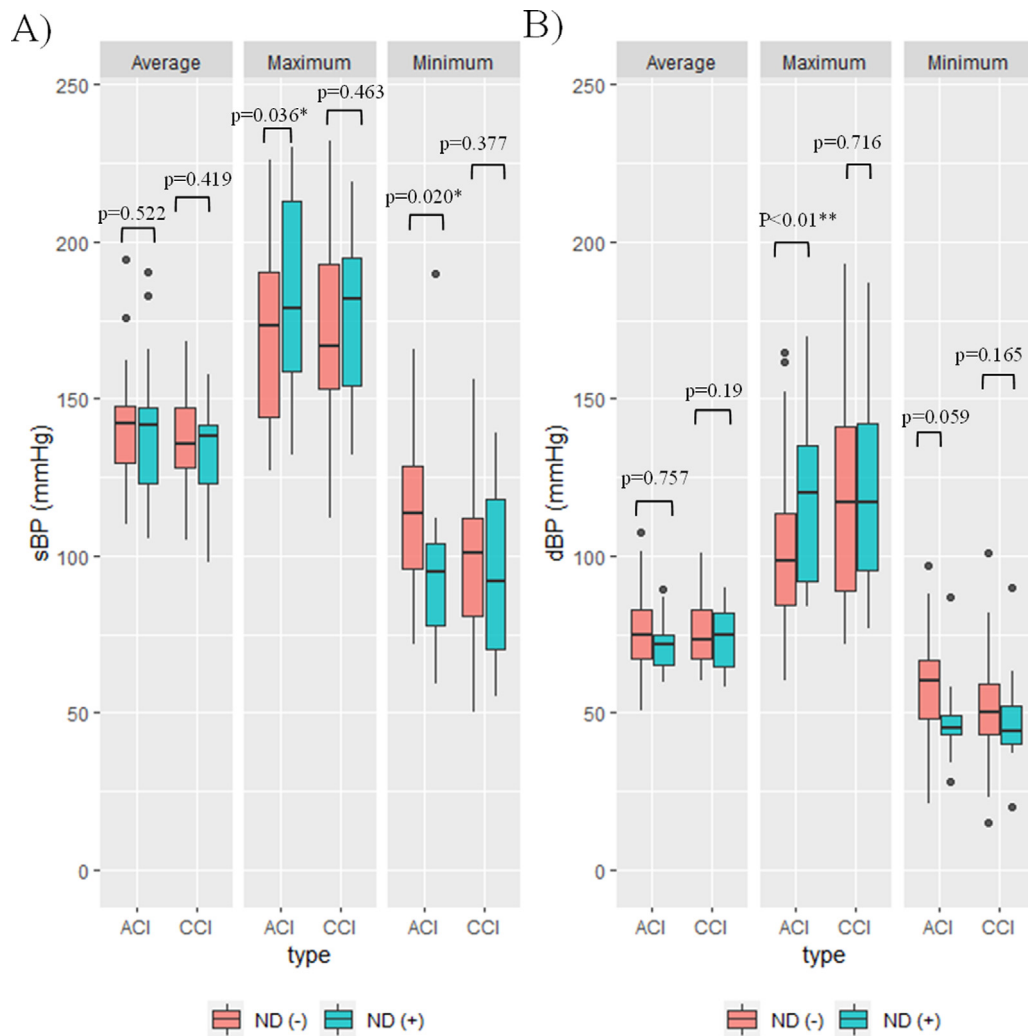
Fig. 3. *BP comparison between ACI vs. CCI. The maximum of systolic BP (sBP)was significant higher and the minimum of systolic BP was lower in the ND (+) group than in the ND (−) group (p = 0.036 and p = 0.020, respectively, in ACI. There was no significant difference in CCI. (A). The maximum of diastolic BP (dBP) was higher in the ND (+) group than in the ND (−) group (p < 0.01) in ACI. There was no significant difference in CCI. (B). BP: Blood pressure, ACI: Atherothrombotic cerebral infarction,CCI; Cardiogenic cerebral infarction, ND: Neurological deterioration, ND (−): ND-negative, ND (+): ND-positive.*

atherosclerosis.[13] Therefore, it is presumed that early ND is mainly predetermined by clinical and neuroradiological characteristics of ischemic damage.

This study focused on the question of whether BP and HR variability may affect ND after 48 h. Consequently, this late ND was associated with greater changes in BP and HR, and the delayed discharge in the ND (+) group seemed to be partly accounted for by an inappropriate rehabilitation program. Consistent with these observations, higher HR was associated with an increased risk of in-hospital mortality among patients with acute ischemic stroke.[20,21] Additionally, a trend has been shown that a poor prognosis was associated with sBP < 100-mmHg within 24 h of admission in patients with acute stroke where an sBP decrease > 26-mmHg occurred predominantly in nighttime-hospitalized patients.[22] A greater BP variability aggravates microcirculatory disturbance in the ischemic penumbra exposed to misery perfusion.[4]

Therefore, it is highly recommended to determine the most suitable cut-off level to minimize the microcirculatory disturbance caused by alteration of the systemic circulation.

From the standpoint of stroke subtypes, ACI was closely associated with sBP max, sBP min, and dBP max as well as HR ave and HR max. The rate of stenosis of the responsible occlusive vessels in the ND (-) group was light in 30%, moderate in 40% sever in 40%. The rate of stenosis of the responsible occlusive vessels in the ND (+) group was light in 47%, moderate in 16% sever in 37%, showing no significant difference between the groups (p = 0.06). However, occlusive vessels in the non-responsible sites were found in 6 of 58 cases in the ND (-) group, whereas in 10 of 17 cases in the ND (+) group, resulting in statistical significance (p< 0.01). Stenosis of internal carotid artery caused a decrease of cerebral blood flow when blood pressure falls. Indeed, ND cases after stroke have
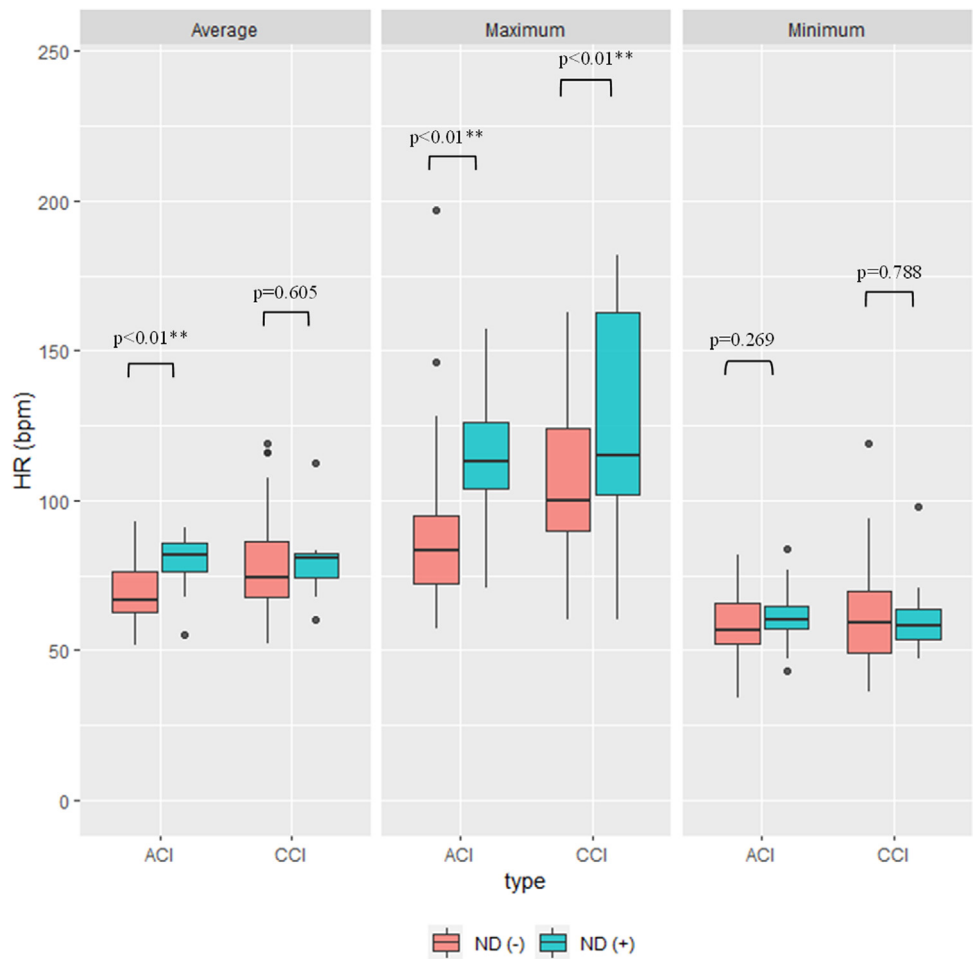
Fig. 4. *HR comparison between ACI vs. CCI groups. The average of HR and the maximum of HR were higher in the ND (+) group than in the ND (−) group (p < 0.01 for both) in ACI. The maximum of HR was higher in the ND (+) group than in the ND (−) group (p < 0.01) in CCI. HR: Heart rate, ACI: Atherothrombotic cerebral infarction, CCI: Cardiogenic cerebral infarction, ND: Neurological deterioration, ND (−): ND-negative, ND (+): ND-positive.*
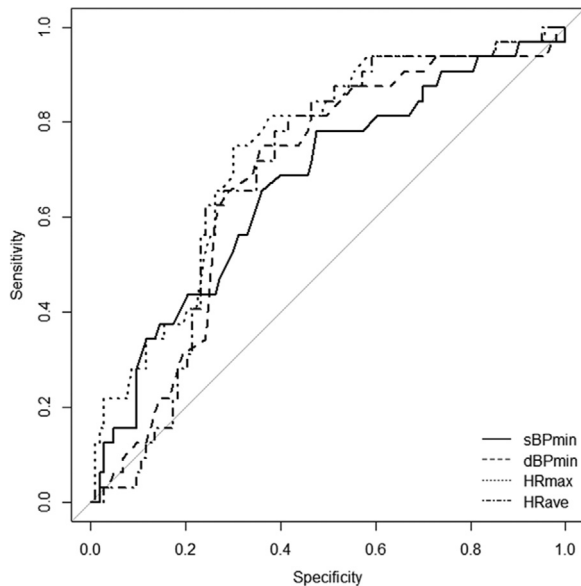

Fig. 5. *Analysis of ROC in the whole subjects; ND (−) vs. ND (+). ROC: Receiver Operating Characteristic Curve, ND: Neurological deterioration, ND (−): ND-negative, ND (+): ND-positive.*

been accompanied by a decrease in cerebral blood flow and an increase in mean transit time were observed.[23] This may indicate that alteration of systemic circulation may affect cerebral circulation and induce ND when vasomotor reactivity is disturbed because of arteriosclerosis. In contrast, in patients with CCI, a significant association was observed exclusively with HR max being in concordance with impaired reserve of cardiac function. ROC analysis for the whole subjects indicated that the cut-off point ranged from 104-mmHg $\geqq$ in the sBP min and 49 $\geqq$ mmHg in the dBP min, and $\geqq$ 79.3 bpm in the HR ave and $\geqq$ 104 bpm in the HR max.

Limitation

In this study, the number of subjects was as small as 135 (ACI 75, CCI 60). Since it was a retrospective study and the data were from a single institution, it can be biased, and the results were not shown in patients with cerebral infarction. Furthermore, no information from the image study does not permit to consider effects on brain perfusion rate and circulatory dynamics due to the size of the

infarcted area and the infarct region. ND during hospitalization decrease functional capacity and prolongs hospitalization. Still, the presence or absence of ND has not been able to compare directly the consequences of functional outcome 90 d after onset. In the future, the functional prognosis will also be considered.

Acknowledgments

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