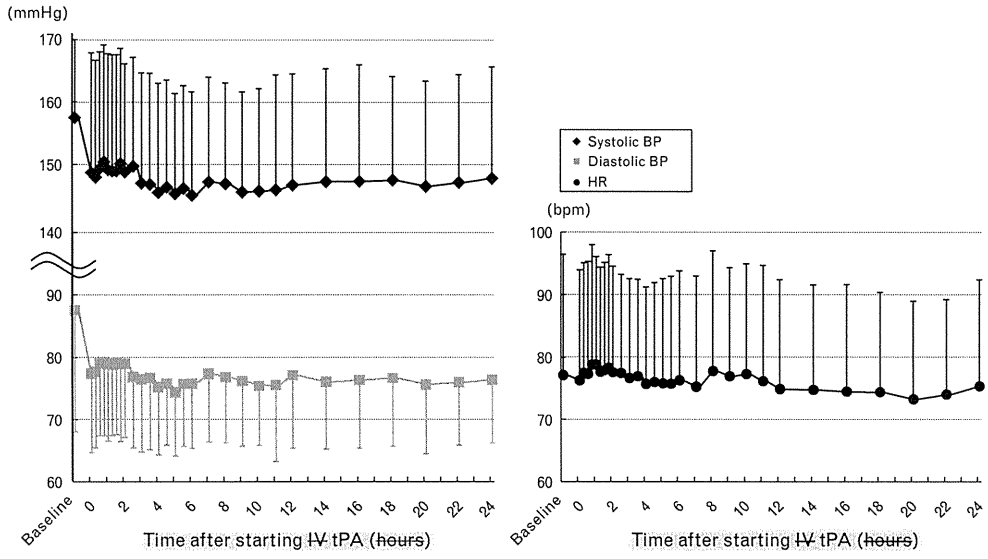
Fig. 1



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.

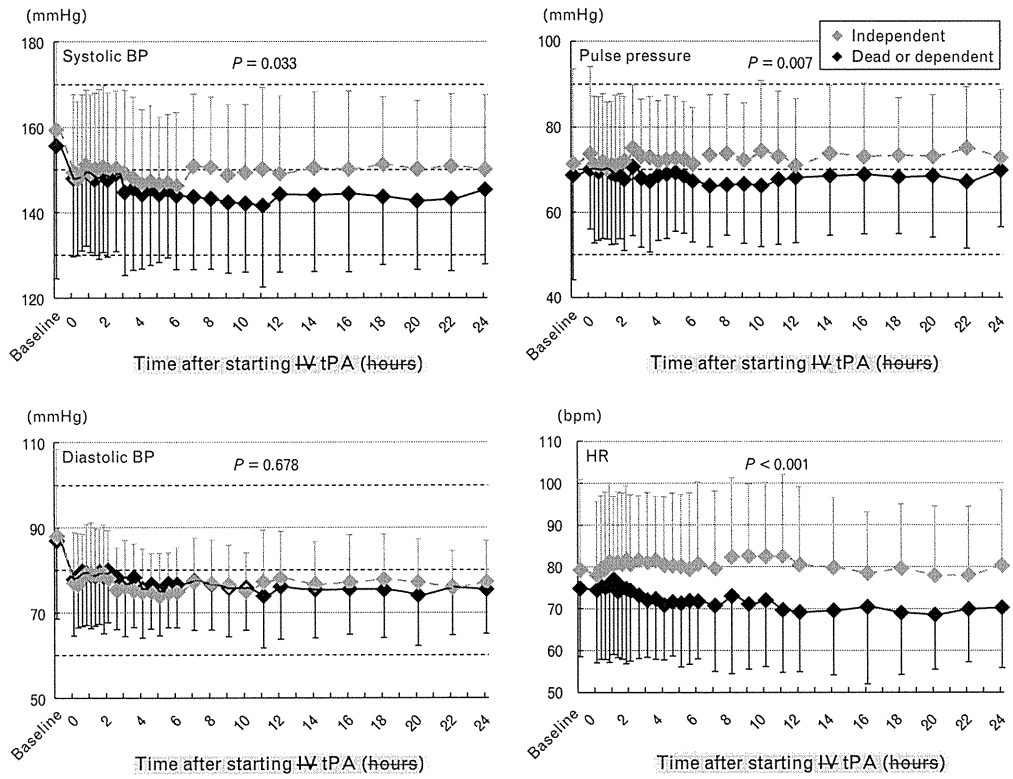
Discussion

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 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

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.

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].

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

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

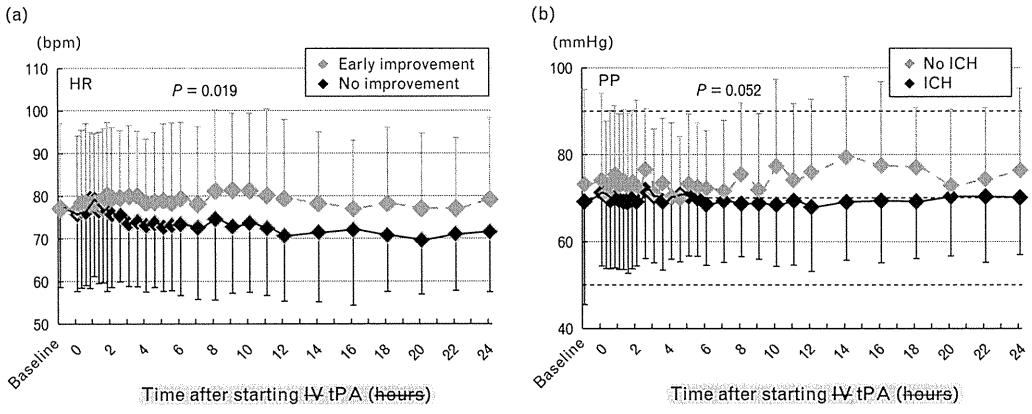
	3-month independence[§]		Early neurological improvement[‖]		ICH[‡]	
	OR	95% CI	OR	95% CI	OR	95% CI
SBP						
Baseline SBP	0.96	0.84–1.08	0.88*	0.77–0.98	1.03	0.89–1.19
Mean 24-h SBP	0.69*	0.48–0.97	0.79	0.58–1.06	1.34	0.91–2.06
Maximum 24-h SBP	0.67*	0.48–0.91	0.73*	0.55–0.95	1.50*	1.06–2.20
Minimum 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 ($P < 0.05$).

AQ4

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, 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].

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.

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.

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AQ3 ## Conflicts of interest

~~None declared.~~

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