each 100 mg/dl increase in glucose was 1·71 (95% confidence interval 1·1–2·7), with NIHSS, age and smoking included in accordance with the methods of the final binary logistic regression models reported in our paper. Not surprisingly, this was very similar to our published estimate of the association between glucose and in-hospital mortality – with a tighter confidence interval that no longer includes one.

Of course, these findings may represent a type II error and/or a manifestation of either the design limitations we noted in our manuscript or those listed by Drs Poppe and Hill. Disagreement between these data and prior studies may also reflect a deeper problem. It may be that all retrospective observations of the association between initial glucose and outcome may over simplify a complex pathology that defies simple interpretations. After all, initial glucose is a snapshot of a time-varying signal that reflects a variety of pathologies and comorbidities, and can result in physiological responses that may differ from patient to patient.

Based on all available clinical and laboratory data, it is likely that glucose metabolism interacts with acute brain injury, but the nature of the interaction requires further exploration. Even the way that we examine the available clinical observational data and our prior assumptions may influence interpretation. For example, should glucose be modeled as a continuous variable or should it be dichotomized as in many prior studies? The statistician in me says that dichotomization is throwing away data. The clinician in me has a difficult time conceptualizing the adverse effects of one milligram per deciliter rise in blood glucose. Should we assume a linear response, or should we model a *U*-shaped or an other type of relationship? Ultimately, we share Drs Poppe and Hill's inclination that hyperglycemia is adverse in brain injury; however, we also recognize the importance of keeping an open mind as data continue to emerge and theories are either confirmed or become more complicated. We strongly support prospective randomized trials of glucose-lowering strategies.

William J. Meurer

Departments of Emergency Medicine and Neurology University of Michigan, Ann Arbor, USA

Correspondence: William J. Meurer
Taubman Center B1354 SPC 5303
1500 E. Medical Center Drive
Ann Arbor, MI 48109-5303 USA.
E-mail: wmeurer@umich.edu
Twitter: willmeurer

DOI: 10.1111/j.1747-4949.2011.00586.x

Reference

1 Scott PA, Frederiksen SM, Kalbfleisch JD *et al.* Safety of intravenous thrombolytic use in four emergency departments without acute stroke teams. *Acad Emerg Med* 2010; **17**:1062–71.

A new ultrasound method for evaluating dysphagia in acute stroke patients

Dysphagia after stroke was a common and serious complication, and conventional methodologies of swallowing evaluation had several limitations. Here, we examined tongue movement during the swallowing process in order to evaluate dysphagia with our unique ultrasound examination, the Tongue and Oral Function test with Ultrasound (TOFU).

For 100 acute stroke patients (65 men, 72·2 ± 10·7 years) in who swallowing status had been evaluated by the modified water swallowing test and the food test, we performed TOFU in addition to videofluoroscopic swallowing study (VFSS). Dysphagia was defined as abnormal swallowing on VFSS. In TOFU, a patient was requested to swallow saliva in the 30° head-up position. Tongue surface was visible as a bright narrow line on an M-mode image (Fig. 1) (1–5). We measured the downward (Vd) and upward movement velocities (Vu) of tongue in the swallowing phase, and the distance from the caudally depressed to the cranially elevated positions (D). We assessed differences in various TOFU findings between the 24 patients with dysphagia and 76 patients without, and configured a ROC curve for Vu.

Vd and Vu were slower in the patients with dysphagia than in those without (Vd, 38·01 ± 21·42 vs. 47·98 ± 20·75 mm/s, $P = 0·007$; Vu, 57·04 ± 16·24 vs. 85·43 ± 24·74 mm/s, $P < 0·001$), and D was shorter (11·63 ± 3·19 vs. 13·49 ± 3·55 mm, $P = 0·027$). With a cut-off value of Vu of 63·55 mm/s, the sensitivity for the detection of dysphagia was 83·3% and the specificity was 88·2%.

A notable finding was that a cut-off value of Vu of 63·55 mm/s could accurately predict dysphagia. The TOFU is not only an easy way at the

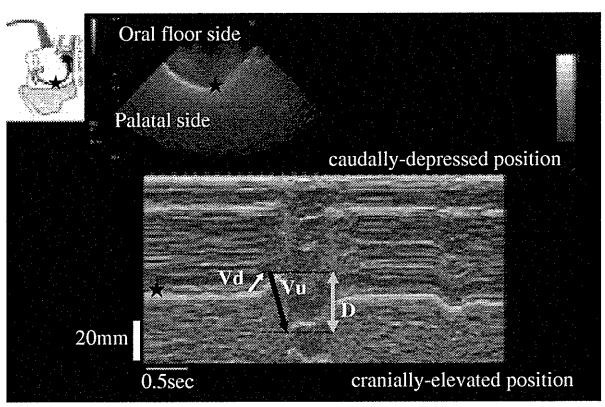


Fig. 1 A representative sagittal B-mode and M-mode ultrasound image of the swallowing process observed in a stroke patient without dysphagia. The viewing point of the tongue, marked by black star, was recognizable by its horizontal trace during the preparatory phase on an M-mode image. It was recognizable by the downward movement (Vd, white arrow), and then the upward movement (Vu, black arrow) in the swallowing phase. The distance from the caudally depressed to the cranially-elevated position was measured (D, gray double-headed arrow).

bedside, but also a quantitative and objective method. It seems to be useful for assessing tongue movement disorders in dysphagia, and may contribute to determining appropriate nutrition.

Acknowledgements

The study mentioned in this letter was supported in part by a Research Grant for Cardiovascular Diseases (21A-4) and a Research Funding of National Cerebral and Cardiovascular Center (22-4-1) from the Ministry of Health, Labour and Welfare, Japan.

Yasuhiro Tomii*, Hideki Matsuoka, Takako Torii, Toshiyuki Uehara, Kazunori Toyoda, and Kazuo Minematsu

Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

Correspondence: Yasuhiro Tomii*, Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan.
E-mail: ytomii@koto.kpu-m.ac.jp

DOI: 10.1111/j.1747-4949.2011.00603.x

References

1 Rastadmehr O, Bressmann T, Smyth R *et al.* Increased midsagittal tongue velocity as indication of articulatory compensation in patients with lateral partial glossectomies. *Head Neck* 2008; **30:**718–26.
2 Daniels SK, Brailey K, Foundas AL. Lingual discoordination and dysphagia following acute stroke: analysis of lesion localization. *Dysphagia* 1999; **14:**85–92.
3 Stone M. A guide to analysing tongue motion from ultrasound images. *Clin Linguist Phon* 2005; **19:**455–501.
4 Shawker TH, Sonies BC, Stone M *et al.* Real time ultrasound visualization of tongue movement during swallowing. *J Clin Ultrasound* 1983; **11:**485–90.
5 Peng CL, Jost-Brinkmann PG, Miethke RR *et al.* Ultrasonographic measurement of tongue movement during swallowing. *J Ultrasound Med* 2000; **19:**15–20.

Role of vasodilation in cognitive impairment

Reduced vasodilation is associated with cognitive impairment in elderly persons with cardiovascular disease (CVD) (1–4), possibly contributing to vascular dementia. Atherosclerosis and cognitive decline both commence in early life. Therefore, deteriorating vasodilation may affect cognition before CVD is clinically detectable. We investigated vasodilation and cognition in 51 people (age = 50·3 ± 11·5) who had a brain MRI for any reason and were free of other neurological disorders. This group had a relatively low cardiovascular burden: 50% were at risk for CVD (e.g. hypercholesterolemia); 10% had CVD and 6% showed more than a mild level of white matter (WM) damage (Fazekas score > 2). Five sub-tests from the Neuropsychological Assessment Battery (Screening Module) and the Stroop task from the Delis Kaplin Executive Function System assessed cognition. Scores for each test varied considerably, ranging from impaired (> 1·5 SD below norms) to superior (> 1·5 SD above norms). Vasodilation was measured using applanation tonometry and pulse wave analysis (5). Norms do not exist for these techniques; consequently it was not possible to identify 'abnormal' cases. The correlations between the cognition tests and both endothelial and nonendothelial vasodilation were all non-significant ($P > 0·05$).

Although these findings require replication in a larger community sample, we propose that diminished vasodilation may be relatively benign until the small cerebral vessels undergo morphological changes associated with age and advanced CVD (i.e. lengthening, stiffening and tortuosity). Once these structural changes occur, inadequate vasodilation may leave WM vulnerable to ischemic damage during periods of low perfusion pressure, which may ultimately lead to cognitive decline.

This is an important area for study. Longitudinal research that tracks changes in vasodilation, WM damage and cognitive decline would provide definitive information about the relationship between these variables, and may provide a basis for treatments targeting vasodilation in order to prevent neurodegeneration.

Skye N. McLennan[1]*, Ada K. Lam[2], Jane L. Mathias[1], Simon A. Koblar[2], Monica A. Hamilton-Bruce[3], and Jim Jannes[3]

[1]School of Psychology, The University of Adelaide, Adelaide, SA, Australia
[2]Stroke Research Programme, The University of Adelaide, Adelaide, SA, Australia
[3]Stroke Research Programme, The Queen Elizabeth Hospital, Woodville West, SA, Australia

Correspondence: Skye N. McLennan*, School of Psychology, The University of Adelaide, Adelaide, SA, 5005, Australia.
E-mail: skye.mclennan@adelaide.edu.au

DOI: 10.1111/j.1747-4949.2011.00601.x

References

1 Moser DJ, Hoth KF, Robinson RG *et al.* Blood vessel function and cognition in elderly patients with atherosclerosis. *Stroke* 2004; **35:**e369–72.
2 Forman D, Cohen R, Hoth K *et al.* Vascular health and cognitive function in older adults with cardiovascular disease. *Artery Res* 2008; **2:**35–43.
3 Moser DJ, Robinson RG, Hynes SM *et al.* Neuropsychological performance is associated with vascular function in patients with atherosclerotic vascular disease. *Arterioscler Thromb Vasc Biol* 2007; **27:**141–6.
4 Moser DJ, Miller IN, Hoth K, Correeia M, Arndt S, Haynes WG. Vascular smooth muscle function is associated with initiation and processing speed in patients with atherosclerotic vascular disease. *J Int Neuropsychol Soc* 2008; **14:**535–41.
5 Hayward CS, Kraidly M, Webb CM, Collins P. Assessment of endothelial function using peripheral waveform analysis: a clinical application. *J Am Coll Cardiol* 2002; **40:**521–8.

Effects of hyperacute blood pressure and heart rate on stroke outcomes after intravenous tissue plasminogen activator

Yasuhiro Tomii[a], Kazunori Toyoda[a], Takahiro Nakashima[a], Tomohisa Nezu[a], Masatoshi Koga[b], Chiaki Yokota[a], Kazuyuki Nagatsuka[c] and Kazuo Minematsu[a]

Background and purpose The present study clarifies associations between stroke outcomes after intravenous tissue plasminogen activator (tPA) and blood pressure (BP) as well as heart rate (HR) profiles.

Methods We assessed 125 patients with stroke who received tPA within 3 h of onset. We obtained baseline, mean, maximum, minimum, and coefficient of variation values for BP and HR during the initial 24 h. The primary outcome was independence at 3 months corresponding to a modified Rankin Scale score of 2 or less. The secondary outcomes were early neurological improvement at 24 h and intracerebral hemorrhage (ICH) within 36 h.

Results Among the patients, 64 (51%) achieved independence, 66 (53%) early improvement, and 26 (21%) developed ICH. The 24-h time courses of SBP ($P = 0.033$), pulse pressure (PP, $P = 0.007$), and HR ($P < 0.001$) were lower among patients who reached independence than among those who did not. After multivariate adjustment, 24-h mean levels of SBP (odds ratio 0.69, 95% confidence interval 0.48–0.97, per 10-mmHg increase), PP (0.63, 0.41–0.94), and HR (0.59, 0.42–0.80, per 10-bpm increase) were inversely associated with independence, as were their maximum and minimum values. In particular, mean SBP values were inversely associated with independence at 8–16 and 16–24 h (0.73, 0.54–0.97 and 0.66, 0.47–0.91, respectively), but not at 0–8 h (0.79, 0.57–1.07). Baseline and maximum SBP were inversely associated with early improvement. Maximum and coefficient of variation of SBP were associated with ICH.

Conclusion Lower SBP, PP, and HR values during the initial 24 h after tPA, especially at 8 h thereafter, were associated with independence at 3 months. *J Hypertens* 29:1980–1987 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Journal of Hypertension 2011, 29:1980–1987

Keywords: blood pressure, heart rate, hypertension, outcome, stroke, thrombolysis, tissue plasminogen activator

Abbreviations: ADL, activities of daily living; BP, blood pressure; HR, heart rate; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator

[a]Department of Cerebrovascular Medicine, [b]Division of Stroke Care Unit and [c]Department of Neurology, National Cerebral and Cardiovascular Center, Suita, Japan

Correspondence to Kazunori Toyoda, MD, PhD, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5–7–1 Fujishirodai, Suita, Osaka 565–8565, Japan
Tel: +81 6 6833 5012; fax: +81 6 6835 5267; e-mail: toyoda@hsp.ncvc.go.jp

Received 7 May 2010 **Revised** 13 April 2011
Accepted 1 July 2011

Introduction

Intravenous (i.v.) thrombolytic therapy using tissue plasminogen activator (tPA) is currently the only evidence-based pharmacotherapy for treating hyperacute ischemic stroke [1–3]. High baseline blood pressure (BP) prior to tPA reportedly results in poor outcomes for some patients after tPA partly because of an increased risk of intracerebral hemorrhage (ICH) [4–6] and favorable outcomes for others [7]. Thus, high baseline BP might not be an ideal outcome predictor. Other studies have revealed a close association between the course of high BP during the initial 24 or 72 h after stroke and poor long-term outcomes [7–9]. Generally, avoidance of an obviously elevated BP is recommended both before and soon after thrombolysis [10]. As BP often fluctuates on the day of stroke occurrence, generally reaching a peak upon hospital admission and falling thereafter [11,12], it is important to clarify which characteristics of acute BP profiles affect outcomes after tPA.

The results of the Japan Alteplase Clinical Trial (J-ACT) led to i.v. thrombolysis with alteplase (0.6 mg/kg) within 3 h of stroke onset being approved in Japan during 2005 [13]. The efficacy of this low-dose tPA strategy was determined by a postmarketing, multicenter, observational study [14]. According to the guidelines published by the Japan Stroke Society (JSS) [15], the vital signs of all of our patients were frequently measured during the initial 24 h after i.v. tPA thrombolysis. Thus, we obtained complete data for consecutive tPA-treated patients to analyze the initial 24-h course of BP. We also postulated that the 24-h course of heart rate (HR), which is another essential, easily measurable and understudied sign, could predict outcomes. We, therefore, clarified the influence of 24-h BP and HR profiles on early and long-term

0263-6352 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e32834a764e

outcomes of stroke patients after receiving i.v. low-dose tPA.

Patients and methods

Patient population

We registered 130 consecutive Japanese patients with stroke who were treated with i.v. tPA within 3 h of symptom onset and admitted to our stroke care unit between October 2005 and August 2008. Patient eligibility for i.v. tPA therapy was determined based principally on the JSS guidelines [15], which follow the inclusion and exclusion criteria applied in the National Institute of Neurological Disorders and Stroke (NINDS) tPA study [1] and J-ACT [13]. All patients received i.v. alteplase at a dose of 0.6 mg/kg with 10% administered as a bolus, followed by continuous i.v. infusion of the remainder over a period of 1 h. Of these, two patients who did not receive the full dose of tPA because of changes in their condition including vomiting during i.v. infusion and three who did not have independent activities of daily living (ADL) corresponding to a modified Rankin Scale (mRS) score of at least 3 before stroke onset were excluded, leaving 125 eligible patients (93 men, 72.7 ± 9.0 years).

Assessment of blood pressure and heart rate

BP was measured in the supine position by trained nurses using a standard mercury sphygmomanometer; the average of two consecutive measurements spaced by 1–2 min, and additional measurements if the first two were quite different, was used for analysis [16]. Baseline BP and HR values of the patients were recorded immediately upon arrival at the emergency room. i.v. tPA therapy was initiated at the stroke care unit, and patients remained there for at least 2 days. After starting tPA infusion, BP and HR were measured every 15 min during the first 2 h, every 30 min from 2 to 6 h, and then hourly from 6 to 24 h. To characterize BP and HR profiles, we calculated the mean, maximum, minimum, and coefficient of variation (coefficient of variation = standard standard deviation/mean value × 100%) values during the initial 24 h after i.v. tPA, as well as the mean values between 0 and 8 h, 8 and 16 h, and 16 and 24 h. According to the guidelines, antihypertensive agents were administered when SBP was at least 185 mmHg or DBP at least 110 mmHg just before i.v. tPA, and SBP more than 180 mmHg or DBP more than 105 mmHg during the initial 24 h after i.v. tPA [10,15]. i.v. nicardipine was the first choice agent.

Baseline characteristics

We determined the following baseline characteristics from the prospective database: sex, age, hypertension (BP ≥140/90 mmHg before stroke onset or taking regular antihypertensive agents), diabetes mellitus (fasting blood glucose ≥7.0 mmol/l, hemoglobin (Hb) A1c ≥6.5%, or taking antidiabetic agents), hyperlipidemia (total cholesterol ≥5.7 mmol/l, triglyceride ≥1.7 mmol/l, or taking antihyperlipidemic agents), atrial fibrillation (documented during hospitalization or a history of atrial fibrillation), previous symptomatic ischemic stroke, current smoking habit, and antihypertensive and antithrombotic use prior to onset. Stroke subtype was determined according to the TOAST subtype classification system [17].

On admission, blood tests included blood glucose and HbA1c. Kidney function was evaluated based on the estimated glomerular filtration rate (eGFR) using a revised equation for the Japanese population [18]; eGFR (ml/min per $1.73\,m^2$) $= 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287} \times 0.739$ (for women). To calculate eGFR, the admission serum creatinine was used.

Before i.v. tPA, all patients underwent brain noncontrast computed tomography (CT), as well as intracranial magnetic resonance angiography (MRA, unless contraindicated). The Alberta Stroke Program Early CT score (ASPECTS) on CT, a 10-point quantitative topographic scoring method of early ischemic signs in the middle cerebral arterial (MCA) territory, as well as the arterial occlusion site ipsilateral to ischemia was assessed by at least two vascular neurologists [19].

Outcomes

The primary outcome was independent ADL at 3 months corresponding to a mRS score of 2 or less. We researched the 3-month outcome by clinical examination at a hospital clinic (or by phone survey for patients whose neurological deficits were too severe to visit the clinic). The secondary outcomes consisted of early neurological improvement defined as a reduction of at least 4 points from the baseline National Institutes of Health Stroke Scale (NIHSS) score or a total NIHSS score of 0 or 1 at 24 h after i.v. tPA, and ICH defined as CT evidence of new ICH within 36 h after i.v. tPA regardless of additional symptoms.

Control of blood pressure and blood glucose

Control of BP and blood glucose after the initial 24 h was achieved principally according to the JSS guidelines 2004 [15]. During the initial weeks, the guidelines recommend to treat high BP only when BP exceeds 220/130 mmHg or patients have underlying severe cardiovascular diseases. However, we usually maintained BP levels in these weeks more strictly to less than 180/105 mmHg as we did during the initial 24 h. During the chronic stage, the guidelines recommend to lower BP to less than 170/95 mmHg as an example. The guidelines advocated that hyperglycemia should be corrected but did not specify absolute goals. We treated patients with antidiabetic agents principally when HbA1c exceeded 6.5%.

Statistical analysis

Data were statistically analyzed using JMP 7.0 software (SAS Institute Inc, Cary, North Carolina, USA). Statistical significance for the two groups was assessed by Mann–Whitney *U*-tests for continuous variables and Pearson χ^2 tests for categorical variables. We compared the 24-h BP or HR time course between patients with and without each outcome using the two-way repeated measures analysis of variance (ANOVA). Predictors for each outcome were determined by multivariate analyses based on the baseline characteristics, blood tests on admission including eGFR, and 24-h BP and HR profiles of the patients. A backward selection procedure was performed for each outcome using *P* more than 0.10 of the likelihood ratio test for exclusion. A level of *P* less than 0.05 was considered statistically significant.

Results

Of the 125 eligible patients, 89 (71%) had hypertension and 49 (39%) were treated with antihypertensive agents before stroke onset. The median baseline NIHSS score was 13 [interquartile range (IQR) 7–18]. With respect to outcomes, 64 (51%) achieved independent ADL at 3 months, 66 (53%) early neurological improvement, and 26 (21%) developed ICH. The baseline characteristics, stroke features, clinical status, and baseline BP and HR were summarized in Table 1. BP was less than 180/105 mmHg during the initial weeks and less than 170/95 mmHg during the following period for all patients.

Figure 1 shows the initial overall 24-h SBP, DBP, and HR courses for all patients. Both SBP and DBP decreased by about 10 mmHg from the baseline measurement to the initiation of i.v. tPA, decreased by about 2 mmHg 2 h after initiation, and reached a plateau thereafter. HR mildly decreased during this period.

Between patients with and without independence, two-way repeated measures ANOVA showed differences in the 24-h time courses of SBP ($P=0.033$), PP ($P=0.007$), and HR ($P<0.001$; Fig. 2). Levels of SBP and PP were similar within the initial hours between patients with and without independence and differed later. After multivariate adjustment, mean, maximum, and minimum levels of SBP ($P=0.035$, $P=0.013$, and $P=0.027$, respectively), PP ($P=0.029$, $P=0.018$, and $P=0.020$, respectively), and HR ($P=0.001$, $P=0.004$, and $P=0.010$, respectively) during the 24 h were inversely associated with independence (Table 2). When these physiological parameters were separately assessed at different intervals, mean SBP at 8–16 ($P=0.037$) and 16–24 h ($P=0.014$), mean PP at 8–16 ($P=0.046$) and 16–24 h ($P=0.023$), and mean HR at 0–8 ($P=0.007$), 8–16 ($P<0.001$), and 16–24 h ($P=0.002$) were inversely associated with independence.

Between patients with and without early improvement, the ANOVA showed differences in the 24-h time course of HR ($P=0.019$; Fig. 3), but not in those of SBP ($P=0.141$), DBP ($P=0.286$), or PP ($P=0.156$). After multivariate adjustment, baseline and maximum levels of SBP ($P=0.031$ and $P=0.023$, respectively) and baseline PP ($P=0.018$) during the 24 h were inversely associated with early improvement.

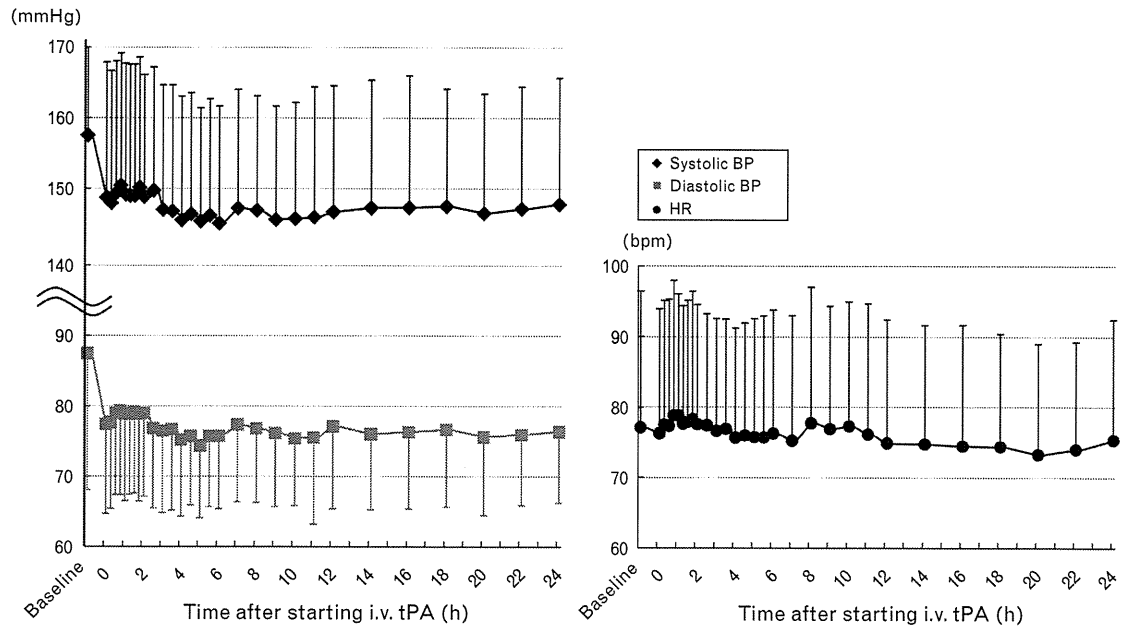
Between patients with and without ICH, the ANOVA did not identify differences in the 24-h time courses of SBP ($P=0.098$), PP ($P=0.052$; Fig. 3), DBP ($P=0.836$), or HR ($P=0.886$). After multivariate adjustment, maximum level and coefficient of variation of SBP ($P=0.028$ and

Table 1 Baseline characteristics

	All patients ($n=125$)
Baseline characteristics	
Men	93 (74%)
Age, years	72.7 ± 9.0[§]
Hypertension	89 (71%)[§]
Diabetes mellitus	25 (20%)
Hyperlipidemia	58 (40%)[§]
Atrial fibrillation	61 (49%)[§]
Previous ischemic stroke	25 (20%)
Current smoking habit	31 (25%)[†]
Antihypertensive use prior to onset	49 (39%)
Antithrombotic use prior to onset	45 (36%)
Blood tests on admission	
Blood glucose, mmol/l	8.23 ± 2.91
HbA1c (%)	5.74 ± 1.15
eGFR (ml/min per 1.73 m^2)	67.81 ± 24.01[§]
Stroke features and clinical status	
Subtypes[§]	
Cardioembolic	71 (57%)
Atherothrombotic	22 (18%)
Lacunar	0 (0%)
Other	32 (25%)
Site of occlusion on MRA[*,§]	
Internal carotid artery	21 (18%)
MCA trunk	28 (24%)
MCA branch	16 (14%)
Vertebral/basilar artery	2 (2%)
Other site/no occlusion	35 (42%)
ASPECTS on CT	9 (7–10)[‡]
Baseline NIHSS score	13 (7–18)[§]
NIHSS score at 24 h	8 (3–15)[‡]
Antihypertensive use within 24 h	28 (22%)
Baseline BP and HR	
SBP (mmHg)	158.4 ± 33.0[†]
DBP (mmHg)	88.1 ± 19.4
PP (mmHg)	70.3 ± 23.4[†]
HR (bpm)	77.9 ± 19.8

Data are expressed as mean ± SD, median (interquartile range), or *n* (%) as appropriate. ASPECTS, Alberta Stroke Program Early CT score; BP, blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; MRA, magnetic resonance angiography; NIHSS, National Institutes of Health Stroke Scale; PP, pulse pressure. *22 patients contraindicated for MRA were excluded. [§]$P<0.05$ between patients with and without independent activities of daily living (ADL); age (70.4 ± 9.2 vs. 75.1 ± 8.2 years, $P=0.007$), hypertension (63 vs. 80%, $P=0.028$), hyperlipidemia (48 vs. 31%, $P=0.049$), atrial fibrillation (39 vs. 59%, $P=0.026$), eGFR (72.92 ± 27.01 vs. 62.44 ± 19.18 ml/min/1.73 m^2, $P=0.021$), stroke subtypes (cardioembolism, 53 vs. 61%; atherothrombotic, 11 vs. 25%; other, 36 vs. 15%; $P=0.011$), site of occlusion on MRA (internal carotid artery, 8 vs. 28%; MCA trunk, 16 vs. 32%; MCA branch, 13 vs. 14%; vertebral/basilar artery, 2 vs. 2%; other site or no occlusion, 61 vs. 24%; $P=0.002$), baseline NIHSS score [12 (7–15) vs. 16 (10–20), $P<0.001$], NIHSS score at 24 h [4 (1–7) vs. 16 (11–20), $P<0.001$]. [†]$P<0.05$ between patients with and without early neurological improvement; current smoking (17 vs. 34%, $P=0.026$), SBP (152.6 ± 32.9 vs. 164.7 ± 32.2 mmHg, $P=0.008$), PP (65.6 ± 23.1 vs. 75.6 ± 22.7 mmHg, $P=0.015$). [‡]$P<0.05$ between patients with and without ICH; NIHSS score at 24 h [14 (11–18) vs. 7 (2–14), $P<0.001$], ASPECTS on CT [8 (6–9) vs. 9 (8–10), $P=0.003$].

Fig. 1



Changes in blood pressure (BP) and heart rate (HR) during the initial 24 h. The vertical bars represent standard deviation. i.v., intravenous; tPA, tissue plasminogen activator.

$P = 0.021$, respectively) and PP ($P = 0.005$ and $P = 0.013$, respectively) during the 24 h were positively associated with ICH.

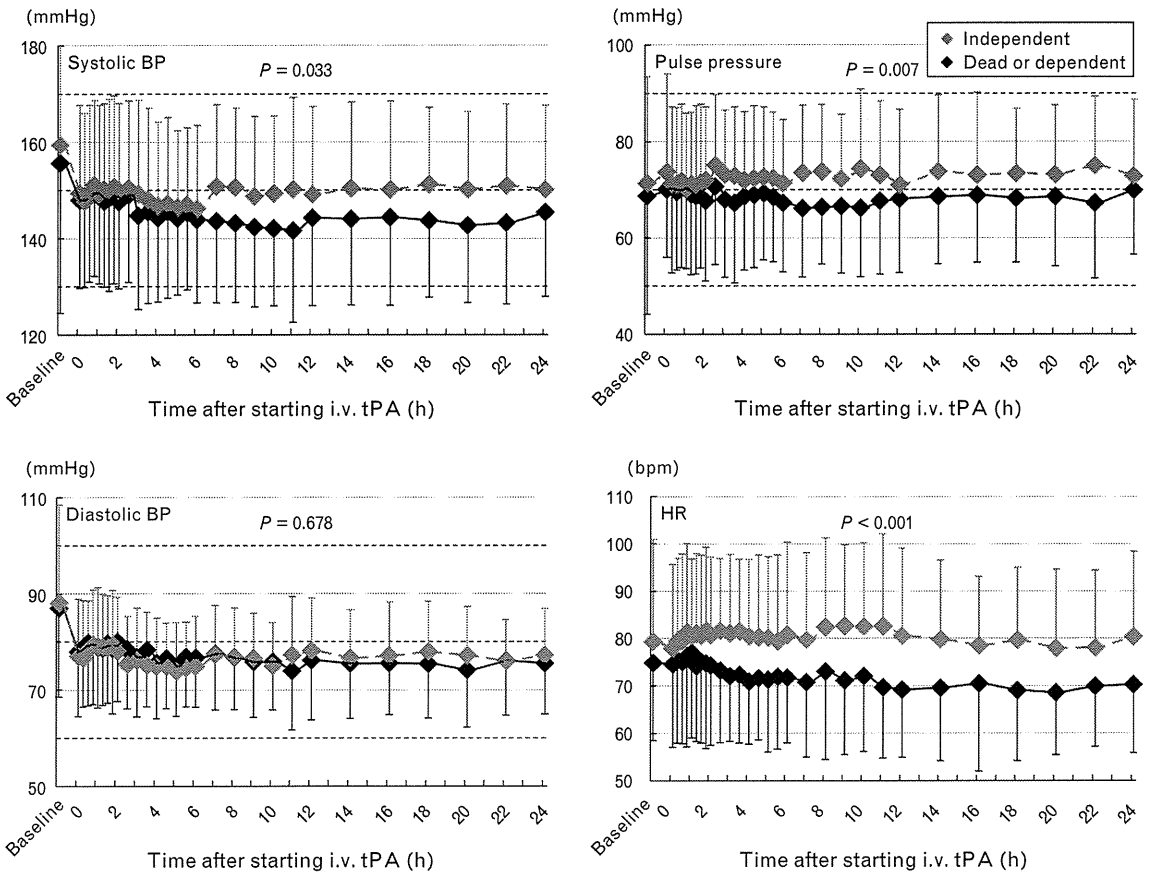
Discussion

This observational study determined the influences of BP and HR during the initial 24 h after starting i.v. tPA therapy on early and long-term outcomes of patients with ischemic stroke. The major finding was that lower SBP, PP, and HR during the initial 24 h, especially at the later hours of this period, were independently related to independent ADL at 3 months.

A pooled analysis from the NINDS tPA study, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS), and the European Cooperative Acute Stroke Study II (ECASS II) identified higher baseline SBP as one of seven major predictors of long-term patient outcomes after i.v. tPA [20]. In addition, subanalyses of major trials and postmarketing surveys including the ECASS II [8] and the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) [9] reported that acute SBP during the initial 24 h is independently related to 3-month outcomes after i.v. tPA. The former found an inverse linear association between mean 24-h SBP and 3-month mRS score of 1 or less [8], and the latter showed a bell-shaped association [9]; 3-month independence was highest when the average SBP at 2 and 24 h was between 141 and 150 mmHg. In the present study, mean 24-h SBP had almost identical statistical power to predict independence along with maximum and minimum SBP during the initial 24 h. In addition, PP played a similar role to SBP as a predictor for independence, mainly due to the close relationship between SBP and PP. As in other studies, DBP did not predict stroke outcome in the present study [8,20].

A notable finding of the present study is that the time course of SBP did not differ over several initial hours after stroke onset between patients with and without independence, whereas mean SBP during later hours (8–16 and 16–24 h) had high odds ratio to predict independence. The subanalyses from ECASS [7], ECASS II [8], and SITS-ISTR [9] described the association between the course of high BP during the initial 24 or 72 h after stroke and poor outcomes. This study stresses the importance of SBP levels, in addition to HR levels, during later hours of this initial period for the outcome prediction. The trends of SBP were similar between patients with and without transcranial Doppler-documented recanalization at 6 h in a study involving stroke patients with MCA occlusion treated with i.v. tPA; a significant SBP decline was identified at around 6 h and later only in patients with recanalization [21]. Arterial recanalization after intraarterial thrombolysis also ended in reduced BP at 12 h [22]. Early reperfusion of the ischemic brain by recanalization seems to restore normal autoregulation and lower SBP [21]. Thus, the influence of low SBP at between 8 and 24 h on the outcomes of our

Fig. 2



Changes in blood pressure (BP) and heart rate (HR) in patients with and without independence at 3 months. *P* values indicate differences in the 24-h courses of each physiological value by two-way repeated measures analysis of variance (ANOVA). i.v., intravenous; tPA, tissue plasminogen activator.

patients might be partly via early recanalization. In addition, our previous study involving stroke patients who were not treated with thrombolysis showed that acute SBP levels at over 6 h after admission predicted neurological deterioration within the initial 3 weeks, whereas those upon admission or at 6 h did not [23]. Several factors, including mental stress, which do not necessarily correlate with stroke severity or arteriosclerotic conditions, affect cardiovascular modulation during the initial several hours, and accordingly BP values at this time point might not be appropriate for predicting stroke outcomes.

SBP variability is strongly associated with stroke risk [24]. In addition, large BP variability during the initial few days after stroke was related to poor outcomes, partly because BP variability influenced cerebral perfusion [21,25]. Although the present study failed to show the association of BP variability with 3-month independence, coefficient of variation of SBP and PP were associated with ICH. Change in cerebral blood flow due to BP variability might trigger hemorrhagic transformation of cerebral ischemia after i.v. tPA.

Another new finding in the present study was that lower HR during the initial 24 h was related to independence. Several potential contributors to poor stroke outcome cause tachycardia in the acute phase, including mass effect due to large infarcts, hemorrhagic transformation, and autonomic dysfunction. As stated above, early reperfusion of the ischemic brain by recanalization seems to both stabilize HR and result in a favorable stroke outcome. Atrial fibrillation is another key factor that influences acute tachycardia; our patients who achieved independence developed atrial fibrillation less frequently than those without (38 vs. 60%, $P = 0.016$). The significance of HR as an outcome predictor should be recognized as it is easily measurable.

Associations between mean 24-h SBP and early neurological improvement or ICH were not identified in this present study, although baseline, maximum, and coefficient of variation of 24-h SBP were associated with these secondary outcomes. In contrast, subanalyses of the ECASS II and the SITS-ISTR revealed a positive linear relationship between mean SBP and ICH [8,9].

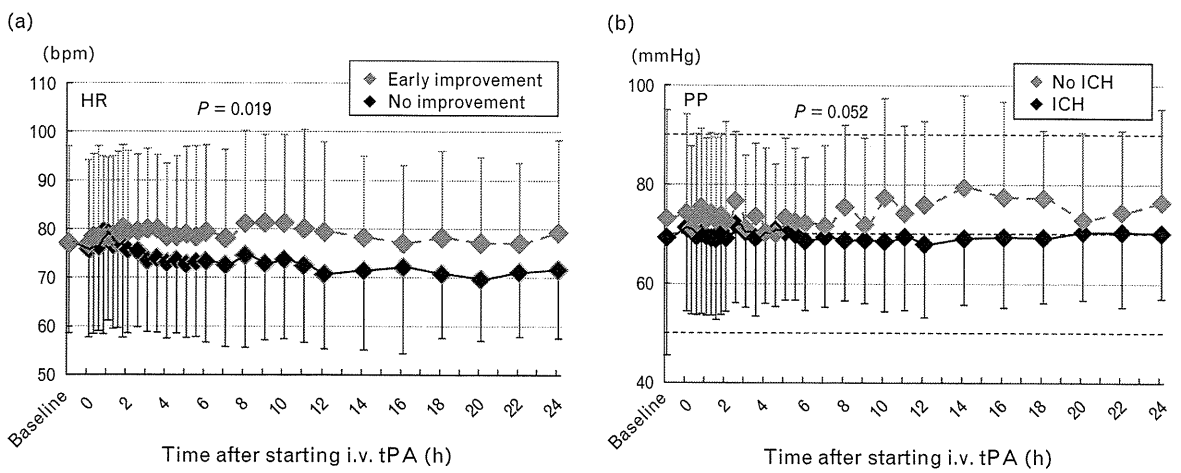
Table 2 Association between each outcome with blood pressure and heart rate

	3-month independence[§]		Early neurological improvement[†]		ICH[‡]	
	OR	95% CI	OR	95% CI	OR	95% CI
SBP						
Baseline SBP	0.96	0.84–1.08	0.88*	0.77–0.98	1.03	0.89–1.19
Mean 24-h SBP	0.69*	0.48–0.97	0.79	0.58–1.06	1.34	0.91–2.06
Maximum 24-h SBP	0.67*	0.48–0.91	0.73*	0.55–0.95	1.50*	1.06–2.20
Minimum 24-h SBP	0.70*	0.51–0.95	0.87	0.66–1.12	0.86	0.61–1.21
CV of 24-h SBP	0.80	0.16–4.06	0.52	0.12–2.24	9.81*	1.47–73.79
Mean 8-h SBP (0–8 h)	0.79	0.57–1.07	0.74*	0.55–0.98	1.17	0.81–1.75
Mean 8-h SBP (8–16 h)	0.73*	0.54–0.97	0.82	0.63–1.06	1.37	0.98–1.98
Mean 8-h SBP (16–24 h)	0.66*	0.47–0.91	0.85	0.65–1.11	1.14	0.81–1.61
Pulse pressure						
Baseline PP	0.98	0.82–1.18	0.81*	0.68–0.96	1.07	0.87–1.31
Mean 24-h PP	0.63*	0.41–0.94	0.82	0.58–1.16	1.51	0.98–2.40
Maximum 24-h PP	0.69*	0.49–0.93	0.78	0.59–1.01	1.64*	1.17–2.35
Minimum 24-h PP	0.65*	0.44–0.92	0.85	0.62–1.14	0.90	0.61–1.32
CV of 24-h PP	0.98	0.46–2.10	0.83	0.41–1.66	3.03*	1.28–7.49
Mean 8-h PP (0–8 h)	0.71	0.48–1.03	0.72	0.50–1.00	1.29	0.85–2.01
Mean 8-h PP (8–16 h)	0.70*	0.48–0.99	0.86	0.63–1.16	1.50*	1.03–2.25
Mean 8-h PP (16–24 h)	0.65*	0.44–0.93	0.94	0.68–1.28	1.24	0.83–1.88
Heart rate						
Baseline HR	0.81	0.61–1.03	0.99	0.82–1.22	0.98	0.76–1.24
Mean 24-h HR	0.59*	0.42–0.80	0.77	0.59–1.01	1.08	0.78–1.49
Maximum 24-h HR	0.75*	0.61–0.90	0.92	0.77–1.09	1.07	0.87–1.31
Minimum 24-h HR	0.61*	0.41–0.88	0.77	0.56–1.05	1.05	0.72–1.55
CV of 24-h HR	0.83	0.40–1.67	1.21	0.63–2.52	1.02	0.42–2.17
Mean 8-h HR (0–8 h)	0.66*	0.48–0.88	0.85	0.66–1.08	1.01	0.73–1.37
Mean 8-h HR (8–16 h)	0.57*	0.41–0.76	0.78*	0.60–0.99	1.13	0.84–1.51
Mean 8-h HR (16–24 h)	0.62*	0.45–0.83	0.75*	0.57–0.97	1.07	0.78–1.46

Odds ratio (OR) and 95% confidence interval (CI) for an increase of 10 mmHg or 10 bpm as appropriate, based on variables appearing in the model of the backward selection procedure. ASPECTS, Alberta Stroke Program Early CT score; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HR, heart rate; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; PP, pulse pressure. [§] On 3-month independence analysis, adjusted for age, hyperlipidemia, atrial fibrillation, stroke subtypes (cardioembolic), baseline NIHSS score, and eGFR. [†] On early neurological improvement at 24 h analysis, adjusted for diabetes mellitus and current smoking habit. [‡] On ICH within 36 h analysis, adjusted for previous ischemic stroke, baseline NIHSS score, and ASPECTS. No parameters on DBP were significantly associated with outcomes. * Represents the statistically significant difference ($P < 0.05$).

Control of BP and several risk factors during the 3-month observation period might affect the outcomes. As shown in our methods, recommended BP goals for stroke patients in the JSS guidelines 2004 were rather modest [15], as guidelines in other nations also were [10,26]. Regarding diabetes, the JSS guidelines 2004 described that there is little evidence that control of diabetes is effective for secondary stroke prevention, as they were published prior to the first successful report on glucose-lowering therapy for secondary stroke prevention,

Fig. 3



Changes in heart rate (HR) among patients with and without early neurological improvement (a) and in pulse pressure (PP) among those with and without intracranial hemorrhage (b). *P* values indicate differences in the 24-h courses of each physiological value by two-way repeated measures analysis of variance (ANOVA). i.v., intravenous; tPA, tissue plasminogen activator.

a subanalysis from the PROactive 04 study [27]. Thus, although the controls for risk factors were done for all patients, they were not as strict as controls based on recent guidelines [28].

The limitations of the present study include its observational nature and that eligibility for tPA administration was determined according to the condition of each patient, although principally based on the JSS guidelines [15]. As some patients were treated with i.v. nicardipine during the initial 24 h after i.v. tPA, the present 24-h BP and HR profiles are not always natural. The effects of antihypertensive therapy before and after i.v. tPA therapy were not studied in detail, as they complicated the results. Although several conditions and events during the 3-month observation period could affect 3-month independence, we did not use such conditions and events for statistical adjustment as such factors themselves might be influenced by 24-h BP and HR levels. In addition, MRA was not repeated within 24 h in all patients; thus, our discussion about the association between arterial recanalization and changes in BP and HR was not solely based on our own results.

The present study demonstrated that continuous measurement of fundamental vital signs after i.v. tPA is important for predicting long-term patient outcome. A randomized trial is warranted to determine whether low SBP and HR values directly cause a favorable outcome or whether patients who are expected to have a favorable outcome tend to have low SBP and HR values.

Acknowledgements

The present study was supported in part by a Research Grant for Cardiovascular Diseases (21A-4), a Research Funding of National Cerebral and Cardiovascular Center, Grant-in-Aid (H20-Junkanki-Ippan-019, H23-Junkanki-Ippan-010) from the Ministry of Health, Labour and Welfare, Japan, and Grant-in-Aid for Scientific Research (C, #20591039) from the Japan Society for the Promotion of Science.

Conflicts of interest

K.M. received research support from the Ministry of Health, Labour and Welfare, Japan, the Mihara Cerebrovascular Disorder Research Promotion Fund, Research Grants for Cardiovascular Diseases, Grant-in-Aid, the Foundation for Biomedical Research and Innovation, Mitsubishi Tanabe Pharma Corporation, and Kyowa Hakko Kirin Pharma, Inc., Hitachi Medical Corporation. K.T. received research support from Grantsin-Aid from the Ministry of Health, Labour and Welfare, Japan. M.K. received research support from a Grant from the Japan Cardiovascular Research Foundation (the Bayer Scholarship for Cardiovascular Research).

References

1 The NINDS rt-PA Stroke Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; **333**:1581–1587.

2 Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, *et al.*, ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 h after acute ischemic stroke. *N Engl J Med* 2008; **359**:1317–1329.

3 Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, *et al.*, SITS-MOST investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007; **369**:275–282.

4 Tanne D, Kasner SE, Demchuk AM, Koren-Morag N, Hanson S, Grond M, Levine SR. Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen activator therapy for acute ischemic stroke in clinical practice: the Multicenter rt-PA Stroke Survey. *Circulation* 2002; **105**:1679–1685.

5 Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Dávalos A, *et al.*, Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy Investigators. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). *Stroke* 2008; **39**:3316–3322.

6 Tsivgoulis G, Frey JL, Flaster M, Sharma VK, Lao AY, Hoover SL, *et al.* Pretissue plasminogen activator blood pressure levels and risk of symptomatic intracerebral hemorrhage. *Stroke* 2009; **40**:3631–3634.

7 Yong M, Diener HC, Kaste M, Mau J. Characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke. *Stroke* 2005; **36**:2619–2625.

8 Yong M, Kaste M. Association of characteristics of blood pressure profiles and stroke outcomes in the ECASS-II trial. *Stroke* 2008; **39**:366–372.

9 Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M, *et al.*, The SITS Investigators. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). *Stroke* 2009; **40**:2442–2449.

10 Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, *et al.*, American Heart Association; American Stroke Association Stroke Council; Clinical Cardiology Council; Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke* 2007; **38**:1655–1711.

11 Castillo J, Leira R, Garcia MM, Serena J, Blanco M, Davalos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. *Stroke* 2004; **35**:520–526.

12 Toyoda K, Okada Y, Fujimoto S, Hagiwara N, Nakachi K, Kitazono T, *et al.* Blood pressure changes during the initial week after different subtypes of ischemic stroke. *Stroke* 2006; **37**:2637–2639.

13 Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, Shinohara Y. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 h of onset: Japan Alteplase Clinical Trial (J-ACT). *Stroke* 2006; **37**:1810–1815.

14 Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, *et al.*, for Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study Investigators. Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. *Stroke* 2009; **40**:3591–3595.

15 Shinohara Y, Yamaguchi T. Outline of the Japanese Guidelines for the Management of Stroke 2004 and subsequent revision. *Int J Stroke* 2008; **3**:55–62.

16 European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**:1011–1053.

17 Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. *Stroke* 1993; **24**:35–41.

18 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, *et al.*, on behalf of the collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**:982–992.

19 Barber PA, Demchuk AM, Zhang J, Buchan AM, for the ASPECTS Study Group. Validity and reliability of a semiquantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet* 2000; **355**:1670–1674.
20 Kent DM, Selker HP, Ruthazer R, Bluhmki E, Hacke W. The stroke-thrombolytic predictive instrument: a predictive instrument for intravenous thrombolysis in acute ischemic stroke. *Stroke* 2006; **37**:2957–2962.
21 Delgado-Mederos R, Ribo M, Rovira A, Rubiera M, Munuera J, Santamarina E, *et al.* Prognostic significance of blood pressure variability after thrombolysis in acute stroke. *Neurology* 2008; **71**:552–558.
22 Mattle HP, Kappeler L, Arnold M, Fischer U, Nedeltchev K, Remonda L, *et al.* Blood pressure and vessel recanalization in the first hours after ischemic stroke. *Stroke* 2005; **36**:264–268.
23 Toyoda K, Fujimoto S, Kamouchi M, Iida M, Okada Y. Acute blood pressure levels and neurological deterioration in different subtypes of ischemic stroke. *Stroke* 2009; **40**:2585–2588.
24 Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, *et al.* Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010; **375**:895–905.
25 Bath PM; for the VISTA Collaboration. Relationship between hyperacute blood pressure and outcome after ischemic stroke. *Stroke* 2009; **40**:2098–2103.
26 Tikhonoff V, Zhang H, Richart T, Staessen JA. Blood pressure as a prognostic factor after acute stroke. *Lancet Neurol* 2009; **8**:938–948.
27 Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Pirags V, Kupfer S, Dormandy J, PROactive Investigators. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* 2007; **38**:865–873.
28 American Diabetes Association. Summary of revisions for the 2009 Clinical Practice Recommendations. *Diabetes Care* 2009; **32 (Suppl 1)**: S3–S5.

Effects of 24-Hour Blood Pressure and Heart Rate Recorded With Ambulatory Blood Pressure Monitoring on Recovery From Acute Ischemic Stroke

Yasuhiro Tomii, MD; Kazunori Toyoda, MD; Rieko Suzuki, MD; Masaki Naganuma, MD; Jun Fujinami, MD; Chiaki Yokota, MD; Kazuo Minematsu, MD

Background and Purpose—This study used ambulatory blood pressure (BP) monitoring to generate BP and heart rate (HR) profiles soon after stroke onset and evaluated the association between determined values and 3-month stroke outcomes.

Methods—We analyzed 24-hour ambulatory BP monitoring records from 104 patients with acute ischemic stroke. Ambulatory BP monitoring was attached at the second and eighth hospitalization days (Days 1 and 7). Both BP and HR were characterized using baseline, mean, maximum, and minimum values and coefficient of variation during 24-hour recording periods. Outcomes at 3 months were assessed as independence according to a modified Rankin Scale score of ≤2 and poor according to the score of ≥5.

Results—Sixty-six (63%) patients achieved independence and 12 (11%) had poor outcomes. Mean ambulatory BP monitoring values changed from 150.5±19.5/85.7±11.3 mm Hg on Day 1 to 139.6±19.3/80.0±11.7 mm Hg on Day 7. After multivariate adjustment, mean values of systolic BP (OR, 0.63; 95% CI, 0.45–0.85), diastolic BP (0.61; 0.37–0.98), pulse pressure (0.55; 0.33–0.85), and HR (0.61; 0.37–0.98) recorded on Day 1 as well as mean HR on Day 7 (0.47; 0.23–0.87) were inversely associated with independence and mean values of systolic BP (1.92; 1.15–3.68), diastolic BP (5.28; 1.92–22.85), and HR (4.07; 1.83–11.88) on Day 1 as well as mean HR on Day 7 (4.92; 1.36–36.99) were positively associated with a poor outcome.

Conclusions—All of systolic BP, diastolic BP, pulse pressure, and HR on Day 1 and HR on Day 7 assessed using ambulatory BP monitoring were associated with outcomes of patients with stroke at 3 months. (***Stroke*. 2011;42: 3511-3517.)**

Key Words: ambulatory blood pressure monitoring ■ cerebral infarction ■ hypertension ■ outcome

An acute hypertensive response occurs in up to 80% of all patients with acute stroke, but management of hypertension remains controversial because of the paucity of reliable evidence from randomized clinical trials.[1–3] Data from observational studies have suggested that high blood pressure (BP) is related to a poor outcome,[1,4–6] whereas BP elevation during the acute phase might help to maintain cerebral perfusion pressure.[7,8]

Elevated BP generally falls and returns to prestroke levels during the initial days without therapeutic intervention.[1,6,9,10] One systematic review found that the admission BP value was a useful indicator of stroke outcomes.[1] On the other hand, admission BP might be unreliable or misleading, because BP can transiently elevate or decline within several hours after stroke onset depending on the level of consciousness, physical activity, and mental stress of hospital admission.[11] Thus, consecutive BP monitoring during the initial hours or days might be a better prognostic predictor than admission BP values alone.

Compared with casually recorded BP, ambulatory BP monitoring (ABPM) has been proposed as a way to accurately evaluate clinical status, because a large number of records can be generated.[12–15] However, whether BP profiles using ABPM during the acute phase are associated with stroke outcomes remains unclear.

The aim of this study was to evaluate the association of BP and heart rate (HR) profiles using ABPM devices early after stroke onset with 3-month outcomes.

Patients and Methods

Patient Population

We registered 136 consecutive Japanese patients with ischemic stroke who were admitted to our stroke care unit within 24 hours of symptom onset between January and December 2008. Of these, we excluded 6 patients who were dependent on activities of daily living (ADL) corresponding to a modified Rankin Scale ≥3 before stroke onset, 2 with severe subcutaneous hemorrhage in the arm, 3 infected with neurovirus, 7 who did not provide informed consent (principally

Received June 9, 2011; final revision received July 19, 2011; accepted July 28, 2011.

From the Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan.

Correspondence to Kazunori Toyoda, MD, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan. E-mail toyoda@hsp.ncvc.go.jp

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.111.628586

Table 1. Baseline Characteristics

	All Patients (n=104)	Independence			Poor Outcome		
		Yes (n=66)	No (n=38)	P	Yes (n=12)	No (n=92)	P
Baseline characteristics							
Woman	40 (38%)	22 (33%)	18 (47%)	0.157	5 (42%)	35 (38%)	0.808
Age, y	71.7±12.5	67.9±12.6	78.1±9.5	<0.001	81.8±8.7	70.3±12.3	<0.001
Hypertension	82 (79%)	52 (79%)	30 (79%)	0.985	9 (75%)	73 (79%)	0.729
Diabetes mellitus	33 (32%)	22 (33%)	11 (29%)	0.644	3 (25%)	30 (33%)	0.594
Hyperlipidemia	46 (44%)	31 (47%)	15 (39%)	0.459	3 (25%)	43 (47%)	0.154
Atrial fibrillation	35 (34%)	18 (27%)	17 (45%)	0.070	7 (58%)	28 (30%)	0.054
Previous ischemic stroke	29 (28%)	14 (21%)	15 (39%)	0.046	6 (50%)	23 (25%)	0.069
Current smoking habits	22 (21%)	16 (24%)	6 (16%)	0.340	1 (8%)	21 (23%)	0.242
Antihypertensive use before onset	53 (51%)	33 (50%)	20 (53%)	0.796	4 (33%)	49 (53%)	0.194
Stroke features and clinical status							
Subtypes							
Cardioembolic	37 (36%)	19 (29%)	18 (47%)	0.209	7 (58%)	30 (32%)	0.363
Atherothrombotic	21 (20%)	15 (23%)	6 (16%)		2 (17%)	19 (21%)	
Lacunar	15 (14%)	9 (13%)	6 (16%)		1 (8%)	14 (15%)	
Other	31 (30%)	23 (35%)	8 (21%)		2 (17%)	29 (32%)	
Baseline NIHSS score	4 [1–8]	2 [1–5]	7 [4–18]	<0.001	16 [5–24]	3 [1–5]	<0.001
Receiving IV rtPA	16 (15%)	4 (6%)	12 (32%)	<0.001	3 (25%)	13 (14%)	0.326
Initiation of antihypertensive therapy							
By Day 1 ABPM	13 (13%)	11 (18%)	2 (6%)	0.086	0 (0%)	13 (15%)	0.148
By Day 7 ABPM	34 (33%)	23 (37%)	11 (31%)	0.512	4 (33%)	30 (35%)	0.916

Data are expressed as mean±SD, median [interquartile range], or no. (%) as appropriate. Comparisons among groups were performed using χ^2 test, Student *t* test, or Mann-Whitney *U* test as appropriate.

NIHSS indicates National Institutes of Health Stroke Scale; IV rtPA, intravenous recombinant tissue plasminogen activator; ABPM, ambulatory blood pressure monitoring.

*$P<0.05$ between patients with and without independence; age (67.9±12.6 y versus 78.1±9.5 y, $P<0.001$), previous ischemic stroke (21% versus 39%, $P=0.046$), and baseline NIHSS score (2 [1–5] versus 7 [4–18], $P<0.001$).

†$P<0.05$ between patients with and without poor outcomes; age (81.8±8.7 y versus 70.3±12.3 y, $P<0.001$) and baseline NIHSS score (16 [5–24] versus 3 [1–5], $P<0.001$).

orally and by written consent if needed), and 14 with incomplete ABPM recordings. Consequently, we analyzed data from 104 patients (40 women, 71.7±12.5 years). The open study design is described on the Web site of the Grant-in-Aid for Scientific Research (C, #20591039) from the Japan Society for the Promotion of Science.

Assessments of BP and HR

Baseline BP and HR values were recorded immediately after arrival at the emergency department (Day 0). Twenty-four-hour ABPM (TM-2431; A&D Company, Ltd) was started at 10 AM of the second and eighth hospitalization days (Days 1 and 7) on the left arm after a relevant difference between the 2 limbs was ruled out by conventional BP checks. Systolic/diastolic BP (SBP/DBP), pulse pressure (PP), and HR were automatically measured every 30 minutes for 24 hours.

We characterized BP and HR profiles by calculating the following values: mean, maximum, minimum, and coefficient of variation ([%]=SD×100/mean value) during 24 hours as well as mean values during 16 hours of the day (6 AM to 10 PM) and 8 hours of the night (10 PM to 6 AM). Patients were classified according to a fall (%) in mean SBP during the nighttime compared with the daytime as: dipper (fall ≥10%), nondipper (0%–10%), and riser (nocturnal SBP increased compared with daytime SBP).

Baseline Characteristics

The following baseline characteristics were investigated using the prospective database: sex, age, hypertension (BP ≥140/90 mm Hg before stroke onset or taking antihypertensive agents), diabetes mellitus (fasting blood glucose ≥7.0 mmol/L, hemoglobin A1c ≥6.5%, or taking antidiabetic agents), hyperlipidemia (total cholesterol ≥5.7 mmol/L, triglyceride ≥1.7 mmol/L, or taking antihyperlipidemic agents), atrial fibrillation (documented during hospitalization or history of atrial fibrillation), history of symptomatic ischemic stroke, and current smoking habit. Stroke subtypes were determined according to the Trial of ORG 10172 in Acute Stroke Treatment subtype classification system.[16]

Outcome

The outcome measurements comprised achieving independent ADL or a poor outcome at 3 months corresponding to modified Rankin Scale scores of ≤2 or ≥5, respectively.

Statistical Analysis

Data were statistically analyzed using JMP 7.0 software (SAS Institute Inc, Cary, NC). Statistical significance for the 2 groups was assessed using Student *t* test or Mann-Whitney *U* tests for continuous variables as appropriate and Pearson χ^2 tests for categorical variables. The 24-hour BP or HR time course between patients with and without each outcome was compared using the 2-way repeated-measures analysis of variance. Predictors for each outcome were determined by multivariate analyses based on the baseline characteristics and the 24-hour BP and HR profiles of the patients. A backward selection procedure was performed for each outcome using $P>0.10$ of the likelihood ratio test for exclusion. In addition, each

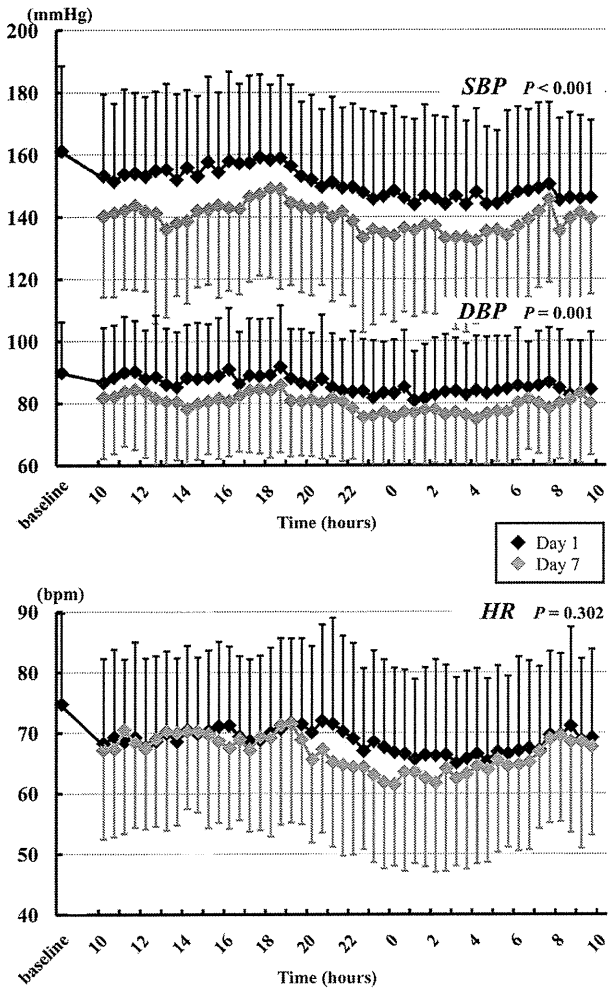


Figure 1. Changes in SBP, DBP, and HR over 24 hours on Days 1 and 7. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

outcome among quintile groups for mean 24-hour SBP on Day 1 was compared using multivariate analyses to search for the U- or J-shaped phenomenon. A level of $P<0.05$ was considered statistically significant.

Results

Outcomes and Related Factors

Of a total of 104 eligible patients, 82 (79%) had hypertension and 53 (51%) were treated with antihypertensive agents before stroke onset. Sixty-six (63%) patients reached independent ADL and 12 (11%) had a poor outcome (including death in 1 patient) at 3 months. Table 1 summarizes the baseline characteristics, stroke features, and clinical status. Thirteen and 34 patients were started on antihypertensive therapy on Days 1 and 7, respectively.

Whole Day BP/HR Measurements

At the emergency department on Day 0, SBP/DBP and HR values were 161.3±27.3/89.9±16.3 mm Hg and 74.8±15.0 beats/min, respectively. The baseline values of SBP, DBP, PP, or HR were not associated with independent ADL (P=0.495, 0.093, 0.706, and 0.240, respectively) or poor outcome (P=0.770, 0.710, 0.513, and 0.919, respectively) at 3 months.

Figure 1 shows the 24-hour SBP, DBP, and HR courses on Days 1 and 7 for all of the patients. Mean SBP/DBP and HR on Day 1 were 150.5±19.5/85.7±11.3 mm Hg and 68.7±11.4 beats/min, respectively, and 139.6±19.3/80.0±11.7 mm Hg and 66.6±11.6 beats/min, respectively, on Day 7. Over the initial week, mean SBP/DBP declined by 10.3±16.2/4.8±7.8 mm Hg, but HR did not significantly change. Two-way repeated-measures analysis of variance revealed significant differences in the 24-hour time courses of SBP and DBP between Days 1 and 7 ($P<0.001$ and $P=0.001$, respectively). Thirty patients were excluded from analysis on Day 7; 9 patients left the hospital, 10 refused to undergo further examination, 1 was not examined due to infection with methicillin-resistant *Staphylococcus aureus*, and recordings from 10 others were incomplete.

Figure 2 shows the 24-hour time course of SBP and HR on Days 1 and 7 in patients with independent ADL (black lines). Between patients with and without independent ADL at 3 months, 2-way repeated measures analysis of variance showed significant differences in the 24-hour time course of SBP, PP, and HR on Day 1 ($P<0.001$, <0.001, and 0.003, respectively) and HR on Day 7 ($P<0.001$). After multivariate adjustment, the mean and minimum SBP ($P=0.004$ and 0.035, respectively), mean DBP ($P=0.044$), mean, minimum, and coefficient of variation of PP ($P=0.010$, 0.010, and 0.031, respectively), and mean and maximum HR on Day 1 ($P=0.045$ and 0.045, respectively) as well as mean HR on Day 7 ($P=0.022$) were inversely associated with independent ADL (Table 2).

Figure 2 also shows the 24-hour time course of SBP and HR on Days 1 and 7 in patients with poor outcomes (gray lines). Two-way repeated-measures analysis of variance revealed significant differences in the 24-hour time course of SBP, DBP, and HR on Day 1 ($P=0.022$, 0.007, and <0.001, respectively) and HR on Day 7 ($P<0.001$) between patients with and without poor outcomes at 3 months. After multivariate adjustment, the mean, maximum, and minimum SBP ($P=0.011$, 0.010, and 0.012, respectively), mean and maximum DBP ($P=0.001$ and 0.046, respectively), and mean, maximum, and minimum HR on Day 1 ($P<0.001$, 0.006, and 0.007, respectively) as well as mean HR on Day 7 ($P=0.012$) were positively associated with a poor outcome (Table 2).

Figure 3 shows a comparison of each outcome among quintile groups for mean 24-hour SBP on Day 1. The frequency of patients who achieved independent ADL gradually decreased and that of patients with a poor outcome gradually increased with increasing SBP. Patients who achieved independent ADL were more common in the bottom (SBP ≤135 mm Hg) as compared with the third quintile group (SBP of 145–153 mm Hg; OR, 9.72; 95% CI, 1.06–191.22; $P=0.044$). Patients with poor outcome were more common in the top (SBP ≥169 mm Hg) as compared with the third quintile group (OR, 17.85; 95% CI, 1.29–649.08; $P=0.030$).

Among the 104 patients, 16 (15%) received intravenous recombinant tissue-type plasminogen activator. Among these, 4 reached independent ADL and 3 had poor outcomes at 3

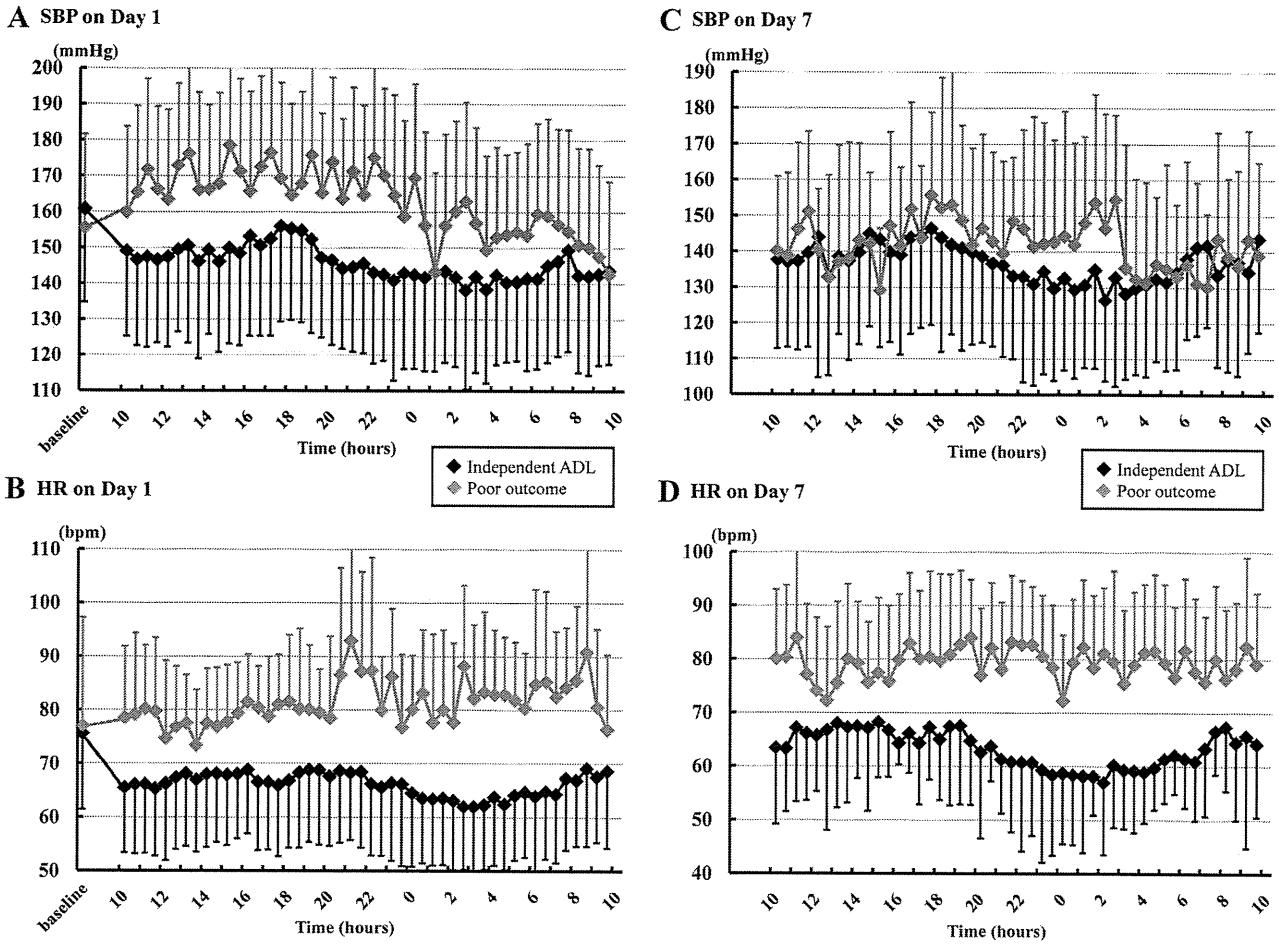


Figure 2. Changes in SBP and HR on Days 1 and 7 in patients who achieved independent ADL and those with poor outcomes. **A**, SBP on Day 1. $P<0.001$ between patients with and without independent ADL; $P=0.022$ between patients with and without poor outcomes. **B**, HR on Day 1. $P=0.003$ between patients with and without independent ADL; $P<0.001$ between patients with and without poor outcomes. **C**, SBP on Day 7. $P=0.052$ between patients with and without independent ADL; $P=0.293$ between patients with and without poor outcomes. **D**, HR on Day 7. $P<0.001$ between patients with and without independent ADL; $P<0.001$ between patients with and without poor outcomes. SBP indicates systolic blood pressure; HR, heart rate; ADL, activities of daily living.

months. The results were generally similar after excluding these patients; mean SBP on Day 1 was inversely associated with independent ADL (OR, 0.61; 95% CI, 0.42–0.86 per 10-mm Hg increase; $P=0.004$) and positively associated with a poor outcome (1.97; 1.06–4.79; $P=0.031$).

Day and Night BP/HR Measurements

On Day 1, mean daytime SBP/DBP and HR values were 152.8±19.1/87.0±11.2 mm Hg and 69.8±11.4 beats/min, respectively, and nighttime values were 146.1±22.0/83.4±12.9 mm Hg and 66.6±12.1 beats/min, respectively. After multivariate adjustment, mean levels of daytime SBP, DBP, PP, and HR ($P=0.007$, 0.047, 0.026, and 0.039, respectively) and nighttime SBP, PP, and HR ($P=0.025$, 0.018, and 0.039, respectively) were inversely associated with independent ADL (Table 2). The mean levels of SBP, DBP, and HR both during the daytime ($P=0.007$, <0.001, and 0.001, respectively) and nighttime ($P=0.022$, 0.004, and <0.001, respectively) were positively associated with a poor outcome. Among the overall patients, 23 (22%) were dippers, 51 (49%) were nondippers, and 30 (29%) were risers (Table 3). Dipper pattern was not associated with either independent ADL or a poor outcome.

Mean daytime SBP/DBP and HR on Day 7 were 142.0±19.8/81.3±11.5 mm Hg and 68.4±11.3 beats/min, respectively, and these nighttime values were 135.5±20.6/76.9±13.1 mm Hg and 63.2±12.9 beats/min, respectively. After multivariate adjustment, the mean levels of both daytime and nighttime HR ($P=0.043$ and 0.033, respectively) were inversely associated with independent ADL ($P=0.042$) and positively associated with a poor outcome ($P=0.002$), whereas mean BP profiles were not (Table 2). Among all of the patients, 18 (24%) were dippers, 36 (49%) were nondippers, and 20 (27%) were risers (Table 3). Dipper pattern was not associated once again with either independent ADL or a poor outcome.

Discussion

In the present study, we measured BP and HR values during acute stroke using ABPM and determined their association with outcomes at 3 months. The first major finding was that lower BP profiles on Day 1 were independently associated

Table 2. Association of BP and HR With 3-Mo Outcomes

	Day 1				Day 7			
	Independence†		Poor Outcome‡		Independence†		Poor Outcome‡	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
SBP								
Mean 24-h SBP	0.63*	0.45–0.85	1.92*	1.15–3.68	0.81	0.56–1.13	1.27	0.73–2.28
Mean daytime SBP	0.65*	0.47–0.88	2.07*	1.20–4.25	0.88	0.62–1.21	1.12	0.65–1.92
Mean nighttime SBP	0.74*	0.57–0.96	1.61*	1.07–2.66	0.84	0.60–1.16	1.57	0.92–3.04
Maximum 24-h SBP	0.87	0.69–1.09	1.93*	1.24–3.44	1.05	0.83–1.33	0.99	0.63–1.47
Minimum 24-h SBP	0.75*	0.56–0.97	1.81*	1.18–3.04	0.78	0.54–1.09	1.00	0.54–1.76
CV of 24-h SBP	2.36	0.56–11.43	1.79	0.16–18.37	2.42	0.40–16.15	0.13	0.00–3.97
DBP								
Mean 24-h DBP	0.61*	0.37–0.98	5.28*	1.92–22.85	0.63	0.34–1.13	1.92	0.76–5.61
Mean daytime DBP	0.62*	0.39–0.99	6.89*	2.08–52.00	0.70	0.38–1.25	1.55	0.63–4.10
Mean nighttime DBP	0.77	0.50–1.17	2.82*	1.38–6.64	0.74	0.43–1.26	2.68*	1.05–8.93
Maximum 24-h DBP	1.15	0.90–1.51	1.55*	1.01–2.57	0.86	0.64–1.15	1.58	0.88–3.44
Minimum 24-h DBP	0.75	0.44–1.24	1.99	0.91–4.78	0.75	0.35–1.60	6.46*	1.38–49.80
CV of 24-h DBP	2.64	0.98–8.39	0.73	0.13–2.94	1.24	0.44–3.56	0.30	0.03–2.04
PP								
Mean 24-h PP	0.55*	0.33–0.85	1.40	0.74–2.69	0.86	0.47–1.50	1.07	0.36–3.33
Mean daytime PP	0.61*	0.39–0.93	1.43	0.79–2.75	0.92	0.53–1.57	0.88	0.31–2.54
Mean nighttime PP	0.62*	0.40–0.91	1.28	0.72–2.30	0.85	0.50–1.43	1.44	0.54–3.76
Maximum 24-h PP	0.97	0.73–1.29	1.34	0.90–2.08	1.20	0.87–1.70	0.64	0.25–1.27
Minimum 24-h PP	0.58*	0.37–0.86	1.43	0.86–2.59	0.69	0.39–1.15	1.27	0.46–3.38
CV of 24-h PP	2.04*	1.07–4.14	0.75	0.27–1.66	2.50	0.95–7.50	0.04*	0.00–0.50
HR								
Mean 24-h HR	0.61*	0.37–0.98	4.07*	1.83–11.88	0.47*	0.23–0.87	4.92*	1.36–36.99
Mean daytime HR	0.61*	0.37–0.96	3.74*	1.66–10.92	0.54*	0.28–0.98	3.26*	1.04–16.38
Mean nighttime HR	0.61*	0.37–0.96	4.04*	1.91–11.29	0.55*	0.30–0.95	6.87*	1.79–81.34
Maximum 24-h HR	0.78*	0.60–0.99	1.85*	1.27–3.19	0.84	0.58–1.18	1.29	0.70–2.57
Minimum 24-h HR	0.79	0.47–1.34	3.04*	1.45–7.94	1.13	0.59–2.24	0.73	0.22–2.15
CV of 24-h HR	0.65	0.22–1.77	1.73	0.43–7.30	1.15	0.35–3.84	0.84	0.08–5.80
Dipper pattern	1.10	0.35–3.70	2.04	0.29–27.74	0.44	0.10–1.81	. . .	. . .

OR and 95% CI for increase of 10 mm Hg or 10 beats/min as appropriate based on variables appearing in backward selection model.

BP indicates blood pressure; HR, heart rate; SBP, systolic blood pressure; CV, coefficient of variation; DBP, diastolic blood pressure; PP, pulse pressure; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; CI, confidence interval.

*Statistically significant difference ($P<0.05$).

†Independence analysis, adjusted for age, previous ischemic stroke, and baseline NIHSS score.

‡Poor outcome analysis, adjusted for age, previous ischemic stroke, current smoking habits, and baseline NIHSS score.

with better clinical outcomes, whereas those on Day 7 were not. The second major finding was that lower HR profiles on Days 1 and 7 were also independently associated with better outcomes. In addition, we clarified SBP patterns during acute stroke as dipper, nondipper, or riser SBP, although they were not associated with outcomes.

Brain edema, hemorrhagic transformation, recanalization of occluded cerebral arteries, mental stress, and antihypertensive therapy are potential factors that could affect acute-phase BP levels. Of these, mass effect due to brain edema and hemorrhagic transformation causes elevated BP and vice versa. Brain edema and hemorrhagic transformation are key factors to link acute high BP and poor outcomes.[4,17–19] The spontaneous decline in BP during the initial hours sometimes reflects the recanalization of occluded cerebral arteries, which often results in favorable outcomes.[20,21] Mental stress of hospital admission contributes to elevated BP[11]; release from the stress can lower BP and possibly improve clinical conditions. Some patients received antihypertensive therapy on the initial day or during the first week, mainly due to having extremely high BP levels or underlying cardiovascular diseases. Such therapy would affect BP and HR levels, although influence of acute BP-lowering on stroke outcomes has not been clarified.[22]

The present results showed a highly significant association between 3-month outcomes and lower SBP and DBP on Day 1 on any whole day, daytime, or nighttime recording. Figure 3 shows a monotonous linear association between SBP levels

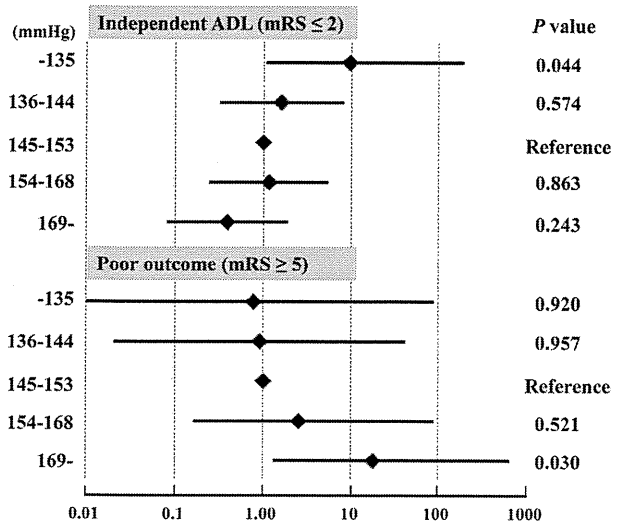


Figure 3. Multivariate-adjusted ORs and 95% CIs for 3-month outcomes among quintiles for mean 24-hour SBP levels on Day 1. Adjusted for age, previous ischemic stroke, and baseline NIHSS score. SBP indicates systolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

and outcomes. Some studies summarized in a meta-analysis[1] have identified a similar monotonous relationship, whereas others have demonstrated a U-shaped relationship between the initial BP and poor outcome with the best outcome being associated with SBP levels between 140 and 180 mm Hg.[23] Our study included few patients with stroke and severe heart failure who were generally hypotensive and had poor outcomes. The BP profiles of these patients on Day 7 did not predict outcomes at 3 months, partly because of a decrease in the effects of acute brain damage on cardiovascular modulation and therapeutic intervention including antihypertensive therapy during the initial week.

The variability of BP in chronic stroke affects long-term outcomes, and the impact of BP variability in acute stroke on outcomes has recently been discussed.[24–26] The present study is unique in that differences in diurnal and nocturnal BP levels, typical BP variability, were assessed in consecutive patients with acute stroke. The nondipper and riser patterns were identified in >75% of our patients on both Days 1 and 7. However, abnormal nocturnal BP dipping and the coefficient of variation of 24-hour BP levels were not associated with outcomes. The circadian rhythm of BP is disrupted during acute stroke and normalizes after a few weeks.[27–29] To determine the significance of the rhythm especially on Day 1 seems difficult because an acute consciousness disturbance as well as early initial intensive care for acute stroke might deprive patients of usual day/night life rhythms.

Table 3. Association Between Fall in BP Between Day and Night and 3-Mo Outcomes

	Dipper	Nondipper	Riser
Day 1			
Overall patients	23 (22%)	51 (49%)	30 (29%)
Patients with independent ADL	14 (21%)	33 (50%)	19 (29%)
Patients with poor outcome	2 (17%)	6 (50%)	4 (33%)
Day 7			
Overall patients	18 (24%)	36 (49%)	20 (27%)
Patients with independent ADL	12 (26%)	23 (50%)	11 (24%)
Patients with poor outcome	0 (0%)	4 (44%)	5 (56%)

No significantly difference in pattern distribution between patients with or without independent ADL or between those with or without poor outcomes.
BP indicates blood pressure; ADL, activities of daily living.

HR is an easily measurable predictor of total, cardiovascular, or noncardiovascular mortality in the general population.[30–32] However, the role of HR seems to be understudied in patients with acute stroke. The present findings of a high HR on Days 1 and 7 as an indicator of poor chronic outcomes might be partly due to the mass effect of large infarcts, hemorrhagic transformation, and autonomic dysfunction during acute stroke, because they all cause tachycardia and poor outcomes. Atrial fibrillation is another key cause of both tachycardia and poor outcomes due to large embolic infarcts.

Our study had some limitations. First, this single-center observational study included a relatively small patient cohort, which would cause statistical bias. A single-center registration would cause institute-specific selection bias. At least, baseline characteristics, stroke subtypes, and baseline National Institutes of Health Stroke Scale score of the present patients were similar with known nationwide registration studies in Japan such as the Japan Multicenter Stroke Investigators' Collaboration study and the Japan Standard Stroke Registry Study.[33,34] The small sample size, especially when grouped into smaller subgroups, caused wide 95% CI after multivariate analyses and limited statistical power. Second, because we started all ABPM measurements at the same time (10 AM), the intervals between stroke onset and ABPM differed among the patients.

Several factors can cause hypertensive response during acute stroke, including inadequately treated or undetected chronic hypertension before stroke onset,[35] increased sympathoadrenal tone with subsequent renin release and vasoconstriction because of impaired cardiac baroreceptor sensitivity,[36,37] and stress responses to hospitalization, urinary retention, or conscious disturbance; some of these do not last long. In our cohort, any components of admission BP or HR did not predict chronic outcomes. Thus, BP should be frequently and consecutively measured to minimize the influence of unexpected factors and to accurately assess the clinical significance of acute BP levels. ABPM appears to be a practical and appropriate method for such assessment. A systemic review involving 20 studies with 5683 patients shows the advantage of ABPM over routine clinical BP measurement as a diagnostic tool for hypertension and suggests that ABPM leads to more appropriate targeting of antihypertensive treatment than the routine measurement.[38] In a general population from the Ohasama study, ABPM had stronger predictive power for stroke risk than did screening routine BP measurement.[39] Thus, ABPM may also have the strong predictive power for stroke outcomes. A randomized trial to control acute BP and HR levels is warranted to determine whether low BP and HR levels can directly improve outcomes or whether patients with predicted improved outcomes tend to have low BP and HR levels.

Sources of Funding

This study was supported in part by a Research Grant for Cardiovascular Diseases (21A-4), Intramural Research Fund (22-4-1) for Cardiovascular Disease of National Cerebral and Cardiovascular Center, Grants-in-Aid (H20-Junkanki-Ippan-019, H23-Junkanki-Ippan-010) from the Ministry of Health, Labour and Welfare, Japan, and a Grant-in-Aid for Scientific Research (C, 20591039) from the Japan Society for the Promotion of Science.

Disclosures

K.M. receives research support from the Ministry of Health, Labour and Welfare, Japan, the Mihara Cerebrovascular Disorder Research Promotion Fund, Research Grants for Cardiovascular Diseases, Grant-in-Aid, the Foundation for Biomedical Research and Innovation, Mitsubishi Tanabe Pharma Corporation, Kyowa Hakko Kirin Pharma, Inc, and Hitachi Medical Corporation. K.T. receives research support from Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan.

References

1. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome. A systemic review. *Hypertension.* 2004; 43:18–24.
2. Qureshi AI. Acute hypertensive response in patients with stroke. Pathophysiology and management. *Circulation.* 2008;118:176–187.
3. Tikhonoff V, Zhang H, Richart T, Staessen JA. Blood pressure as a prognostic factor after acute stroke. *Lancet Neurol.* 2009;8:938–948.
4. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke.* 2002;33: 1315–1320.
5. Abboud H, Labreuche J, Plouin F, Amarenco P; the GENIC Investigators. High blood pressure in early acute stroke: a sign of a poor outcome? *J Hypertens.* 2006;24:381–386.
6. Castillo J, Leira R, Garcia MM, Serena J, Blanco M, Davalos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. *Stroke.* 2004;35:520–526.
7. Meyer JS, Shimazu K, Fukuuchi Y, Ohuchi T, Okamoto S, Koto A, et al. Impaired neurogenic cerebrovascular control and dysautoregulation after stroke. *Stroke.* 1973;4:169–186.
8. Powers W. Hemodynamics and metabolism in ischemic cerebrovascular disease. *Neurol Clin.* 1992;10:31–48.
9. Toyoda K, Okada Y, Fujimoto S, Hagiwara N, Nakachi K, Kitazono T, et al. Blood pressure changes during the initial week after different subtypes of ischemic stroke. *Stroke.* 2006;37:2637–2639.
10. Toyoda K, Fujimoto S, Kamouchi M, Iida M, Okada Y. Acute blood pressure levels and neurological deterioration in different subtypes of ischemic stroke. *Stroke.* 2009;40:2585–2588.
11. Carlberg B, Asplund K, Hagg E. Factors influencing admission blood pressure levels in patients with acute stroke. *Stroke.* 1991;22:527–530.
12. Fotherby MD, Critchley D, Potter JF. Effect of hospitalization on conventional and 24-hour blood pressure. *Age Ageing.* 1995;24:25–29.
13. Coats AJ. Reproducibility or variability of casual and ambulatory blood pressure data: implications for clinical trials. *J Hypertens Suppl.* 1990;8: S17–S20.
14. Tsivgoulis G, Spengos K, Zakopoulos N, Manios E, Xinos K, Vassilopoulos D, et al. Twenty four hour pulse pressure predicts long term recurrence in acute stroke patients. *J Neurol Neurosurg Psychiatry.* 2005; 76:1360–1365.
15. Harper G, Fotherby MD, Panayiotou BJ, Castleden CM, Potter JF. The changes in blood pressure after stroke: abolishing the 'white coat effect' with 24 h ambulatory monitoring. *J Intern Med.* 1994;235:343–346.
16. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. *Stroke.* 1993;24:35–41.
17. Ogata J, Yutani C, Imakita M, Ishibashi-Ueda H, Saku Y, Minematsu K, et al. Hemorrhagic infarct of the brain without a reopening of the occluded arteries in cardioembolic stroke. *Stroke.* 1989;20:876–883.
18. Selim M, Fink JN, Kumar S, Caplan LR, Horkan C, Chen Y, et al. Predictors of hemorrhagic transformation after intravenous recombinant tissue plasminogen activator: prognostic value of the initial apparent diffusion coefficient and diffusion-weighted lesion volume. *Stroke.* 2002; 33:2047–2052.
19. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Kotsis V, et al. Association between 24-h blood pressure monitoring variables and brain oedema in patients with hyperacute stroke. *J Hypertens.* 2003; 21:2167–2173.
20. Mattle HP, Kappeler L, Arnold M, Fischer U, Nedeltchev K, Remonda L, et al. Blood pressure and vessel recanalization in the first hours after ischemic stroke. *Stroke.* 2005;36:264–268.
21. Delgado-Mederos R, Ribo M, Rovira A, Rubiera M, Munuera J, Santamarina E, et al. Prognostic significance of blood pressure variability after thrombolysis in acute stroke. *Neurology.* 2008;71:552–558.
22. Sandset EC, Bath PM, Boysen G, Jatuzis D, Kõrv J, Lüders S, et al; SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet.* 2011;377:741–750.
23. Okumura K, Ohya Y, Maehara A, Wakugami K, Iseki K, Takishita S. Effects of blood pressure levels on case fatality after acute stroke. *J Hypertens.* 2005;23:1217–1223.
24. Yong M, Diener HC, Kaste M, Mau J. Characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke. *Stroke.* 2005;36:2619–2625.
25. Cuffe RL, Howard SC, Algra A, Warlow CP, Rothwell PM. Medium-term variability of blood pressure and potential underdiagnosis of hypertension in patients with previous transient ischemic attack or minor stroke. *Stroke.* 2006;37:2776–2783.
26. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet Neurol.* 2010;375:938–948.
27. Jain S, Namboodri KK, Kumari S, Prabhakar S. Loss of circadian rhythm of blood pressure following acute stroke. *BMC Neurol.* 2004;1:1–6.
28. Castilla-Guerra L, Fernandez-Moreno Mdel C, Espino-Montoro A, Lopez-Chozas JM. Ambulatory blood pressure monitoring in stroke survivors: do we really control our patients? *Eur J Intern Med.* 2009;20: 760–763.
29. Dawson SL, Evans SN, Mankletow BN, Fotherby MD, Robinson TG, Potter JF. Diurnal blood pressure change varies with stroke subtype in the acute phase. *Stroke.* 1998;29:1519–1524.
30. Hansen TW, Thijs L, Boggia J, Li Y, Kikuya M, Björklund-Bodegård K, et al; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Prognostic value of ambulatory heart rate revisited in 6928 subjects from 6 populations. *Hypertension.* 2008;52:229–235.
31. Imai Y, Hozawa A, Ohkubo T, Ohmori K, Kikuya M, Hashimoto J, et al. Heart rate measurement and outcome. *Blood Press Monit.* 2003;8:53–55.
32. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population. Follow-up results from the Pressioni Arteriose Monitorate e Loro Associazione (PAMELA) Study. *Circulation.* 2005;111:1777–1783.
33. Kimura K, Kazui S, Minematsu K, Yamaguchi T; Japan Multicenter Stroke Investigator's Collaboration. Analysis of 16 922 patients with acute ischemic stroke and transient ischemic attack in Japan. A hospital-based prospective registration study. *Cerebrovasc Dis.* 2004;18: 47–56.
34. Kobayashi S, ed. *Stroke Databank 2009 (Japan Standard Stroke Registry Study)* [in Japanese]. Tokyo: Nakayama Shoten Co, Ltd; 2009.
35. Arboix A, Roig H, Rossich R, Martinez EM, Garcia-Eroles L. Differences between hypertensive and non-hypertensive ischemic stroke. *Eur J Neurol.* 2004;11:687–692.
36. Robinson TG, James M, Youde J, Panerai R, Potter J. Cardiac baroreceptor sensitivity is impaired after acute stroke. *Stroke.* 1997;28: 1671–1676.
37. Sykora M, Diedler J, Poli S, Rupp A, Turcani P, Steiner T. Blood pressure course in acute stroke relates to baroreflex dysfunction. *Cerebrovasc Dis.* 2010;30:172–179.
38. Hodgkinson J, Mant J, Martin U, Guo B, Hobbs FD, Deeks JJ, et al. Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review. *BMJ.* 2011;342:d3621.
39. Ohkubo T, Hozawa A, Nagai K, Kikuya M, Tsuji I, Ito S, et al. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens.* 2000;18:847–854.

Conceptual Design of High Spatial-Resolution SPECT System for Human Brain

Tsutomu Zeniya, Yoshiyuki Hirano, Takanori Tominaga, Yuki Hori, Hiroshi Watabe, *Member, IEEE*, Tomonori Sakimoto, Antti Sohlberg, Kotaro Minato, *Member, IEEE*, Jun Hatazawa, and Hidehiro Iida, *Member, IEEE*

I. Introduction

Recently, high spatial-resolution SPECT systems employing solid-state detectors are developed [1,2]. However, these are expensive. Here, we propose a compact and high-resolution brain SPECT system using NaI(Tl) scintillator coupled to photomultiplier tube (PMT) which is not expensive. In this paper, we design a concept of our high spatial-resolution SPECT system for human brain. This system is aimed at achieving high resolution less than 5 mm like PET.

II. Conceptual Design

A. High spatial-resolution detector

Improvement of precision of detection-position estimation is expected by using position-sensitive PMT (PSPMT) with multiple anodes of small diameter as shown in Fig. 1. The detector for human brain consists of an NaI(Tl) scintillator plate (Saint-Gobain) coupled to a 5× 3 array of a 2 inch flat panel PSPMT with 8 × 8 multiple anodes (H8500, Hamamatsu) (Fig. 2). Experiment by Hirano et al. demonstrated that intrinsic resolution of the detector is improved to 3.3 mm [3].

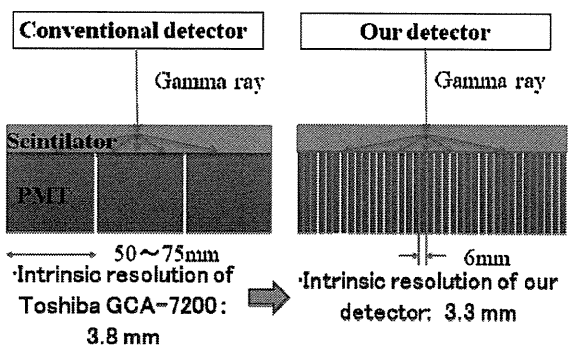


Fig. 1. Schematic diagram of improvement of precision of detection-position estimation by using PSPMTs with multiple anodes.

T. Zeniya, Y. Hirano, Y. Hori and H. Iida are with the Department of Investigative Radiology, National Cerebral and Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565-8565 Japan (e-mail: zeniya @ri.ncvc.go.jp).

T. Tominaga, T. Sakimoto and K. Minato are with the Graduate School of Information Science, Nara Institute of Science and Technology, Japan.

H. Watabe is with the Faculty of Molecular Imaging in Medicine, Osaka University Graduate School of Medicine, Japan.

J. Hatazawa is with the Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine, Japan.

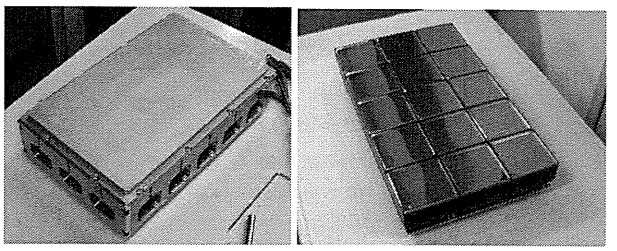


Fig. 2. NaI(Tl) scintillator plate of 250 mm× 150mm× 6.4 mm (Saint-Gobain) (left) and 5× 3 array of 2 inch flat panel PSPMT with 8× 8 multiple anodes (H8500, Hamamatsu).

The 3.3-mm intrinsic resolution of the detector above was not enough. To achieve detector intrinsic less than 2 mm, we combine PSPMTs with full-digital circuit which converts the outputs from all anodes to the digital signals. The digital calculation makes it possible to optimize the position-calculation logic of the detector. For example, use of local Anger logic can estimate the detection position with high S/N (Fig. 3). Hirano et al. proposed the method using reference dataset and their Monte-Carlo simulation showed spatial resolution of 1.8 mm [3].

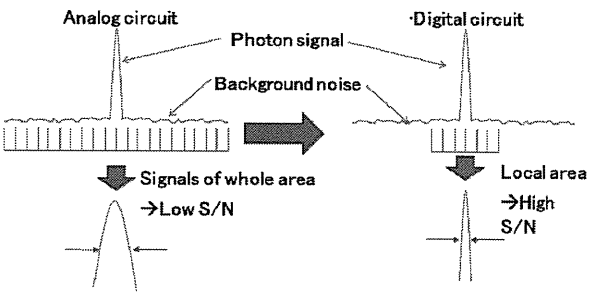


Fig. 3. Schematic diagram of improvement of resolution by local-area position calculation.

The size of the detector is 250 mm × 150 mm × 6.4 mm to view whole brain. For this detector, we are manufacturing three kinds of parallel-hole collimators as shown in Table I. Figure 4 shows parallel-hole collimator with 1.22-mm holes and 30-mm length. The geometrical detection efficiency of this collimator almost equals to that of Toshiba SPECT LEHR collimator. Theoretical system resolution was calculated using (1) and (2). Geometrical resolution of parallel-hole collimator R_g is expressed using (1).

978-1-4673-0119-0/11/$26.00 ©2011 IEEE

$$R_g = \frac{d(a_e + b + c)}{a_e} \quad (1)$$

where a_e is effective thickness of collimator: a_e=a-2/ μ , a is thickness of collimator, μ is attenuation coefficient of collimator material, b is distance between collimator surface and source, c is distance between collimator base and average detection position and d is hole diameter. And system resolution R_s is expressed using (2).

$$R_s \cong \sqrt{R_i^{\,2} + R_g^{\,2}} \quad (2)$$

where R_i is intrinsic resolution of detector. When a is 50 mm, μ is 2.92 mm^{-1} for lead at 140 keV, c is 2.24 mm for NaI of 6.4-mm thickness, d is 0.8 mm and R_i is 1.8 mm, the system resolution with varying b was shown as Fig. 5. Assuming Toshiba SPECT GCA-7200, the system resolution for R_i of 3.8 mm and LEHR collimator was plotted together for comparison. From Fig. 5, when ultra high resolution (UHR) is used, high system resolution of 3.4 mm at the radius of rotation of 130 mm can be theoretically achieved in this system.

TABLE I. TYPE OF OUR COLLIMATORS

Collimator type	Length (mm)	Hole diameter (mm)	Wall thickness (mm)
Standard	1.22	30	0.18
High resolution (HR)	0.8	30	0.18
Ultra high resolution (UHR)	0.8	50	0.18

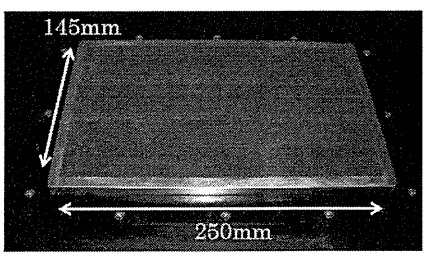


Fig. 4. Parallel-hole collimator for our detector.

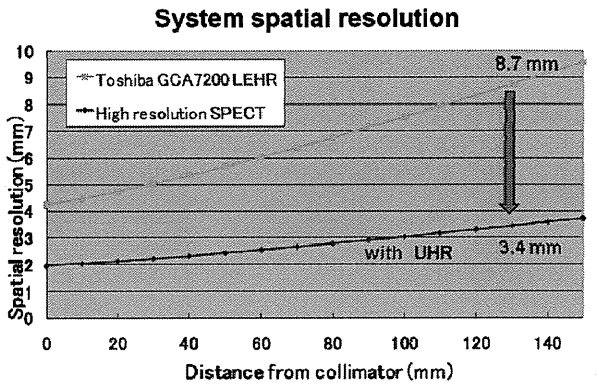


Fig. 5. The theoretical system resolutions of high-resolution SPECT system based on our conceptual design and Toshiba SPECT GCA 7200 with LEHR collimator.

B. Sensitivity improvement by reconstruction software with collimator response correction

However, the sensitivity of this collimator is low, approximately 12% of that of conventional collimator (e.g. LEHR) used in clinical SPECT system (Fig. 6). Here, the image reconstruction software with collimator response correction (CRC) is effective to overcome such a low sensitivity. Since it is capable of significantly suppressing statistical noise [4,5], the sensitivity can be increased. Figure 7 shows the effect of suppression of statistical noise. Three-dimensional brain phantom was scanned 12 times using clinical SPECT system (GCA-7200, Toshiba) with LEHR collimator. Data acquired were reconstructed by OSEM based image reconstruction software with/without CRC [3]. Images of coefficient of variance (COV) from 12 frames reconstructed were generated. The COV images generated with/without CRC were compared. The CRC decreased statistical-noise level to quarter. This means that the sensitivity can be increased by 16 times. Therefore, the CRC can recover the low sensitivity due to high resolution collimator.

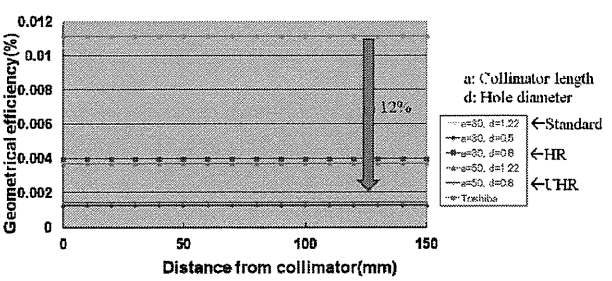


Fig. 6. Theoretical collimator geometrical detection efficiency.

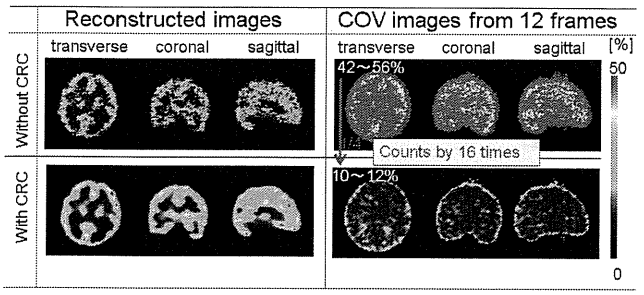


Fig. 7. The effect of suppression of statistical noise by OSEM based image reconstruction with collimator response correction.

C. *SPECT system under development*

We are developing high resolution SPECT system with two high-resolution detectors (Fig. 8). It is compact one of 1-m width and 1-m height.

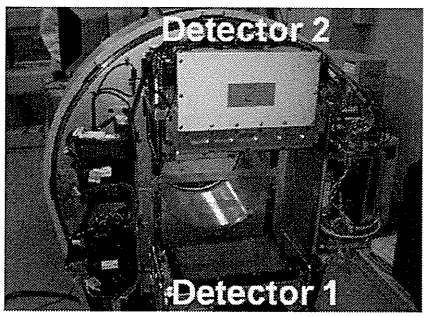


Fig. 8.Our high spatial-resolution SPECT system with two high-resolution detectors.

III. SUMMARY

We have designed the concept of practical high spatial-resolution SPECT for human brain. This study suggested combination PSPMTs with full-digital circuit can achieve detector intrinsic spatial resolution less than 2 mm. Image reconstruction software will compensate decrease of sensitivity due to collimator for high resolution. This system is expected to have the system resolution of 3-4 mm and the sensitivity higher than that in conventional clinical SPECT system.

REFERENCES

[1] K. Erlandsson, K. Kacperski, D. Gramberg and B. F. Hutton, "Performance evaluation of D-SPECT: a novel SPECT system for nuclear cardiology," *Phys. Med. Biol..*, vol. 54, pp. 2635-2649, 2009.

[2] K. Tsuchiya, I. Takahashi, T. Kawaguchi, K. Yokoi, Y. Morimoto, T. Ishitsu, A. Suzuki, Y. Ueno and K. Kobashi, "Basic performance and stability of a CdTe solid-state detector panel," *Ann. Nucl. Med.*, vol. 24, pp. 301-311, 2010.

[3] Y. Hirano, "Applications to development of PET/SPECT system by use of Geant4," in *Applications of Monte Carlo Methods in Biology, Medicine and Other Fields of Science,* C. J. Mode, Ed. InTech, 2011, pp. 77-94.

[4] G. L. Zeng, G. T. Gullberg, B. M. W. Tsui and J. A. Terry, "3-dimensional iterative reconstruction algorithms with attenuation and geometric point response correction," *IEEE Trans. Nucl. Sci.*, vol. 38, no. 2, pp. 693-702, 1991.

[5] T. Sakimoto, T. Zeniya, K. Ishida, H. Watabe, Y. Hirano, A. Sohlberg *et al.*, "Evaluation of the quantitative accuracy of a novel image reconstruction method with Monte Carlo-based scatter compensation and collimator blurring compensation for brain SPECT," *Med. Imag. Tech.*, vol. 28, no. 2, pp. 135-144, 2010.