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.

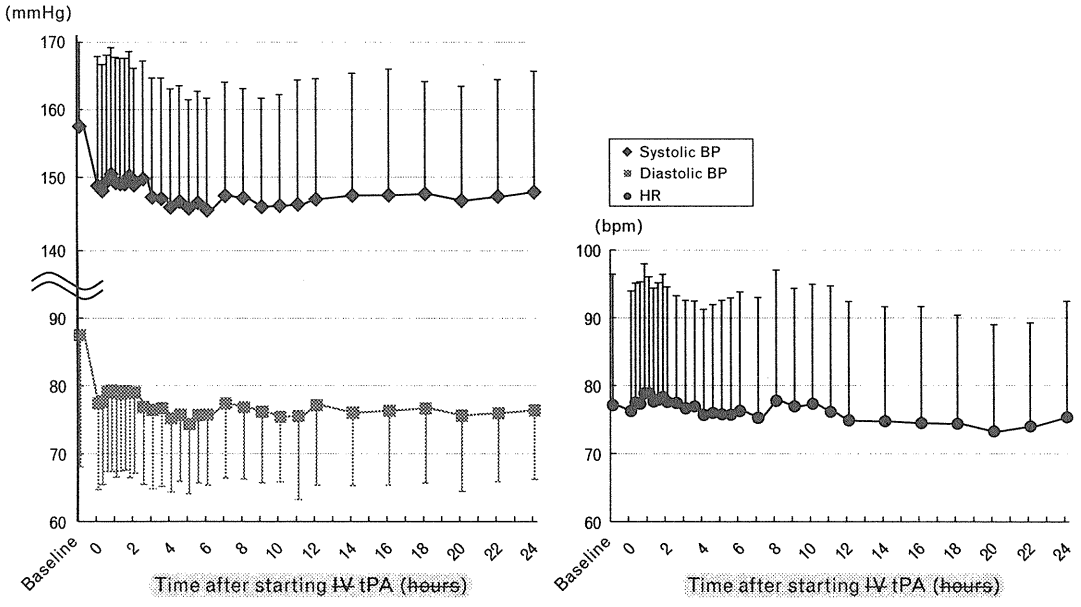
Between patients with and without ICH, the ANOVA did not identify differences in the 24-h time courses of SBP ($P=0.098$), PP ($P=0.052$; Fig. 3), DBP ($P=0.836$), or HR ($P=0.886$). After multivariate adjustment, maximum level and coefficient of variation of SBP ($P=0.028$ and $P=0.021$, respectively) and PP ($P=0.005$ and $P=0.013$, respectively) during the 24 h were positively associated with ICH.

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/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.

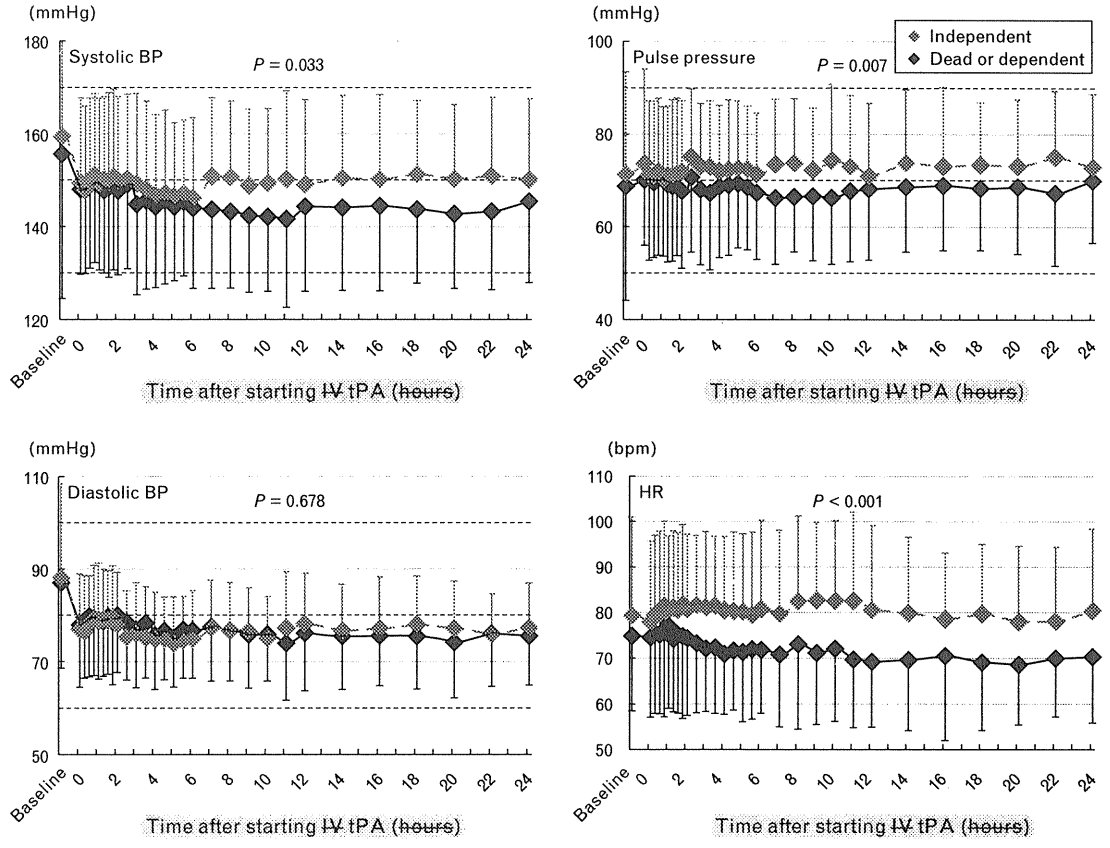
Discussion

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

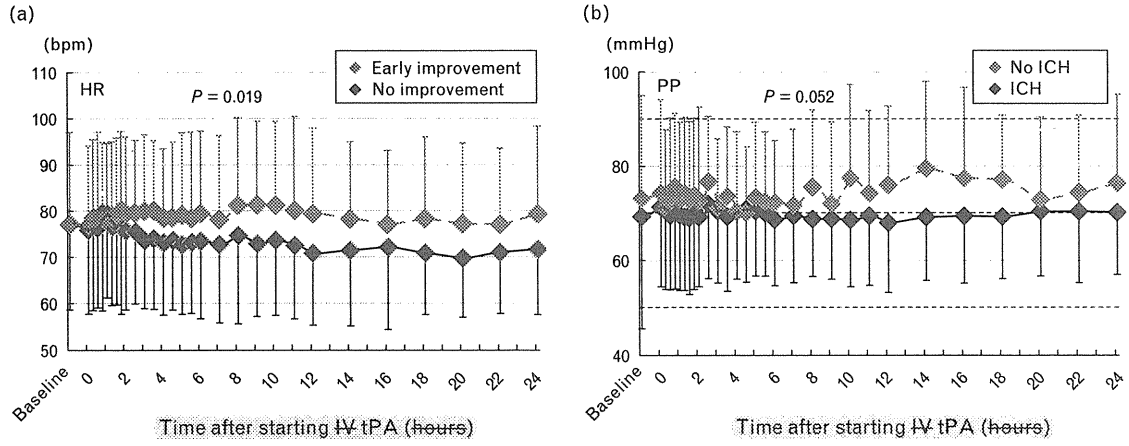
	3-month independence[§]		Early neurological improvement[†]		ICH[‡]	
	OR	95% CI	OR	95% CI	OR	95% CI
SBP						
Baseline SBP	0.96	0.84–1.08	0.88*	0.77–0.98	1.03	0.89–1.19
Mean 24-h SBP	0.69*	0.48–0.97	0.79	0.58–1.06	1.34	0.91–2.06
Maximum 24-h SBP	0.67*	0.48–0.91	0.73*	0.55–0.95	1.50*	1.06–2.20
Minimum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

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.

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

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

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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

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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

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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

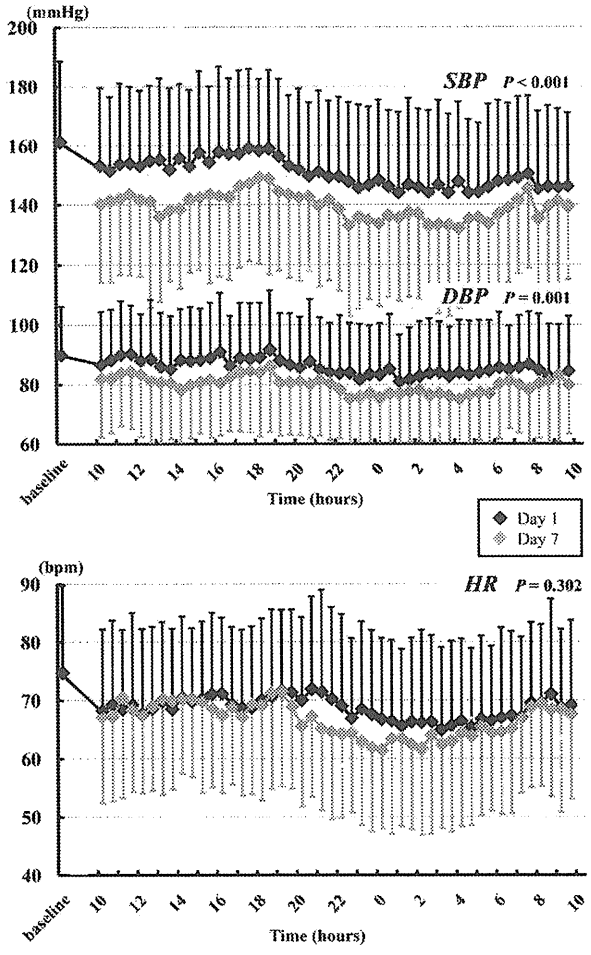

Figure 1. Changes in SBP, DBP, and HR over 24 hours on Days 1 and 7. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

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

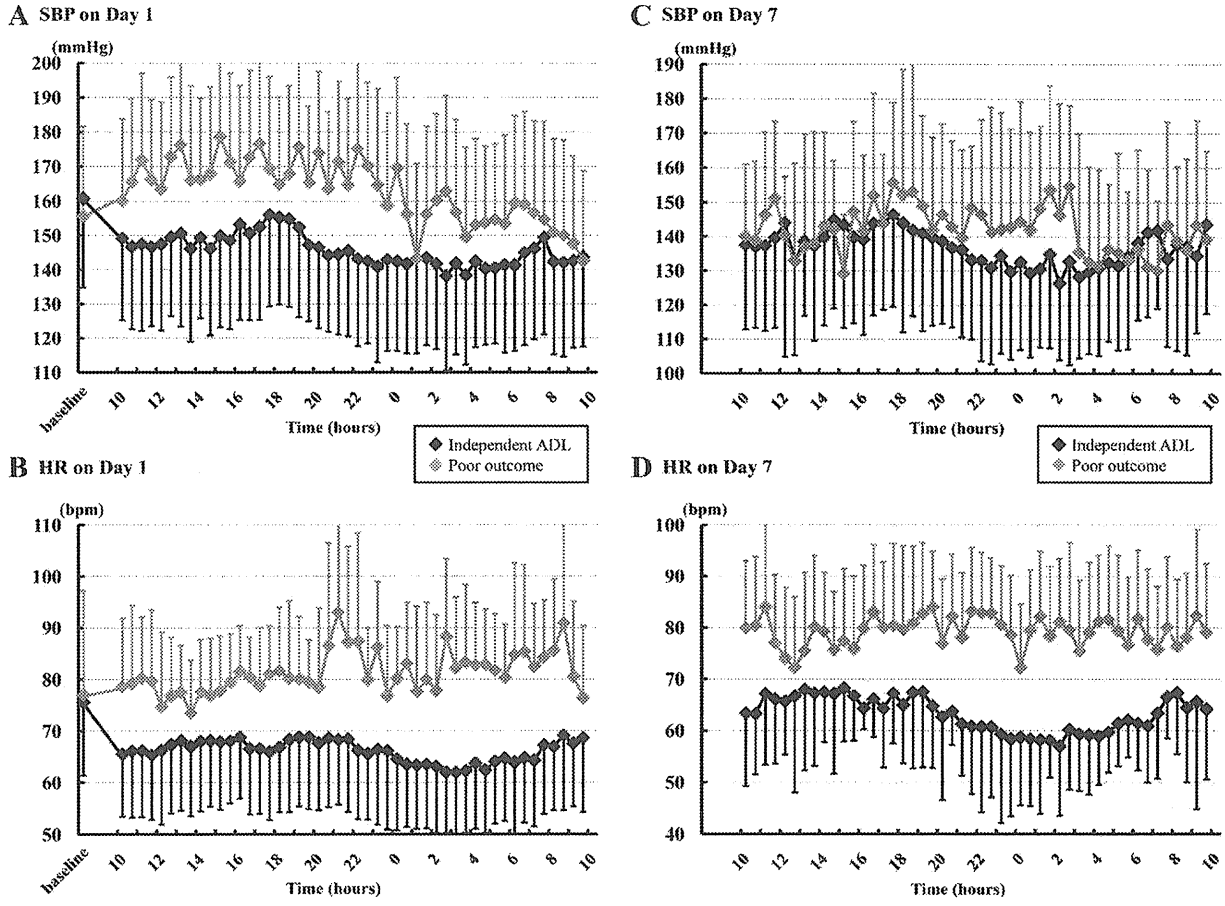

Figure 2. Changes in SBP and HR on Days 1 and 7 in patients who achieved independent ADL and those with poor outcomes. **A**, SBP on Day 1. $P<0.001$ between patients with and without independent ADL; $P=0.022$ between patients with and without poor outcomes. **B**, HR on Day 1. $P=0.003$ between patients 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

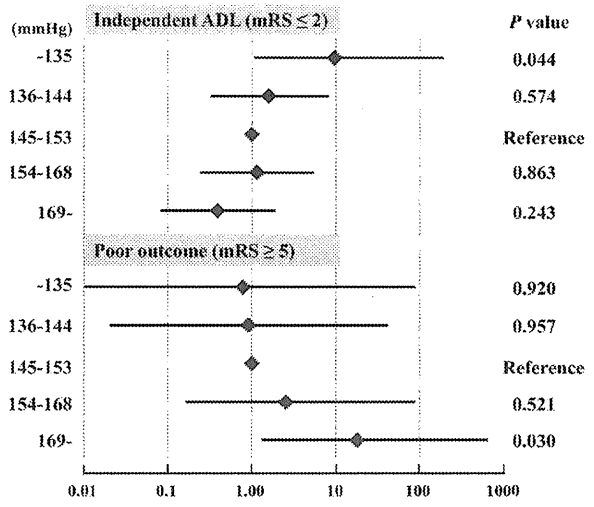

Figure 3. Multivariate-adjusted ORs and 95% CIs for 3-month outcomes among quintiles for mean 24-hour SBP levels on Day 1. Adjusted for age, previous ischemic stroke, and baseline NIHSS score. SBP indicates systolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin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

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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.

Age-Specific Differences in Outcomes After Out-of-Hospital Cardiac Arrests

WHAT'S KNOWN ON THIS SUBJECT: Recent data indicate that pediatric out-of-hospital cardiac arrests (OHCAs) are not rare, and survival rates are greater than those for adults. However, it remains unclear whether children are more likely to survive with favorable neurologic outcomes after OHCAs.

WHAT THIS STUDY ADDS: Pediatric patients with OHCAs had higher rates of survival with favorable neurologic outcomes than did adults. Outcomes and patient characteristics differed among age groups. This study's results suggest the importance of age-specific approaches to address this important public health problem.

AUTHORS: Masahiko Nitta, MD, PhD,[a,b] Taku Iwami, MD, PhD,[c] Tetsuhisa Kitamura, MD, MS, DPH,[c] Vinay M. Nadkarni, MD, MS,[d] Robert A. Berg, MD,[d] Naoki Shimizu, MD, PhD,[e] Kunio Ohta, MD, PhD,[f] Tatsuya Nishiuchi, MD, PhD,[g] Yasuyuki Hayashi, MD, PhD,[h] Atsushi Hiraide, MD, PhD,[i] Hiroshi Tamai, MD, PhD,[b] Masanao Kobayashi, MD, PhD,[a] and Hiroshi Morita, MD, PhD,[a] for the Utstein Osaka Project

Departments of [a]Emergency Medicine and [b]Pediatrics, Osaka Medical College, Takatsuki, Japan; [c]Kyoto University Health Service, Kyoto, Japan; [d]Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, Pennsylvania; [e]Department of Paediatric Emergency and Critical Care Medicine, Tokyo Metropolitan Children's Medical Center, Fuchu, Japan; [f]Department of Pediatrics, School of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan; [g]Department of Critical Care and Emergency Medicine, Graduate School of Medicine, Osaka City University, Osaka, Japan; [h]Senri Critical Care Medical Center, Osaka Saiseikai Senri Hospital, Suita, Japan; and [i]Department of Acute Medicine, Faculty of Medicine, Kinki University, Sayama, Japan

KEY WORDS
cardiac arrest, cardiopulmonary resuscitation, epidemiology, outcomes analysis

ABBREVIATIONS
OHCA—out-of-hospital cardiac arrest
EMS—emergency medical service
CPR—cardiopulmonary resuscitation
VF—ventricular fibrillation
PEA—pulseless electrical activity
CI—confidence interval
OR—odds ratio
VT—ventricular tachycardia
SIDS—sudden infant death syndrome

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Address correspondence to Masahiko Nitta, MD, PhD, Department of Emergency Medicine, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki City, Osaka 569-8686, Japan. E-mail: nittam@poh.osaka-med.ac.jp

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abstract

OBJECTIVE: We assessed out-of-hospital cardiac arrests (OHCAs) for various pediatric age groups.

METHODS: This prospective, population-based, observational study included all emergency medical service-treated OHCAs in Osaka, Japan, between 1999 and 2006 (excluding 2004). Patients were grouped as adults (>17 years), infants (<1 year), younger children (1–4 years), older children (5–12 years), and adolescents (13–17 years). The primary outcome measure was 1-month survival with favorable neurologic outcome.

RESULTS: Of 950 pediatric OHCAs, resuscitations were attempted for 875 patients (92%; 347 infants, 203 younger children, 135 older children, and 190 adolescents). The overall incidence of nontraumatic pediatric OHCAs was 7.3 cases per 100 000 person-years, compared with 64.7 cases per 100 000 person-years for adults and 65.5 cases per 100 000 person-years for infants. Most infant OHCAs occurred in homes (93%) and were not witnessed (90%). Adolescent OHCAs often occurred outside the home (45%), were witnessed by bystanders (37%), and had shockable rhythms (18%). One-month survival was more common after nontraumatic pediatric OHCAs than adult OHCAs (8% [56 of 740 patients] vs 5% [1677 of 33 091 patients]; adjusted odds ratio: 2.26 [95% confidence interval: 1.63–3.13]). One-month survival with favorable neurologic outcome was more common among children than adults (3% [21 of 740 patients] vs 2% [648 of 33 091 patients]; adjusted odds ratio: 2.46 [95% confidence interval: 1.45–4.18]). Rates of 1-month survival with favorable neurologic outcome were 1% for infants, 2% for younger children, 2% for older children, and 11% for adolescents.

CONCLUSION: Survival and favorable neurologic outcome at 1 month were more common after pediatric OHCAs than adult OHCAs. *Pediatrics* 2011;128:e812–e820

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death among adults in industrialized countries.[1] Extensive emergency medical service (EMS) systems have focused on improving outcomes for this major public health problem. However, pediatric OHCAs have engendered relatively less public health interest, in part because they have been considered rare events with dismal outcomes.[2]

More-recent data indicated that pediatric OHCAs are not so rare and children are more likely to survive OHCAs than are adults.[3–6] Importantly, those data did not include postresuscitation neurologic outcomes; therefore, it remains unclear whether children are more likely than adults to survive OHCAs with favorable neurologic outcomes.

The Utstein Osaka Project, which was launched in 1998, is a large, prospective, population-based, cohort study of OHCAs in Osaka, Japan, covering ~8.8 million residents with 1.4 million children (<18 years of age).[7,8] During the initial 7 years of this project, there were ~1000 EMS-assessed pediatric OHCAs. This study aims to elucidate epidemiological features of these pediatric OHCAs. We hypothesized that (1) children would be more likely to experience neurologically favorable 1-month survival after nontraumatic OHCAs, compared with adults, and (2) the incidences, characteristics, and outcomes of OHCAs would differ among pediatric age groups.

METHODS

Study Design, Setting, and Population

This observational study enrolled all EMS-treated pediatric and adult patients who suffered OHCAs in Osaka Prefecture between January 1, 1999, and December 31, 2006. Patients from 2004 were excluded from analyses because of differences in data collected that year. Osaka has an area of 1892 km^2 and both urban and rural communities. The population of Osaka in 2005 was 8 817 166, and 1 452 489 people (16%) were younger than 18 years.[9]

Cardiac arrest was defined as the cessation of cardiac mechanical activity, confirmed by the absence of signs of circulation.[10] The arrest was presumed to be of cardiac origin unless it was caused by trauma, drowning (submersion), drug overdose, foreign-body asphyxia, exsanguination, or any other noncardiac causes, according to the Utstein-style international guidelines.[10] These diagnoses were determined by the physician in charge in collaboration with the EMS rescuers. The research protocol was approved by the institutional review board of Osaka University, with the assent of the EMS authorities of the local governments in Osaka Prefecture.

EMS Systems in Osaka

In Osaka Prefecture, there were 34 fire stations with emergency dispatch centers in 2006. The EMS system is operated by the local fire stations. The most highly trained prehospital emergency care providers are emergency life-saving technicians, who are authorized to insert intravenous lines and adjunct airways and to use semiautomated external defibrillators for patients with OHCA. Specially trained emergency life-saving technicians were permitted to provide tracheal intubation for adults after July 2004 and to administer epinephrine intravenously for adults after April 2006.[11] However, they are not supposed to provide either tracheal intubation or intravenously administered epinephrine for children. The use of automated external defibrillators by citizens was legally approved in July 2004.[11] Do-not-resuscitate orders or living wills are not generally accepted in Japan, and EMS providers are not permitted to terminate resuscitation in the field.[12,13] Therefore, all patients with OHCAs who were treated by EMS personnel were transported to a hospital and were registered in this study. Details of the EMS system in Osaka were described previously.[14]

Data Collection and Quality Control

Data were collected prospectively by using a form that included all core data recommended in the Utstein-style reporting guidelines for cardiac arrests.[10] The initial rhythm was recorded and diagnosed by EMS personnel with semiautomated defibrillators on the scene and was confirmed by the physician who was responsible for online medical direction. The times of EMS call receipt and vehicle arrival at the scene were recorded automatically at the dispatch center. The times of collapse and initiation of bystander cardiopulmonary resuscitation (CPR) were obtained through EMS interviews with bystanders before departure from the scene. The time of defibrillation was recorded by the semiautomated defibrillator. Defibrillators were synchronized with the clock at the dispatch center, as were other relevant EMS time devices (eg, clocks and watches).

The data form was filled out by the EMS personnel in cooperation with the physicians in charge of the patient, transferred to the Osaka EMS Information Center, and then checked by the investigators. If the data sheet was incomplete, then the relevant EMS personnel were contacted and questioned and the data sheet was completed. All survivors were monitored for up to 1 month after the event by the EMS personnel and investigators, with the cooperation of the Osaka Medical Association and relevant local medical institutions.

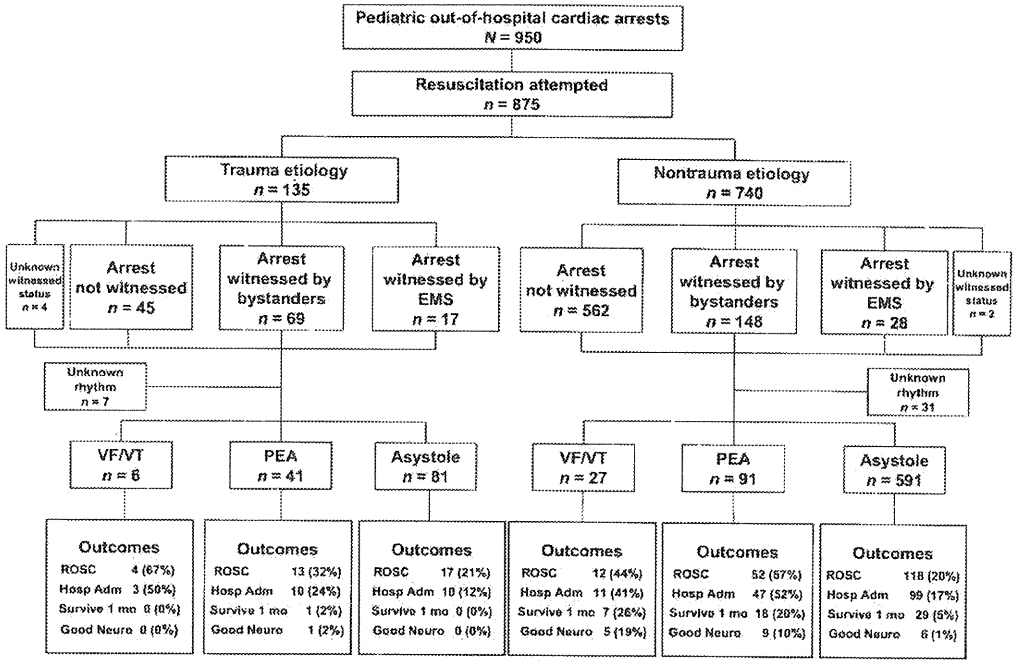

FIGURE 1
Utstein enrollment and outcomes of pediatric OHCAs. ROSC indicates return of spontaneous circulation; Hosp Adm, hospital admission; Good Neuro, good neurologic outcome.

Study End Points

Neurologic outcomes were assessed with the Glasgow-Pittsburgh Cerebral Performance Category scale (1 = good performance, 2 = moderate disability, 3 = severe cerebral disability, 4 = coma/vegetative state, and 5 = death).[15] The primary end point was a favorable neurologic outcome 1 month after OHCA, which was defined prospectively as a Cerebral Performance Category scale score of 1 or 2 or no change in the Cerebral Performance Category scale score from the prearrest baseline score.[16] Secondary outcome measures included return of spontaneous circulation, admission to the hospital, and 1-month survival.[10]

Statistical Analyses

Patient characteristics and outcomes were evaluated according to cause and age group. The cause of OHCA was initially categorized as traumatic or nontraumatic, and the latter category was subcategorized as cardiac, noncardiac (intracranial, respiratory, or other), injury (submersion, foreign-body asphyxia, hanging, drug overdose, or unknown), or unknown.[12] Patients were categorized into 1 of the following pediatric age groups: infants (<1 year of age; $n = 347$); younger children (1–4 years of age; $n = 203$); older children (5–12 years of age; $n = 135$); and adolescents (13–17 years of age; $n = 190$). Adults were defined as older than 17 years ($n = 35\,140$).[4,8,16–18] The denominators for annual incidences of OHCA were derived from 2005 Japanese census data.[9]

Continuous variables were evaluated with unpaired t tests and categorical variables with χ^2 tests. Multivariate logistic regression analyses were used to assess the factors associated with better neurologic outcomes. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. We adjusted for potential confounders including age, gender, location of arrest, activities of daily living before arrest, bystander-witnessed status, bystander CPR status, first documented rhythm, and time interval from the call to the initiation of CPR by EMS personnel. All of the tests were 2-tailed, and P values of $<.05$ were considered statistically significant. All statistical analyses were performed by using SPSS 16.0J (SPSS, Chicago, IL).

RESULTS

Overall Characteristics and Rates

During these 7 years, 950 pediatric OHCAs (subjects <18 years of age) were documented, and resuscitation was attempted by EMS personnel in 875 cases (92%). Figure 1 shows an overview of the EMS-treated pediatric OHCAs, with the outcomes, according to cause, witness status, and first documented rhythm. Of 740 OHCAs with nontraumatic causes (85%), 148 (20%) were witnessed by bystanders. Among the 740 nontraumatic OHCAs, the first

TABLE 1 Incidence Rates of OHCAs According to Age Group

	All Pediatric Patients, 0–17 y (N = 1 452 489)	Infants, <1 y (N = 72 824)	Younger Children, 1–4 y (N = 319 855)	Older Children, 5–12 y (N = 658 585)	Adolescents, 13–17 y (N = 399 225)	Adults, >17 y (N = 7 306 544)
All						
No. of cases	875	347	203	135	190	35 140
Incidence, estimate (95% CI), cases per 100 000 person-y	8.6 (7.6–9.6)	66.3 (55.9–76.6)	9.1 (7.1–11.0)	2.9 (2.5–3.4)	6.8 (6.0–7.6)	68.7 (64.0–73.4)
Nontraumatic						
No. of cases	740	343	172	117	108	33 091
Incidence, estimate (95% CI), cases per 100 000 person-y	7.3 (6.4–8.2)	65.5 (55.1–75.9)	7.7 (6.1–9.3)	2.5 (2.1–3.0)	3.9 (3.4–4.4)	64.7 (60.2–69.2)
Traumatic						
No. of cases	135	4	31	18	82	2049
Incidence, estimate (95% CI), cases per 100 000 person-y	1.3 (1.2–1.5)	0.8 (0.0–1.6)	1.4 (0.6–2.2)	0.4 (0.3–0.5)	2.9 (2.4–3.4)	4.0 (3.7–4.4)

documented rhythms were ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) in 27 cases (4%), pulseless electrical activity (PEA) in 91 cases (12%), and asystole in 591 cases (80%). Among the traumatic OHCAs, 69 (51%) were witnessed by bystanders; the first documented rhythms were VF/VT in 6 cases (4%), PEA in 41 cases (30%), and asystole in 81 cases (60%).

Among patients with nontraumatic OHCAs, rates of 1-month survival with neurologically favorable outcomes after VF/VT, PEA, and asystole were 19%, 10%, and 1%, respectively. Among patients with traumatic OHCAs, only 1 (1%) survived with a neurologically favorable outcome. Among 875 eligible victims, we could not obtain data on gender for 2 (<1%), witnessed status for 6 (1%), bystander CPR for 17 (2%), cause for 5 (1%), first documented rhythm for 38 (4%), return of spontaneous circulation for 6 (1%), 1-month survival for 17 (2%), and neurologic outcome for 1 (<1%). For OHCAs with a nontraumatic cause, we could not obtain detailed information on cause for 5 victims.

Event Characteristics According to Age Group

The mean annual, population-based, incidence rates of EMS-treated OHCAs (traumatic and nontraumatic) according to age group are shown in Table 1. The overall annual incidence rate for pediatric OHCAs was 8.6 cases per 100 000 person-years (95% CI: 7.6–9.6 cases per 100 000 person-years), and the overall annual incidence rate for adult OHCAs was 68.7 cases per 100 000 person-years (95% CI: 64.0–73.4 cases per 100 000 person-years). The pediatric and adult annual incidence rates of nontraumatic OHCAs were 7.3 cases per 100 000 person-years (95% CI: 6.4–8.2 cases per 100 000 person-years) and 64.7 cases per 100 000 person-years (95% CI: 60.2–69.2 cases per 100 000 person-years), respectively. The incidences of nontraumatic OHCAs were 65.5 cases per 100 000 person-years (95% CI: 55.1–75.9 cases per 100 000 person-years) among infants, 7.7 cases per 100 000 person-years (95% CI: 6.1–9.3 cases per 100 000 person-years) among younger children, 2.5 cases per 100 000 person-years (95% CI: 2.1–3.0 cases per 100 000 person-years) among older children, and 3.9 cases per 100 000 person-years (95% CI: 3.4–4.4 cases per 100 000 person-years) among adolescents.

Table 2 shows the causes of EMS-treated OHCAs according to age group. Overall, pediatric victims had a significantly smaller proportion of OHCAs with presumed cardiac causes, compared with adults (30% vs 58%; OR: 0.53 [95% CI: 0.48–0.58]). The proportions of OHCAs with presumed cardiac causes were 34% for infants, 31% for younger children, 30% for older children, and 25% for adolescents. The proportions of OHCAs attributable to respiratory causes, submersion, or foreign-body asphyxia (ie, all primary respiratory arrest–precipitated cardiac arrests) were greater among children than among adults (30% vs 16%; OR: 1.86 [95% CI: 1.67–2.06]). The proportions of pediatric OHCAs precipitated by respiratory arrest were 36% for infants, 35% for younger children, 29% for older children, and 14% for adolescents.

Patient Characteristics

Characteristics of patients with OHCAs with nontraumatic causes, according to age group, are presented in Table 3. For all pediatric age ranges (0–17 years), 59% (436 of 740 cases) of nontraumatic OHCAs occurred in boys. Most infants suffered OHCAs at home (93%) and without witnesses (90%). Adolescent OHCAs often occurred out of the home (45%), often were witnessed by bystanders

TABLE 2 Causes of OHCAs According to Age Group

	n (%)					
	All Pediatric Patients (*N* = 875)	Infants (*N* = 347)	Younger Children (*N* = 203)	Older Children (*N* = 135)	Adolescents (*N* = 190)	Adults (*N* = 35 140)
Nontraumatic						
Cardiac	266 (30)	117 (34)	62 (31)	40 (30)	47 (25)	20 349 (58)
Noncardiac						
Intracranial event	27 (3)	6 (2)	11 (5)	8 (6)	2 (1)	1444 (4)
Respiratory[a]	82 (9)	36 (10)	22 (11)	13 (10)	11 (6)	2423 (7)
Other	114 (13)	72 (21)	15 (7)	18 (13)	9 (5)	3118 (9)
Injury						
Submersion[a]	41 (5)	3 (1)	18 (9)	12 (9)	8 (4)	1106 (3)
Asphyxia[a]	138 (16)	86 (25)	31 (15)	13 (10)	8 (4)	2124 (6)
Hanging	22 (3)	2 (1)	0 (0)	6 (4)	14 (7)	1900 (5)
Drug overdose	16 (2)	0 (0)	6 (3)	5 (4)	5 (3)	186 (1)
Unknown	29 (3)	17 (5)	6 (3)	2 (1)	4 (2)	258 (1)
Unknown	5 (1)	4 (1)	1 (0)	0 (0)	0 (0)	183 (1)
Traumatic						
Fall	43 (5)	3 (1)	10 (5)	1 (1)	29 (15)	1023 (3)
Traffic injury	92 (11)	1 (0)	21 (10)	17 (13)	53 (28)	1026 (3)

[a] All cases in these categories were primary respiratory arrest–precipitated OHCAs

TABLE 3 Characteristics of Nontraumatic OHCAs According to Age Group

	All Pediatric Patients (*N* = 740)	Infants (*N* = 343)	Younger Children (*N* = 172)	Older Children (*N* = 117)	Adolescents (*N* = 108)	Adults (*N* = 33 091)
Male, *n* (%)	436 (59)	193 (56)	103 (60)	68 (58)	72 (67)	19 411 (59)
OHCA occurred at home, *n* (%)	619 (84)	320 (93)	150 (87)	90 (77)	59 (55)	23 675 (72)
Witness status, *n* (%)						
Bystander-witnessed	148 (20)	27 (8)	45 (26)	36 (31)	40 (37)	11 425 (35)
EMS personnel-witnessed	28 (4)	6 (2)	8 (5)	4 (3)	10 (9)	2496 (8)
Not witnessed	562 (76)	310 (90)	118 (69)	76 (65)	58 (54)	19 106 (58)
Unknown	2 (0)	0 (0)	1 (1)	1 (1)	0 (0)	64 (0)
Bystander CPR, *n* (%)	302 (41)	152 (44)	53 (31)	56 (49)	41 (38)	9143 (28)
First documented rhythm, *n* (%)						
VF/VT	27 (4)	3 (1)	2 (1)	3 (3)	19 (18)	2529 (8)
PEA	91 (12)	34 (10)	25 (15)	21 (18)	11 (10)	6241 (19)
Asystole	591 (80)	286 (83)	142 (83)	88 (75)	75 (69)	23 490 (71)
Unknown	31 (4)	20 (6)	3 (2)	5 (4)	3 (3)	595 (2)
Interval from call to CPR by EMS personnel, median (interquartile range), min	7 (6–9)	7 (6–9)	7 (6–8)	8 (6–11)	7 (5–9)	7 (6–9)

(37%), and had VF/VT as the first documented rhythm in 18% of cases. Bystander CPR was provided for 41% of pediatric OHCAs, compared with 28% of adult OHCAs (OR: 1.85 [95% CI: 1.59–2.14]).

Survival Outcomes

Outcomes after nontraumatic OHCAs, according to age group and first documented rhythm, are shown in Table 4. Overall 1-month survival after nontraumatic OHCA was more common among children than among adults (8% [56 of 740 patients] vs 5% [1677 of 33 091 patients]; unadjusted OR: 1.48 [95% CI: 1.15–1.91]; adjusted OR: 2.26 [95% CI: 1.63–3.13]). One-month survival rates after nontraumatic OHCAs were 5% for infants, 9% for younger children, 7% for older children, and 14% for adolescents. Neurologically favorable 1-month survival also was more common among children, compared with adults (3% [21 of 740 patients] vs 2% [648 of 33 091 patients]; unadjusted OR: 1.46 [95% CI: 0.94–2.28]; adjusted OR: 2.46 [95% CI: 1.45–4.18]). Neurologically favorable 1-month survival rates after nontraumatic OHCAs were 1% for infants, 2% for younger children, 2% for older children, and 11% for adolescents. Among 56 patients who survived 1 month, 21 (38%) survived with favorable neurologic outcomes.

The rates of 1-month survival with neurologically favorable outcomes after VF were 19% (5 of 27 patients) among all children and 11% (285 of 2529 patients) among adults (unadjusted OR: 1.79 [95% CI: 0.67–4.76]). The rate of neurologically favorable 1-month survival after PEA was higher among all children than among adults (10% [9 of 91 patients] vs 3% [211 of 6241 patients]; unadjusted OR: 3.14 [95% CI:

TABLE 4 Outcomes After Nontraumatic OHCAs According to Age Group and First Documented Rhythm

	n (%)					
	All Pediatric Patients	Infants	Younger Children	Older Children	Adolescents	Adults
All	740	343	172	117	108	33 091
ROSC	190 (26)	68 (20)	48 (28)	37 (32)	37 (34)	9754 (30)
1-mo survival	56 (8)	18 (5)	15 (9)	8 (7)	15 (14)	1677 (5)
Neurologically favorable outcome	21 (3)	4 (1)	3 (2)	2 (2)	12 (11)	648 (2)
VF/VT	27	3	2	3	19	2529
ROSC	12 (44)	3 (100)	0 (0)	2 (67)	7 (37)	1202 (46)
1-mo survival	7 (26)	1 (33)	0 (0)	0 (0)	6 (32)	525 (21)
Neurologically favorable outcome	5 (19)	0 (0)	0 (0)	0 (0)	5 (26)	285 (11)
PEA	91	34	25	21	11	6241
ROSC	52 (57)	17 (50)	16 (64)	11 (52)	8 (73)	2658 (43)
1-mo survival	18 (21)	5 (15)	6 (24)	3 (14)	4 (36)	515 (8)
Neurologically favorable outcome	9 (10)	2 (6)	3 (12)	1 (5)	3 (27)	211 (3)
Asystole	591	286	142	88	75	23 490
ROSC	118 (20)	45 (16)	31 (22)	22 (25)	20 (27)	5484 (23)
1-mo survival	29 (5)	12 (4)	9 (6)	4 (5)	4 (5)	533 (2)
Neurologically favorable outcome	6 (1)	2 (1)	0 (0)	1 (1)	3 (4)	100 (0)

ROSC indicates return of spontaneous circulation.

1.56–6.33]). The rates of neurologically favorable 1-month survival after PEA for infants, younger children, older children, and adolescents were 6%, 12%, 5%, and 27%, respectively.

Table 5 shows adjusted ORs and their 95% CIs for neurologically favorable outcomes after nontraumatic OHCAs. Adolescents were more likely to have favorable neurologic outcomes than were adults (11% vs 2%; adjusted OR: 5.44 [95% CI: 2.55–11.58]). In contrast, the rates of favorable neurologic outcomes among infants, younger children, and older children were not demonstrably different from the frequency among adults. Favorable neurologic outcomes were associated with VF/VT in comparison with asystole (adjusted OR: 14.51 [95% CI: 11.09–19.00]), PEA in comparison with asystole (adjusted OR: 4.43 [95% CI: 3.40–5.76]), and shorter time to CPR by EMS personnel (adjusted OR for 1-minute increase: 0.81 [95% CI: 0.78–0.84]).

TABLE 5 Factors Contributing to Neurologically Favorable Outcomes After Nontraumatic OHCAs

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Male	1.40 (1.19–1.46)	0.92 (0.76–1.12)
Good activities of daily living[a]	2.63 (2.09–3.31)	1.89 (1.46–2.44)
OHCA occurred at home	0.24 (0.20–0.28)	0.56 (0.46–0.68)
Bystander-witnessed	2.29 (1.96–2.67)	2.47 (1.99–3.07)
Bystander-initiated CPR	0.89 (0.75–1.06)	1.15 (0.94–1.42)
Interval from call to CPR by EMS personnel[b]	0.80 (0.78–0.82)	0.81 (0.78–0.84)
Initial rhythm		
Asystole	Reference	Reference
PEA	8.14 (6.45–10.28)	4.43 (3.40–5.76)
VF/VT	28.94 (23.08–36.31)	14.51 (11.09–19.00)
Cardiac cause	1.81 (1.52–2.15)	0.96 (0.77–1.19)
Age group		
Adults (>17 y)	Reference	Reference
Infants (<1 y)	0.59 (0.22–1.59)	1.13 (0.28–4.66)
Younger children (1–4 y)	0.89 (0.28–2.79)	1.42 (0.34–5.97)
Older children (5–12 y)	0.87 (0.22–3.53)	1.46 (0.33–6.38)
Adolescents (13–17 y)	6.32 (3.45–11.59)	5.44 (2.55–11.58)

[a] Good activities of daily living were defined as performance of age-appropriate and premorbid condition–appropriate daily self-care activities within a person's place of residence.
[b] OR for 1-minute increase in time.

DISCUSSION

This large-scale, population-based, cohort study establishes that pediatric victims of OHCAs had higher survival rates and higher rates of survival with favorable neurologic outcomes 1 month after resuscitation, compared with adults. In addition, epidemiological characteristics and outcomes for pediatric OHCAs differed according to age group. In particular, only adolescents had better outcomes than adults.

Among adolescents, 45% of OHCAs occurred outside the home, 46% were witnessed, and 18% had VF as the first documented rhythm. Favorable neurologic outcomes were most common in this age group, compared with younger age groups or adults. Interestingly, adolescents were more likely to survive with neurologically favorable outcomes, compared with other age groups, irrespective of the initial rhythm. The adjusted OR for survival with a neurologically favorable outcome for adolescents was 5.4 times that for adults, with controlling for other potentially confounding factors including initial rhythm. Perhaps adolescents are physiologically more fit