The Changing Effect of Blood Pressure on Stroke Outcomes Through Acute to Subacute Stage of Ischemic Stroke

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Background: This study explored the associations of blood pressure (BP) with various stroke outcomes and investigated their changes by the elapsed time after stroke onset. *Methods:* Patients who arrived within 48 hours of stroke onset between April 2008 and September 2014 were consecutively enrolled. For 10 days of hospitalization, all measured systolic BP (SBP) was summarized into mean at acute (first 3 days) and subacute stage (afterward to 7 days) for each patient. Coprimary outcomes were unfavorable outcome (modified Rankin Scale >2) at discharge and time to composite cardiovascular event of stroke, myocardial infarction, and vascular death for 1-year follow-up. Adjusted odds ratios (AOR) through SBP_{mean} in both acute and subacute stages were interpolated using restricted cubic spline technique and adopted logistic regression models with predetermined covariates. The adjusted hazard ratios for cardiovascular event by SBP_{mean} in both stages were interpolated. *Results:* The study enrolled 3723 subjects (mean age, 66.7 ± 13.2 years old and median baseline National Institute of Health Stroke Scale score, 3). SBP_{mean} in both stages showed linear trends for risks of unfavorable outcome, while the increase of AOR was observed explicitly in acute stage rather than subacute stage, especially in higher values. In contrast, SBP_{mean} demonstrated the U-shaped associations with cardiovascular event in subacute stage rather than acute stage. *Conclusions:* In ischemic stroke, association patterns of BP would be different depending on stroke outcomes. The risky interval of BP would be changed by the elapsed time after stroke onset.

Key Words: Blood pressure—acute stage—time—ischemic stroke—recurrence—outcome

Introduction

High and uncontrolled blood pressure (BP) involve in developing into cerebral atherosclerosis and arteriolosclerosis, which consequently attribute to about 70% of stroke.[1-3] In case of stroke event, BP takes an important role in maintaining cerebral perfusion and affecting stroke prognosis.

Taking those features into account, previous studies have attempted to improve functional outcome[4-7] and to prevent subsequent cardiovascular event by controlling the high BP from acute stage of ischemic stroke.[1] Unfortunately, most of them showed inconsistent, even disappointing results. In line with these results, current stroke guidelines suggest to control extreme values during the acute stage, and then to use antihypertensive treatment targeted the same level as in the general population.[2]

However, the close relationship of BP with hemodynamic status in vulnerable penumbra area and adverse effect on cerebral steno-occlusive disease of patients with stroke still request more delicate and reasonable investigations. Specifically, it is necessary to estimate the effect of BP according to the elapsed time after stroke onset, as some recent studies indicate the changing effect sizes of BP variability over time.[3,4] Moreover, a clarification of target outcomes, that is, distinguish functional outcome of index event from subsequent cardiovascular event, have

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to be considered in that the high BP would need to maintain the adequate perfusion status, while would further damage the cerebral artery.

In this study, BP after ischemic stroke was divided into acute stage and subacute stage according to the time interval after stroke onset. Herein, we will investigate the association of BP with two different and major stroke outcomes, namely, functional status and cardiovascular event.

Methods

Study Protocol Approval, Patient Consent, and De-identification

This study was approved by the local institutional review board with a waiver of informed consent because of its retrospective observational study design and had a minimal risk for the enrolled subjects. Any kind of personal information was preferentially deleted, and the database was deidentified before the analysis.

Study Subjects and Data Collection

A series of consecutive patients admitted with an ischemic stroke within 48 hours of symptom onset between April 2008 and September 2014 were retrospectively identified from the prospective institutional stroke registry.[5] The electronic health recording and depository of registration database was reviewed, and demographic and stroke information, such as cardiovascular risk factors, baseline National Institute of Health Stroke Scale (NIHSS) score, acute recanalization therapy modalities, and stroke mechanism, were obtained.

All measured BP information during hospitalization were downloaded and summarized as mean and standard deviation (SD) per patient in each period of acute (days 1-3) and subacute (days 4-10 or until discharge) stages.[3] The elapsed days after ischemic stroke was calculated based on the symptom onset time when a patient or bystander first recognized the neurologic symptom or sign.

In the stroke and intensive care units, BP was routinely measured every hour according to stroke management guidelines and intermittently adjusted depending on subject's condition, and in the general ward, it was monitored every 4-8 hours intervals until discharge or transfer to rehabilitation facilities under the decision of attending physicians. By standards, BP was measured in the nonhemiparetic arm in supine position using a noninvasive BP monitoring device (IntelliVue MP20; Philips Medizin Systeme, Böblingen, Germany). The BP management was individually planned and treated under the decision of charged physician based on the stroke guideline.[2] In addition to the rescue depressor for recanalization therapy, antihypertensive medications were allowed for starting after 2 days of onset if deemed necessary.

Primary Outcome

According to the institutional monitoring program, data on the modified Rankin Scale, cardiovascular event of stroke recurrence, myocardial infarction, and vascular death for 1 year were prospectively collected. This study defined coprimary outcomes, which were unfavorable outcome at discharge (modified Rankin Scale >2) and time to composite cardiovascular event.

Statistical Analysis

The baseline characteristics, systolic BP (SBP), parameters, and coprimary outcomes of total subjects were summarized. In bivariate analyses, baseline characteristics and SBP_{mean} in acute and subacute stages were compared using appropriate methods.

The restricted cubic spline technique (RCST)-adopted logistic regression models were constructed with predetermined adjustment variables and investigated the association trend of SBP_{mean} in both stages with unfavorable outcome. The Cox proportional hazard models (CPH) with RCST analyzed the association trend of SBP_{mean} in both stages for cardiovascular event. Statistical analysis was conducted using the SPSS (version 18.0, IBM) and R program (version 3.4.3.0, R-project). The $P < .05$ was set up for statistical significance.

Results

Baseline Characteristics and SBP Parameters

This study enrolled 3723 study subjects, and their baseline characteristics were summarized (Table 1). SBP_{mean} in acute and subacute stages were 134.3 ± 15.9 mmHg and 135.2 ± 14.8 mmHg, respectively (Fig. 1, A) and SBP_{SD} were 14.3 ± 4.1 mmHg and 13.0 ± 4.1 mmHg. The SBP_{mean} in the acute stage showed significant association with change of SBP_{mean} from the acute stage to the subacute stage (Fig. 1, B).

Comparisons of baseline characteristics and SBP_{mean} demonstrated that most baseline characteristics had similar associations in both stages, while baseline NIHSS score showed opposite directional associations by stages (Table 2).

SBP_{mean} and Functional Outcome

Of the total subjects, unfavorable outcome was observed in 39.2%. In bivariate analysis, SBP_{mean} in the acute stage was significantly associated with functional outcome, which were 132.2 ± 15.3 mmHg and 137.5 ± 16.4 mmHg for favorable and unfavorable outcomes, respectively ($P < .001$). SBP_{mean} in the subacute stage also showed significant difference with 134.9 ± 14.6 and 136.6 ± 15.0 mmHg, respectively ($P = .001$).

The RCST-adopted multivariable logistic regression model showed that the SBP_{mean} in the acute stage was

Table 1. *Baseline characteristics of study subjects (n = 3723)*

Variables	Number of patients (n = 372
Male	2204 (59.2%)
Age, years, mean ± SD	66.8 ± 13.5
Baseline NIHSS score, median (IQR)	3 (1-7)
Hypertension	2581 (69.3%)
Diabetes mellitus	1093 (29.4%)
Dyslipidemia	1083 (29.1%)
Atrial fibrillation	757 (20.3%)
Recanalization therapy, acute stage	455 (12.2%)

Values were number of patients (percentage) except for specific description.
Abbreviations: IQR, interquartile range; SD, standard deviation.

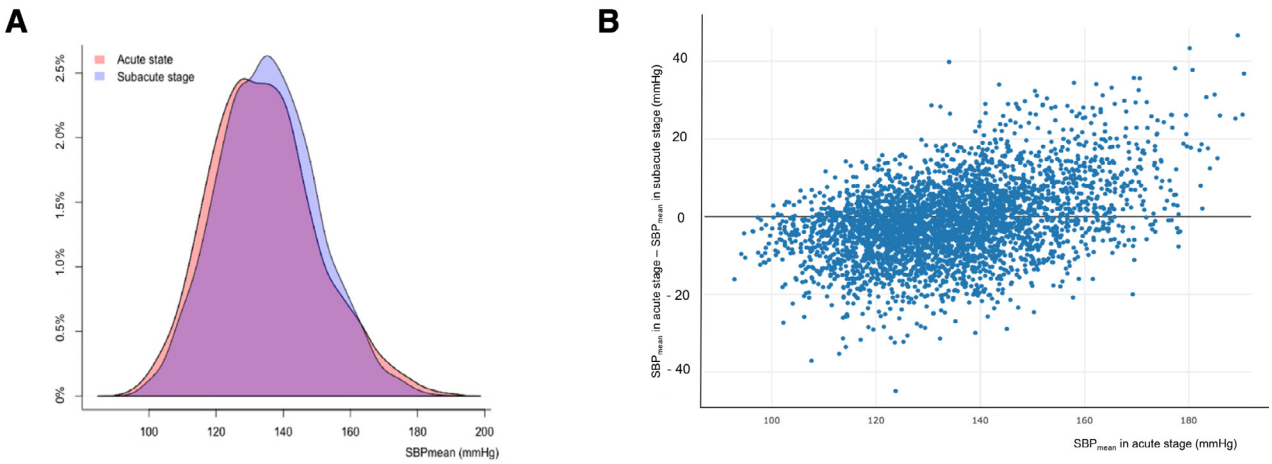

Figure 1. *Histogram of mean systolic blood pressure (SBP_{mean}) of ischemic stroke (A) and change of SBP_{mean} during hospital stay (B). In the left figure, the pink color denotes acute stage, and sky blue color denotes the subacute stage. The x-axis presented the SBP_{mean} in the acute stage (mmHg), and y-axis indicates the difference from SBP_{mean} in the acute stage to the subacute stage (mmHg). (Color version of figure is available online.) Abbreviations: SBP, systolic BP.*

fitted in a linear trend (*P* for nonlinearity = .95). The SBP_{mean} in the acute stage independently increased the odds for unfavorable outcome (adjusted odds ratio [AOR], 1.02; 95% CI, 1.02-1.03) with adjustments for age, SBP_{SD} in the acute stage, baseline NIHSS score, stroke mechanism, hypertension, diabetes, atrial fibrillation, and recanalization therapy. The interpolating plot of AOR through SBP_{mean} presented a dose-dependent trend and change of risk direction around an SBP_{mean} of 160 mmHg (Fig. 2, A). In the subacute stage, SBP_{mean} is similar but in a more gradual trend and demonstrated a marginally independent association (AOR, 1.01; 95% CI, 1.00-1.02, Fig. 2, B).

SBP_{mean} and Cardiovascular Event

For 1 year of observation, cumulative cardiovascular event rates were estimated as 2.7% at 30 days, 6.2% % at 90 days, and 13.3% at 1 year. In bivariate analysis, the SBP_{mean} in the acute stage was not significant different by cardiovascular events, with values at 135.0 ± 15.7 mmHg for patients with cardiovascular event and 134.2 ± 16.5 mmHg for those without (*P* = .25). In the subacute stage, the SBP_{mean} did not show statistical difference (134.7 ± 15.7 versus 135.7 ± 14.6 mmHg, *P* = .13).

In the RCST-adopted CPH model, the SBP_{mean} in the acute stage showed significant nonlinear trend of hazards for cardiovascular event (P for nonlinearity = 0.02). Interpolation of adjusted hazard ratio (AHR) of the SBP_{mean} in the acute stage presented a "U"-shaped association (AHR, 0.97; 95% CI, 0.85-1.11, Fig. 3, A). With reference to SBP_{mean} of ≤133.2 mmHg, the hazards of cardiovascular event were significantly increased when the SBP_{mean} was above 156.0 mmHg (Table 2).

The SBP_{mean} in the subacute stage was also fitted in the nonlinear trend in the CPH model (P for nonlinearity <0.001) and showed a more definite "U"-shaped association (AHR, 0.82; 95% CI, 0.72-0.93) than that in the acute stage. With reference to SBP_{mean} of ≤135.2 mmHg in the subacute stage, significant changes in hazards were found depending on the SBP (Table 3).

Table 2. *Comparisons of baseline characteristics and SBP_{mean} in both stages*

Variables		SBP_{mean} at acute stage		SBP_{mean} at subacute stage	
		Values	*P*	Values	*P*
Sex	Female	134.3 ± 16.5	0.97	135.2 ± 14.9	0.18
	Male	134.3 ± 15.5		135.8 ± 14.7	
Age, years		r = 0.14	< 0.001	r = 0.14	<0.001
Baseline NIHSS score		*P* = .31	0.056	ρ = -0.05	0.002
Hypertension	No	126.8 ± 14.6	< 0.001	128.1 ± 13.8	<0. 001
	Yes	137.6 ± 15.4		138.9 ± 13.9	
Diabetes mellitus	No	132.7 ± 15.8	<0.001	134.5 ± 14.8	<0.001
	Yes	138.1 ± 15.7		138.2 ± 14.3	
Dyslipidemia	No	134.0 ± 16.0	0.07	135.3 ± 14.9	0.12
	Yes	135.2 ± 15.6		136.2 ± 14.3	
Atrial fibrillation	No	135.3 ± 16.0	<0.001	136.8 ± 14.8	<0.001
	Yes	130.4 ± 14.9		130.7 ± 13.7	
Stroke mechanisms			<0.001		<0.001
Small vessel occlusion		139.2 ± 16.5		141.4 ± 14.3	
Large artery disease		138.0 ± 15.1		138.6 ± 13.7	
Cardioembolism		130.0 ± 14.7		130.3 ± 13.5	
Other determined		126.0 ± 14.5		127.7 ± 15.1	
Undetermined		133.7 ± 16.2		135.3 ± 15.0	
Transient ischemic attack		127.8 ± 13.7		132.2 ± 14.6	
Recanalization therapy	No	135.4 ± 16.1	<0.001	136.7 ± 14.7	<0.001
	Yes	129.1 ± 13.7		130.1 ± 13.5	

Values were mean ± SD except for specific description. *P* values were obtained by *t*-test, ANOVA test, Pearson correlation test, and Spearman's test as appropriate.

Abbreviations: NIHSS, ρ, Spearman correlation coefficient; SBP_{mean}, mean systolic blood pressure; r, Pearson correlation coefficient.

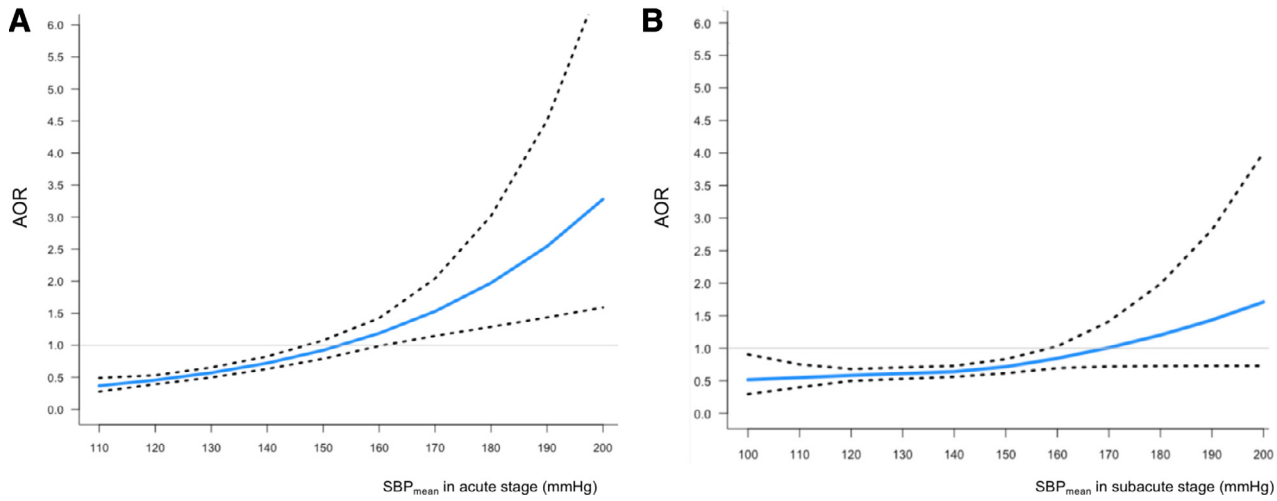

Figure 2. *Interpolated plot of mean systolic blood pressure (SBP_{mean}) in acute (A) and subacute stages (B) of ischemic stroke for unfavorable outcome. The blue line denotes the adjusted odds ratio, and black dot line indicated the 95% confidence interval estimated using the multivariable logistic regression model with adjustments for age, SBP_{SD}, baseline NIHSS score, stroke mechanism, hypertension, diabetes, atrial fibrillation, and recanalization therapy. (Color version of figure is available online.) Abbreviations: SBP, systolic BP; NIHSS, National Institute of Health Stroke Scale.*

Discussion

This study showed that BP would have different effects depending on the elapsed time after ischemic stroke, and critical risk level ranges differently by the target outcomes, i.e., functional outcome and secondary cardiovascular events.

In terms of functional outcome, BP in the acute stage showed a clear association, that is, the higher the BP is, the worse is the outcome.[6,7] The high-risk range of SBP would be approximately more than 160 mmHg, which is similar to previous reports.[7] BP in the subacute stage had marginal or neutral effect on the functional outcome, although statistically significant.

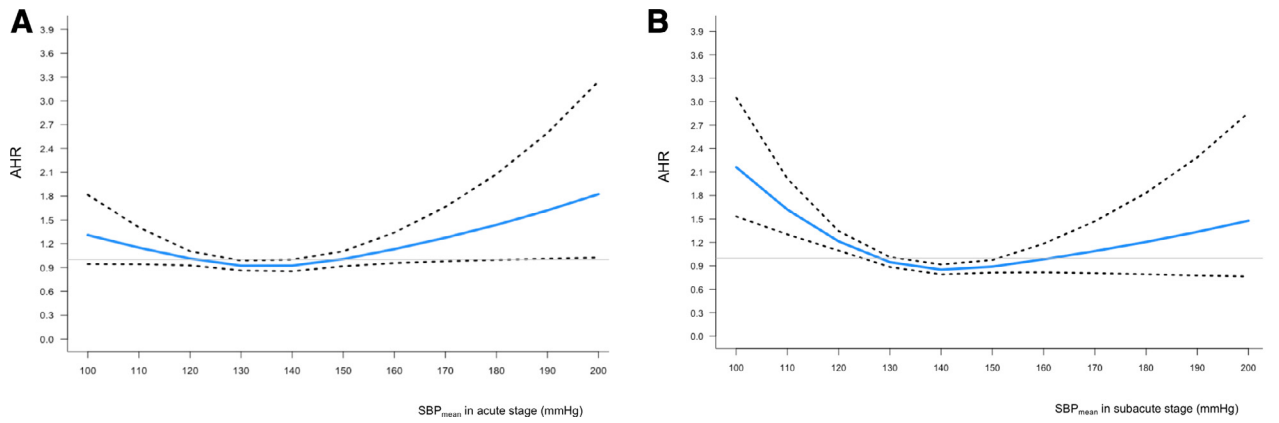

Figure 3. *Plots for adjusted hazard ratio (AHR) through range of SBP_{mean} in the acute stage (A) and subacute stage (B) for cardiovascular event. The blue line indicates AHRs and dotted line denotes 95% confidence interval. The Cox proportional hazard model was adjusted by age, baseline NIHSS score, standard deviations of SBP, diabetes, hypertension, atrial fibrillation, and stroke mechanism. (Color version of figure is available online.) Abbreviations: SBP, systolic BP; NIHSS, National Institute of Health Stroke Scale; AHR, adjusted hazard ratios.*

Table 3. *Adjusted hazard ratios of SBP_{mean} in acute and subacute stages of ischemic stroke for cardiovascular event*

SBP_{mean} in acute stage (mmHg)	AHR (95% CI)	SBP_{mean} in subacute stage (mmHg)	AHR (95% CI)
≤133.2	1.00 (reference)	≤135.2	1.00 (reference)
133.3-156.0	0.99 (0.97-1.00)	135.3-155.3	0.97 (0.96-0.98)
≥156.1	1.02 (1.00-1.03)	≥155.4	1.03 (1.01-1.04)

AHR (95% CI) were estimated using the Cox proportional hazard model with adjustments for age, baseline NIHSS score, standard deviation of SBP in each stage, diabetes mellitus, hypertension, atrial fibrillation, and stroke mechanism.

Abbreviations: AHR, adjusted hazard ration; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

It may partially explain the reason why antihypertensive trials in patients with acute ischemic stroke failed to show meaningful results.[8-12] Although they enrolled the target study population during the acute stage, interventions were mainly conducted in the subacute stage, suggesting less opportunities to improve functional outcome. Another reason is thought that the significant association of BP in the acute stage is related to the elevated BP in response to the stroke event, especially for those with higher neurologic severity, so the intervening effect may not be the same for all victims.[13-15]

In previous studies, the contrary observation that lower BP would have a detrimental effect on stroke outcome is mainly due to U-shaped association between BP and mortality.[16-18] Our study presented the U-shaped association with cardiovascular event including postdischarge state vascular death.

Since this study excluded death during hospitalization and observed vascular death after discharge, it would be possible to measure in small size the effect of lower BP. However, since early deaths are inevitably accompanied by increased intracranial pressure and concomitant medical illness that eventually result in hypotensive state, even shock state, it would have a risk of execrating the effect of lower BP; hence, this population was regarded to exclude for prompt estimation.

For the perspective of secondary event, the subacute stage of ischemic stroke can be used as an appropriate time for predicting individual risk. Considering that initially higher BP gradually stabilizes over next few days,[3,19] it may be more prompt to determine individual BP status and to start the secondary prevention according to cardiovascular risk in the subacute stage.[20]

In the subacute stage, the marginal or nonsignificant association of higher BP, that is, right wing of the U-curve (Fig. 3, B), seemed to be related with retrospective study design and treatment issue. Because most subjects with higher BP would be treated with antihypertensive medication, the harmful effect would be controlled and consequently estimated smaller than expected.[21,22]

Nadir or optimal level is the one of the interesting issues. The lowest risk levels of BP were slightly different in each study, ranging from about 150 mmHg in the acute stage to 121-140 mmHg in the subacute stage[23]. Our results showed similar values, around 130-150 mmHg, namely, normotensive or mild hypertensive state.[24] These findings may partially account for the neutral outcome of Continue or Stop PostStroke Antihypertensives Collaborative Study and Scandinavian Candesartan Acute Stroke Trial, where most of the control and treatment arms would be at lower risk level; hence, they showed similar event rates.[10,25]

Notably, this study has several limitations. First, it was conducted retrospectively in a single hospital, which had a risk of bias. Although a large number of patients was enrolled from prospective registry would be helpful, prospective confirmatory studies are requested. Second, we

used the measured BP information. Third, treatment issue including antihypertensive medications was also considered. Finally, it had relatively small number of patients with extreme BP values, which would be linked to inhospital management.

Conclusions

In summary, BP at acute stage showed significant linear associations with functional outcome, while, it would be prompt to predict the cardiovascular event with BP at subacute stage of ischemic stroke.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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