Efficacy of Cilostazol in Prevention of Bradycardia during Carotid Artery Stenting

Daizo Ishii, MD,* Tetsu Satow, MD, PhD,* Kenichi Murao, MD, PhD,† Kunihiro Nishimura, MD, PhD,‡ and Koji Iihara, MD, PhD*

Background: Hypotension and bradycardia are known to occur frequently in carotid artery stenting (CAS), which may lead to postprocedural complications. The purpose of this retrospective study was to assess the efficacy of cilostazol, a phosphodiesterase 3 inhibitor, for preventing bradycardia and hypotension in the periprocedural period. *Methods:* The study population comprised 53 patients (54 lesions) with carotid artery stenosis who underwent CAS at our institution between 2004 and 2008. The patients were categorized by the use (group C, n = 26) or nonuse of cilostazol (group N, n = 28). The incidences of intraprocedural and postprocedural hypotension and bradycardia in each group were statistically assessed. *Results:* Intraprocedural hypotension and bradycardia occurred in 9 cases (34.6%) and 4 cases (15.3%) in group C and in 5 cases (17.9%) and 15 cases (53.6%) in group N, respectively. Postprocedural hypotension and bradycardia occurred in 4 cases (15.4%) and 0 cases in group C and in 1 case (3.6%) and 3 cases (10.7%) in group N, respectively. The incidence of intraprocedural bradycardia (IBc) was significantly lower in group C ($P = .0035$). Logistic regression analysis revealed that the use of cilostazol decreased the risk of IBc 99.5% (odds ratio [OR] = .01, 95% confidence interval [CI]: 5.46×10^{-6} to .04, $P = .001$) and distance from carotid bifurcation to maximum stenotic lesion was independently associated with IBc (OR = .46, 95% CI: .29-.74, $P = .001$). *Conclusion:* Use of cilostazol was associated with a lower incidence of IBc. Cilostazol may be a useful drug for the prevention of this complication. **Key Words:** Bradycardia—carotid artery stenting—cilostazol—hypotension.

Introduction

Carotid artery stenting (CAS) is indicated as an alternative to carotid endarterectomy for symptomatic patients at average or low risk of complications associated with endovascular intervention.[1] It is well recognized that hemodynamic instability (hypertension, hypotension, and bradycardia) often occurs after carotid endarterectomy, which may lead to postprocedural complications such as stroke or ischemic heart disease. Several risk factors, such as distance between bifurcation and maximum stenotic lesion, calcification at carotid bifurcation, and history of myocardial infarction,[2] have been documented. However, there are no reports regarding the relationship between preprocedural medication and hemodynamic instability in the periprocedural period for CAS. In this retrospective study, the efficacy of cilostazol for preventing bradycardia and hypotension during and after CAS was assessed.

Patients and Methods

Between January 2004 and March 2008, 53 patients (54 lesions) with carotid artery stenosis underwent CAS.

From the *Department of Neurosurgery, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan;; †Department of Neuroendovascular Therapy, Shiroyama Hospital, Osaka, Japan; and ‡Department of Preventive Medicine and Epidemiologic Informatics, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan.

Received March 19, 2013; revision received May 28, 2013; accepted June 7, 2013.

Address correspondence to Daizo Ishii, MD, Department of Neurosurgery, National Cerebral and Cardiovascular Center, 5-7-1, Fujishirodai, Suita, Osaka 565-8565, Japan. E-mail: zokun@xd6.so-net.ne.jp.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2013.06.011

The average age was 72.3 (59-86), and 49 were men. All patients received dual antiplatelet therapy (DAPT) before the procedure. The combination of drugs for DAPT was decided in the following manner: (1) for patients who had already received DAPT before referral, their prescription was continued (aspirin 100mg and cilostazol 200mg daily: 14 cases, aspirin 100mg and ticlopidine 200mg: 17 cases, aspirin 100mg and clopidogrel 75mg: 2 cases), (2) for patients who only received aspirin 100mg at the time of referral, cilostazol 200mg (12 cases) was added until 2006, and clopidogrel 75mg (5 cases) was used thereafter as an adjuvant, and (3) for patients who only received ticlopidine 200mg (3 cases) or clopidogrel 75mg (1 case) at the time of referral, aspirin 100mg was added before the procedure. DAPT was continued for at least 3 months postoperatively, followed by a single antiplatelet therapy with aspirin for another 3 months in most case. In some cases with prior coronary artery disease and/or peripheral artery disease, DAPT was continued if necessary.

For the assessment of carotid artery plaque, preoperative carotid artery magnetic resonance imaging using 3-dimensional inversion-recovery–based T1-weighted imaging (magnetization-prepared rapid acquisition gradient-echo [MPRAGE][3]) was performed. The signal intensity of the carotid artery plaque on MPRAGE sequences was classified as "high" when the intensity was more than 200% that of the adjacent muscle.

Procedure

An 8F guiding catheter was introduced via the femoral artery. During the procedure, heparin was intra-arterially and intravenously administered to achieve an activated clotting time of more than 250 seconds. In all, .25 mg of atropine sulfate was administered before predilatation for prophylaxis to prevent bradycardia and hypotension. PercuSurge balloon catheter (Medtronic, Inc., Minneapolis, MN) was used as a device to protect against distal embolism. Predilatation was performed with a balloon catheter (3.5-4.0 mm). A self-expandable stent with a small-cell design was used for the stenting. Stents used in this series were PRECISE (Cordis Endovascular, Miami Lakes, FL) in 29 patients, SMARTeR (Cordis Endovascular, Miami Lakes, FL) in 15 patients, PROTÈGÈ (ev3, Inc., Plymouth, MN) in 5 patients, XPert (Abbott Vascular, Santa Clara, CA) in 2 patients, Wallstent (Boston Scientific Corporation, Natick, MA) in 1 patient, PENTA (Abbott Vascular, Santa Clara, CA) in 1 patient, and Multilink Zeta (Abbott Vascular, Santa Clara, CA) in 1 patient. In cases in which more than 50% remaining stenosis according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria was observed after stenting, postdilatation was performed. If residual stenosis was less than 50% or the plaque was vulnerable, which was defined as a high-intensity lesion detected by MPRAGE, postdilatation was not carried out. The definitions of bradycardia and hypotension were 50 beats per minute and less than 90 mm Hg (systolic blood pressure), respectively. In cases of intraprocedural bradycardia (IBc), .25-.50 mg of atropine sulfate was used, and in intraprocedural hypotension (IHo), 1-4 mg of etilefrine was administered.

Patients were divided into 2 groups: those who were prescribed cilostazol (group C, n = 26) and those who were not (group N, n = 28). Changes of blood pressure and heart rate were measured via an invasive arterial catheter in the radial artery and an electrocardiogram monitor during and after the procedure.

Statistical Analyses

All statistical analyses were performed using JMP version 9.0 (SAS Institute, Cary, NC) and STATA version 11(STATA Corp, College Station, TX). Values are presented as the mean ± SD. Categorical variables were compared by Fisher exact probability test. Continuous variables with normal distributions were analyzed by Student *t* test and those with non-normal distributions were analyzed by the Mann–Whitney *U* test. The incidences of intraprocedural and postprocedural bradycardia and hypotension were calculated, and statistical analyses were performed among subgroups sorted by the use or nonuse of cilostazol. Furthermore, IBc was tested using age, sex, distance from carotid bifurcation to maximum stenotic lesion, side of the lesion, history of coronary artery disease, postdilatation, calcification at the carotid bifurcation, and cilostazol using univariate and multivariate analyses by logistic regression. Stepwise logistic regression with backward elimination was used to select the most significant predictors. Statistical significance was defined as a *P* value less than .05.

Results

Successful dilation of the carotid lesion was obtained in all patients. Temporary transcutaneous pacing was not used in this study. Also, we did not experience hazardous complication, such as cardiac failure, which was considered to be the side effect of colostazol in this series. No hemorrhagic complications were observed in this series. Ischemic complications occurred in 1 case in group C and in 1 case in group N. There was no significant difference in the incidence of ischemic complications among the groups.

The characteristics of the patients in each group are summarized in Table 1. Demographic data, risk factors, population with symptomatic stenosis, degree of stenosis, MPRAGE signal intensity, and calcification at the carotid bifurcation were similar between the groups. There were significant differences in side of lesion (61.5% versus 32.1%; $P = .029$), distance from carotid bifurcation to maximum stenotic lesion (4.5 ± 3.9 versus 9.5 ± 5.0; $P < .001$), and application of postdilatation (23.1% versus 50.0%; $P = .038$). There were no significant differences in

Table 1. *Baseline characteristics of the study patients*

	Cilostazol (group C, n = 26)	Noncilostazol (group N, n = 28)	*P* value
Demographic data			
Mean age, y	70.9 ± 6.9	73.6 ± 7.7	.18
Male sex	88.5%	96.4%	.27
Risk factors			
Hypertension	92.3%	75.0%	.09
Diabetes mellitus	42.3%	42.9%	.59
Dyslipidemia	61.5%	67.9%	.42
Current smoking	29.2%	29.6%	.61
Previous coronary artery disease	46.2%	64.3%	.14
Carotid artery stenosis			
Symptomatic stenosis	30.1%	42.9%	.26
Mean degree of stenosis (NASCET criteria)	76.6% ± 8.5%	74.7% ± 17.5%	.61
Right side	61.5%	32.1%	.029*
Distance (from carotid bifurcation to maximum stenotic lesion), mm	4.5 ± 3.9	9.5 ± 5.0	<.001*
MPRAGE, high	58.3%	70.8%	.27
Calcification at carotid bifurcation	73.1%	53.6%	.11
Procedure			
Postdilatation	23.1%	50.0%	.038*
Antiplatelet drugs			
Aspirin	96.2%	100%	.48
Ticlopidine	3.8%	67.9%	<.001*
Clopidogrel	3.8%	28.6%	.016*
Preprocedural conditions			
Systolic blood pressure, mm Hg	139.5 ± 16.4	135.6 ± 12.3	.34
Heart rate, beats per min	78.5 ± 16.7	70.5 ± 14.5	.06

Abbreviations: MPRAGE, magnetization-prepared rapid acquisition gradient-echo; NASCET, North American Symptomatic Carotid Endarterectomy Trial.
*Statistically significant.

preprocedural systolic blood pressure and heart rate between the 2 groups. In 12 cases in which cilostazol was added preoperatively, their heart rates did not change dramatically during the follow-up.

Table 2. *Incidence of intra- and postprocedural hemodynamic instability among the groups with or without cilostazol*

	Yes, n (%)	No, n (%)	*P*
Intraprocedural bradycardia			
Group C	4 (15.3)	22 (84.6)	.0035*
Group N	15 (53.6)	13 (46.4)	
Intraprocedural hypotension			
Group C	9 (34.6)	17 (65.4)	.137
Group N	5 (17.9)	23 (82.1)	
Postprocedural bradycardia			
Group C	0 (0)	26 (100)	.132
Group N	3 (10.7)	25 (89.3)	
Postprocedural hypotension			
Group C	4 (15.4)	22 (84.6)	.153
Group N	1 (3.6)	27 (96.4)	

*Statistically significant.

As shown in Table 2, IBc and IHo took place in 4 cases (15.3%) and 9 cases (34.6%) in group C, whereas in 15 cases (53.6%) and 5 cases (17.9%) in group N, respectively. Postprocedural bradycardia and hypotension took place in 0 case and 4 cases (15.4%) in group C, whereas in 3 cases (10.7%) and 1 case (3.6%) in group N, respectively (Table 2). The incidence of IBc was significantly lower in group C ($P = .0035$) (Table 2). There were no significant differences in the incidences of IHo, postprocedural bradycardia, and hypotension between the groups.

As to the timing, IBc occurred in all cases at predilatation in group C, whereas in 8 cases (53.3%) at predilatation, 4 cases (26.7%) at stenting, and 3 cases (20.0%) at postdilatation in group N (Table 3). IHo occurred in 5 cases (55.6%) at predilatation, 3 cases (33.3%) at stenting, and 1 case (11.1%) at postdilatation in group C, whereas it occurred in 2 cases (40.0%) at predilatation and 3 cases (60.0%) at stenting in group N (Table 3).

Univariate regression analysis was used to examine the relationships between IBc and age, sex, distance from carotid bifurcation to maximum stenotic lesion, side of the lesion, history of coronary artery disease, postdilatation, cilostazol, and calcification. Distance from carotid bifurcation

Table 3. *Timing of intraprocedural bradycardia and hypotension*

	Intraprocedural bradycardia		Intraprocedural hypotension	
Timing	Group C, n (%)	Group N, n (%)	Group C, n (%)	Group N, n (%)
Predilatation	4 (100)	8 (53.3)	5 (55.6)	2 (40.0)
Stenting	0	4 (26.7)	3 (33.3)	3 (60.0)
Postdilatation	0	3 (20.0)	1 (11.1)	0

to maximum stenotic lesion ($P = .019$), postdilatation ($P = .020$), and cilostazol ($P = .003$) were significantly associated with the IBc (Table 4). In multivariate logistic regression analysis using all these factors, distance from carotid bifurcation to maximum stenotic lesion ($P = .005$), side of the lesion ($P = .024$), and cilostazol ($P = .007$) were found to be independent factors for the IBc (Table 4). After the stepwise selection, distance and cilostazol were selected as significant predictors (Table 5). The risk of IBc decreased 54% with every 1 mm further from carotid bifurcation under the use of cilostazol ($P = .001$) and cilostazol decreased the risk of IBc 99% ($P = .001$). Furthermore, IBc did not occur when the distance was more than 10 mm in this series. Excluding these cases, only cilostazol had a high predictive power, and distance was not significantly associated with IBc.

Discussion

The incidences of bradycardia and hypotension in the periprocedural period of CAS were reported to range from 10% to 42% and 27% to 37%,[4] respectively. The risk factors that have been found to be independently associated with a higher risk of bradycardia and hypotension during or after CAS are as follows: distance between bifurcation and maximum stenotic lesion, type of stenosis (eccentric), fibrous plaque, calcification at carotid bifurcation,[5] history of myocardial infarction,[2] employment of Nitinol stent[6] or balloon-expandable stent,[7] degree of stenosis, bilateral stenting, balloon dilatation pressure greater than 8 atm,[8] and CAS of the right side.[9]

In this series, the incidence of IBc was significantly lower in group C. Cilostazol, a phosphodiesterase (PDE3) inhibitor, has antiplatelet activity, vasodilatory effects, causes vascular endothelial function improvement, and suppresses vascular smooth muscle cell proliferation.[10] The Cilostazol for Prevention of Secondary Stroke II study demonstrated the superiority of cilostazol compared with aspirin in preventing cerebral infarction and hemorrhagic events.[11] Previous studies reported that cilostazol reduced the incidence of restenosis of carotid artery after CAS.[10,12,13] Furthermore, the inhibition of PDE3 by cilostazol causes an increase in cyclic adenosine monophosphate (cAMP), resulting in increased contractility of the myocardium and accelerated heart rate.[14] A possible mechanism of prevention of bradycardia in this study is that heart rate acceleration because of the positive effect of this agent might compensate for the bradycardia caused by carotid sinus reflex.

Unfortunately, the baseline of this retrospective study was not well balanced between the 2 groups in terms of the side of the lesion, distance from carotid bifurcation to maximum stenotic lesion, and application of postdilatation. The proportion on which postdilatation was performed differed between the 2 groups (23.1% in group C and 50.0% in group N); postdilatations were not performed when the remaining stenoses less than 50% after stenting or vulnerable plaques were suggested by

Table 4. *Factors associated with intraprocedural bradycardia*

	95% CI							
	Univariate analysis				Multivariate analysis			
Variable	OR	Lower	Upper	*P* value	OR	Lower	Upper	*P* value
Age	1.01	.91	1.06	.714	1.07	.81	1.40	.641
Sex	1.69	.20	35.50	.649	2172.00	.06	7.34×10^{7}	.149
Distance	.87	1.02	1.33	.019*	.23	.08	.64	.005*
Side	.86	.27	2.66	.799	110.98	1.84	6676.35	.024*
Coronary disease	3.15	.84	15.42	.090	.19	.01	6.02	.344
Postdilatation	3.97	1.24	13.55	.020*	5.34	.29	98.44	.260
Cilostazol	.16	.04	.54	.003*	4.07×10^{-7}	9.07×10^{-12}	.02	.007*
Calcification	1.01	.32	3.32	.983	61.55	.95	3989.40	.053

Abbreviations: CI, confidence interval; OR, odds ratio.
*Statistically significant.

Table 5. *Determinants of intraprocedural bradycardia derived from multiple logistic regression analysis*

		95% CI		
	OR	Lower	Upper	*P* value
Variable				
Cilostazol	.01	5.46×10^{-6}	.04	.001*
Distance	.46	.29	.74	.001*
Variable (<10 mm)				
Cilostazol	.04	0	.25	.004*
Distance	.15	.51	2.67	.841

Abbreviations: CI, confidence interval; OR, odds ratio.
*Statistically significant.

MPRAGE as mentioned earlier in this series, and univariate analysis showed a significant difference in execution of this procedure. However, there were no case in group C and only 3 cases in group N in which IBc occurred at the time of postdilatation (Table 3). Furthermore, multiple logistic regression analysis indicated that postdilatation was not an independent factor for IBc. Therefore, the application of postdilatation itself was not considered to be significantly associated with the occurrence of IBc in this series.

CAS on the right side[9] and distance from carotid bifurcation to maximum stenotic lesion[5] were reported to be the risk factors for bradycardia in the periprocedural period for CAS. The former was because of the sidedness of the autonomic neural input,[15] and the latter influenced the strength of mechanical stress to the carotid sinus baroreceptors.[4] The distance from the carotid bifurcation to maximum stenotic lesion was significantly shorter in group C, which is a risk factor for the occurrence of hemodynamic instability such as hypotension and bradycardia, and the right-sided predominance was noted in group C. Nevertheless, the incidence of IBc was significantly lower in group C.

Stepwise logistic regression analyses, as shown in Table 5, indicated that the distance reduced the risk of IBc, and IBc did not occur when the distance was more than 10 mm regardless of the cilostazol use. However, when the distance was less than 10 mm, cilostazol dramatically reduced the risk of IBc by 96% regardless of the distance from bifurcation. This result suggested the efficacy of cilostazol in preventing IBc during CAS.

Our data indicated that cilostazol could reduce the incidence of bradycardia during CAS. Together with the low incidence of postprocedural ischemic complications in this series, the use of cilostazol might be beneficial for patients undergoing CAS when the distance from bifurcation was less than 10 mm.

This study was limited in that it was a nonrandomized, retrospective study in a single center with a rather small sample size. For further evaluation, a prospective randomized study involving a greater number of patients may be needed for confirmation of these initial results. Nevertheless, our study showed that cilostazol might be an effective drug for the prevention of periprocedural bradycardia in CAS.

Conclusion

In this retrospective study, cilostazol seems to be effective in preventing bradycardia during CAS. The use of cilostazol might be considered for patients who are at risk for the occurrence of bradycardia on performing CAS.

References

1. Brott TG, Hobson RW II, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11-23.
2. Qureshi AI, Luft AR, Sharma M, et al. Frequency and determinants of postprocedural hemodynamic instability after carotid angioplasty and stenting. Stroke 1999; 30:2086-2093.
3. Yamada N, Higashi M, Otsubo R, et al. Association between signal hyperintensity on T1-weighted MR imaging of carotid plaques and ipsilateral ischemic events. AJNR 2007;28:287-292.
4. Lavoie P, Rutledge J, Dawoud MA, et al. Predictors and timing of hypotension and bradycardia after carotid artery stenting. AJNR 2008;29:1942-1947.
5. Nonaka T, Oka S, Miyata K, et al. Prediction of prolonged postprocedural hypotension after carotid artery stenting. Neurosurgery 2005;57:472-477.
6. Diehm N, Katzen BT, Dick F, et al. Influence of stent type on hemodynamic depression after carotid artery stent placement. J Vasc Interv Radiol 2008;19:23-30.
7. Dangas G, Laird JR Jr, Satler LF, et al. Postprocedural hypotension after carotid artery stent placement: predictors and short- and long-term clinical outcomes. Radiology 2000;215:677-683.
8. Lian X, Lin M, Zhu S, et al. Risk factors associated with haemodynamic depression during and after carotid artery stenting. J Clin Neurosci 2011;18:1325-1328.
9. Taha MM, Toma N, Sakaida H, et al. Periprocedural hemodynamic instability with carotid angioplasty and stenting. Surg Neurol 2008;70:279-285.
10. Yamagami H, Sakai N, Matsumaru Y, et al. Periprocedural cilostazol treatment and restenosis after carotid artery stenting: the Retrospective Study of In-Stent Restenosis after Carotid Artery Stenting (ReSISteR-CAS). J Stroke Cerebrovasc Dis 2012;21:193-199.
11. Shinohara Y, Katayama Y, Uchiyama S, et al. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. Lancet Neurol 2010;9:959-968.
12. Takayama K, Taoka T, Nakagawa H, et al. Effect of cilostazol in preventing restenosis after carotid artery stenting using the carotid wallstent: a multicenter retrospective study. AJNR 2012;33:2167-2170.
13. Takigawa T, Matsumaru Y, Hayakawa M, et al. Cilostazol reduces restenosis after carotid artery stenting. J Vasc Surg 2010;51:51-56.
14. Toyonaga S, Nakatsu T, Murakami T, et al. Effects of cilostazol on heart rate and its variation in patients with atrial fibrillation associated with bradycardia. J Cardiovasc Pharmacol Ther 2000;5:183-191.
15. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. Lancet Neurol 2002;1:477-482.

Case Report

Fatal Multiple Systemic Emboli after Intravenous Thrombolysis for Cardioembolic Stroke

Koji Tanaka, MD,* Tomoyuki Ohara, MD,* Akiko Ishigami, MD,* Yoshihiko Ikeda, MD,† Toshinori Matsushige, MD,‡ Tetsu Satow, MD,‡ Hatsue Ishibashi-Ueda, MD,† Koji Iihara, MD,‡ and Kazunori Toyoda, MD*

Our objective is to present a case of fatal multiple systemic emboli after intravenous thrombolysis for cardioembolic stroke. A 64-year-old woman with atrial fibrillation was admitted for evaluation of sudden consciousness disturbance, right hemiplegia, and aphasia. Diffusion-weighted imaging showed no early ischemic changes of the brain, and magnetic resonance angiography (MRA) showed occlusion of the left middle cerebral artery (MCA). One hour after initiation of 0.6 mg/kg of intravenous alteplase, the MCA was partially recanalized. Her symptoms disappeared the following day. We began intravenous heparin for secondary prevention of cardioembolic stroke. However, on the third day (52 hours after thrombolysis), she suddenly developed a coma and left hemiplegia. MRA showed acute occlusion of the right internal carotid artery (ICA). She developed acute kidney injury and sudden shock and then died of fatal cardiorespiratory arrest on the fourth day.

Autopsy revealed occlusion of the mitral valve orifice by a spherical fresh red thrombus that led from the left atrial appendage. Acute embolic infarcts were identified in the spleen and right kidney, the latter secondary to occlusion of the right renal artery with fresh red thrombus.

Intravenous thrombolysis and subsequent anticoagulation therapy may destabilize pre-existing intracardiac thrombus, potentially leading to recurrent stroke, multiple systemic embolisms, and the fatal "hole-in-one" effect. **Key Words:** Acute stroke—autopsy—cardioembolism—ischemic stroke—systemic embolism—thrombolysis.

From the *Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita; †Department of Pathology, National Cerebral and Cardiovascular Center, Suita; and ‡Department of Neurosurgery, National Cerebral and Cardiovascular Center, Suita, Japan.

Received January 25, 2013; revision received March 1, 2013; accepted March 5, 2013.

This report was supported by Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (grant number 24791521).

Address correspondence to Tomoyuki Ohara, MD, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan. E-mail: ohatomo@hsp.ncvc.go.jp.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2013.03.007

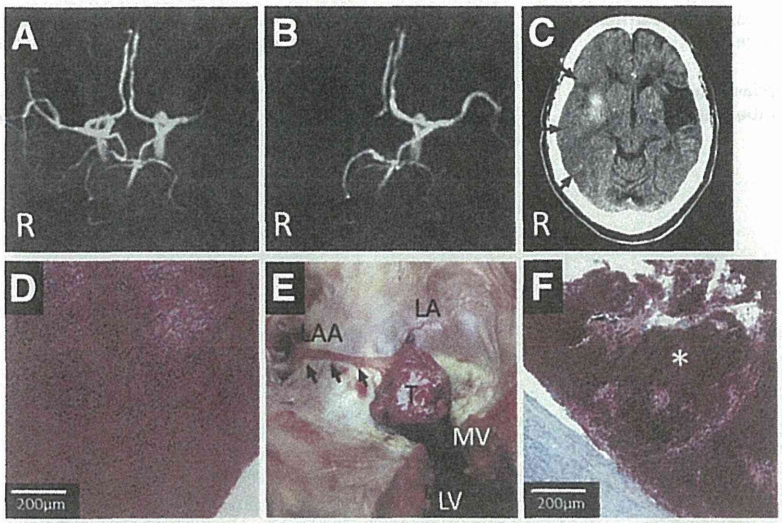

Figure 1. *MRA, CT, and pathological findings. (A) MRA on admission showed left MCA occlusion. (B) MRA on day 3 showed right ICA occlusion and left MCA recanalization. (C) CT on day 4 showed large infarcts in the right MCA territory (arrows). (D) Fresh red thrombus retrieved from the right ICA by mechanical thrombectomy (Masson's trichrome staining). (E) "Hole-in-one" effect; mitral valve (MV) occluded by a spherical fresh red thrombus (T) with a stalk (arrows) adhered to the LAA. (F): Fresh red thrombus (*) in the occluded right renal artery (Masson's trichrome staining). Abbreviations: CT, computed tomography; ICA, internal carotid artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MV, mitral valve; LAA, left atrial appendage.*

Case Report

A 64-year-old woman with atrial fibrillation (AF) was admitted for evaluation of sudden consciousness disturbance, right hemiplegia, and aphasia. She was taking warfarin and her international normalized ratio on admission was 1.10. Diffusion-weighted imaging showed no early ischemic changes of the brain, and magnetic resonance angiography (MRA) showed occlusion of the left middle cerebral artery (MCA) (Fig 1A). Transthoracic echocardiography showed no visible thrombus in the left atrium. One hour after initiation of 0.6 mg/kg of intravenous alteplase, the MCA was partially recanalized. Her symptoms disappeared on the following day. We began intravenous heparin (10,000 U daily) for secondary prevention of cardioembolic stroke. However, on the third day (52 hours after thrombolysis), she suddenly developed a coma and left hemiplegia. MRA showed acute occlusion of the right internal carotid artery (ICA) (Fig 1B). Her activated partial thromboplastin time was 36 seconds (29 seconds at baseline). Because of recent intravenous thrombolysis, emergent endovascular thrombectomy using Merci Retrieval System was performed for ICA occlusion. Although a fresh red thrombus was retrieved by the procedure, complete recanalization was not achieved (Fig 1C, D). She developed acute kidney injury and sudden shock and then died of fatal cardiorespiratory arrest on the fourth day.

Autopsy revealed occlusion of the mitral valve orifice by a spherical fresh red thrombus that led from the left atrial appendage (Fig 1E), showing pathological findings similar to those of the thrombus retrieved from the right ICA. Acute embolic infarcts were identified in the spleen and right kidney, the latter secondary to occlusion of the right renal artery with fresh red thrombus (Fig 1F). Ischemic changes were also identified in the small intestine.

Discussion

Early recurrent ischemic stroke after intravenous thrombolysis is an uncommon complication of thrombolysis. Early recurrent ischemic stroke was associated with AF and has been presumed to occur mainly because of the disintegration of pre-existing intracardiac thrombus by thrombolysis.[1] Early embolism to other vascular beds after thrombolysis, including coronary arteries and peripheral arteries, has also been reported.[2,3,4] This is the first report to demonstrate fatal multiple systemic emboli after thrombolysis in autopsy.

Although thrombus was not shown in the left atrium by transthoracic echocardiography on admission in this case, intravenous thrombolysis and subsequent anticoagulation therapy may destabilize pre-existing intracardiac thrombus, leading to recurrent stroke, multiple systemic embolisms, and the fatal "hole-in-one" effect.[5] A previous study reported that the presence of intracardiac thrombus was not associated with a high risk of recurrent embolism in acute stroke patients treated with intravenous thrombolysis.[6] Therefore, thrombolysis should not be withdrawn simply because of the risk of recurrent embolism in patients with AF who have a high potential for intracardiac thrombus. However, clinicians should pay attention to early embolic events after thrombolysis, especially in patients with AF.

References

1. Awadh M, MacDougall N, Santosh C, et al. Early recurrent ischemic stroke complicating intravenous thrombolysis for stroke: incidence and association with atrial fibrillation. Stroke 2010;41:1990-1995.
2. Meissner W, Lempert T, Saeuberlich-Knigge S, et al. Fatal embolic myocardial infarction after systemic thrombolysis for stroke. Cerebrovasc Dis 2006;22:213-214.

3. Mehdiratta M, Murphy C, Al-Harthi A, et al. Myocardial infarction following t-PA for acute stroke. Can J Neurol Sci 2007;34:417-420.
4. Gomez-Beldarrain M, Telleria M, Garcia-Monco JC. Peripheral arterial embolism during thrombolysis for stroke. Neurology 2006;67:1096-1097.
5. Lie JT, Entman ML. "Hole-in-one" sudden death: mitral stenosis and left atrial ball thrombus. Am Heart J 1976; 91:798-804.
6. Derex L, Nighoghossian N, Perinetti M, et al. Thrombolytic therapy in acute ischemic stroke patients with cardiac thrombus. Neurology 2001;57:2122-2125.

Neurol Med Chir (Tokyo) 54, 1–8, 2014

doi: 10.2176/nmc.oa.2013-0197
Online December 27, 2013

Special Theme Topic: Japanese Surveillance of Neuroendovascular Therapy in JR-NET/JR-NET2—Part I

Recent Trends in Neuroendovascular Therapy in Japan: Analysis of a Nationwide Survey—Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2

Nobuyuki SAKAI,[1] Shinichi YOSHIMURA,[2] Waro TAKI,[3] Akio HYODO,[4] Shigeru MIYACHI,[5] Yoji NAGAI,[6] Chiaki SAKAI,[7] Tetsu SATOW,[8] Tomoaki TERADA,[9] Masayuki EZURA,[10] Toshio HYOGO,[11] Shunji MATSUBARA,[12] Kentaro HAYASHI,[13] Toshiyuki FUJINAKA,[14] Yasushi ITO,[15] Shigeki KOBAYASHI,[16] Masaki KOMIYAMA,[17] Naoya KUWAYAMA,[18] Yuji MATSUMARU,[19] Yasushi MATSUMOTO,[20] Yuichi MURAYAMA,[21] Ichiro NAKAHARA,[22] Shigeru NEMOTO,[23] Koichi SATOH,[24] Kenji SUGIU,[25] Akira ISHII,[26] Hirotoshi IMAMURA,[1] and Japanese Registry of Neuroendovascular Therapy (JR-NET) Investigators

[1]Department of Neurosurgery, Kobe City Medical Center, Kobe, Hyogo;
[2]Department of Neurosurgery, Gifu University, Gifu, Gifu;
[3]Department of Neurosurgery, Mie University, Tsu, Mie;
[4]Department of Neurosurgery, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Saitama;
[5]Department of Neurosurgery, Nagoya University, Nagoya, Aichi;
[6]Translational Research Informatics Center, Kobe, Hyogo;
[7]Division of Neuroendovascular Therapy, Institute of Biomedical Research and Innovation, Kobe, Hyogo;
[8]Department of Neurosurgery, National Cerebral and Cardiovascular Center, Suita, Osaka;
[9]Department of Neurosurgery, Wakayama Rosai Hospital, Wakayama, Wakayama;
[10]Department of Neurosurgery, Sendai Medical Center, Sendai, Miyagi;
[11]Department of Neurosurgery, Nakamura Memorial Hospital, Sapporo, Hokkaido;
[12]Department of Neurosurgery, Tokushima University, Tokushima, Tokushima;
[13]Department of Neurosurgery, Nagasaki University, Nagasaki, Nagasaki;
[14]Department of Neurosurgery, Osaka University, Suita, Osaka;
[15]Department of Neurosurgery, Niigata University, Niigata, Niigata;
[16]Department of Neurosurgery, Chiba Emergency Medical Center, Chiba, Chiba;
[17]Department of Neurosurgery, Osaka City General Hospital, Suita, Osaka;
[18]Department of Neurosurgery, Toyama University, Toyama, Toyama;
[19]Department of Endovascular Neurosurgery, Toranomon Hospital, Tokyo;
[20]Department of Neuroendovascular Therapy, Kohnan Hospital, Sendai, Miyagi;
[21]Department of Neurosurgery, Jikei University, Tokyo;
[22]Department of Neurosurgery, Kokura Memorial Hospital, Kokura, Fukuoka;
[23]Department of Neuroendovascular Surgery, Jichi Medical University, Shimotsuke, Tochigi;
[24]Department of Neurosurgery, Tokushima Red Cross Hospital, Tokushima, Tokushima;
[25]Department of Neurosurgery, Okayama University, Okayama, Okayama;
[26]Department of Neurosurgery, Kyoto University, Kyoto, Kyoto

Received June 8, 2013; Accepted November 1, 2013

Abstract

The present study retrospectively analyzed the database of the Japanese Registry of Neuroendovascular Therapy 1 and 2 (JR-NET1&2) to determine annual trends, including adverse events and clinical outcomes at 30 days after undergoing neuroendovascular therapy. JR-NET1&2 are surveys that targeted all patients in Japan who underwent neuroendovascular therapy delivered by physicians certified by the Japanese Society of Neuroendovascular Therapy (JSNET) between 2005 and 2009. Medical information about the patients was anonymized and retrospectively registered via a website. Data from 32,608 patients were analyzed. The number of treated patients constantly increased from 5,040 in 2005 to 7,406 in 2009 and the rate of octogenarians increased from 7.0% in 2005 to 10.4% in 2009. The proportion of procedures remained relatively constant, but ratios of angioplasty slightly increased from 32.8% in 2005 to 33.7% in 2009. Procedural complications were associated more frequently with acute stroke (9.6%), ruptured aneurysms (7.4%), intracranial artery disease (ICAD) (5.4%), and arteriovenous malformation (AVM, 5.2%). The number of patients requiring neuroendovascular treatment in Japan is increasing and the outcomes of such therapy are clinically acceptable. Details of each type of treatment will be investigated in sub-analyses of the database.

Key words: nationwide survey, endovascular treatment, cerebral aneurysm, angioplasty, clinical outcome

Introduction

Neuroendovascular therapy is a less invasive method of treating various cerebrovascular diseases such as cerebral aneurysm, supra-aortic artery stenosis/occlusion, arteriovenous shunts, and acute stroke[1–8] that has become increasingly popular. However, the current status of this therapy including numbers of procedures, clinical outcomes, and adverse events remain unknown.[9,10]

The Japanese Society of Neuroendovascular Therapy (JSNET) established a board certification system in 2000 that certified physicians with ≥200 primary operator experiences, ≥10 presentations at medical meetings, and ≥3 publications as primary author as senior trainers and specialists through a board examination. The JSNET produced an expert consensus document in 2009 when a systematic review revealed a scarcity of high-quality clinical evidence in this field, especially in Japan. Thus, the society implemented retrospective studies (Japanese Registry of Neuroendovascular Therapy 1 and 2; JR-NET1&2) to clarify the general status of neuroendovascular therapy delivered by JSNET-certified physicians. Clinical and procedural data were retrospectively collected from January 2005 through December 2007 (JR-NET1) and from January 2008 through December 2009 (JR-NET2).

These studies aimed to determine annual changes in neuroendovascular treatment modalities and in major adverse events within 30 days thereafter.

Methods

I. Study design

JR-NET1 (2005–2006): This was the first nationwide survey of neuroendovascular treatments in Japan. The registry targeted all patients treated by JSNET board-certified physicians between January 2005 and December 2006, except for those whom their physicians judged unsuitable for this registry. Medical information about the patients was anonymized and retrospectively registered via a website (https://jr-net.tri-kobe.net/jr-net/).

JR-NET2 (2007–2009): This second nationwide survey of neuroendovascular treatment in Japan targeted all patients treated by JSNET board-certified physicians between January 2007 and December 2009. Medical information of the patients was anonymized and registered as described above.

Data were collected at the Translational Research Informatics Center (TRI, http://www.tri-kobe.org/). The study protocol, which is summarized briefly here, is available on line with the full text of this article (https://jr-net.tri-kobe.net/jr-net/). All members of the writing committee assumed responsibility for the accuracy and completeness of the data and for the fidelity of the study with regard to the protocol.

II. Patients

All patients treated by neuroendovascular treatment at participating centers during the study period were basically enrolled in the study. The local institutional review boards at each institution approved the study protocol before the investigators proceeded with the study.

III. Primary and secondary endpoints

The primary endpoint was activities of daily life (ADL) determined according to modified Rankin scale (mRS) scores. The secondary endpoints comprised the technical success of procedures and major adverse events (MAEs) that occurred within and at 30 days after procedures.

A score of 0 on the mRS indicates no disability, whereas scores of 1 or 2 indicate slight disability (some help required with ADL but basically independent), scores of 3 to 5 indicate moderate disability (some help required with ADL) to severe disability (bedridden or constant specific care required), and a score of 6 indicates death.

Adverse events were classified as minor and major when mRS scores deteriorated by 1 and ≥2 points, respectively.

IV. Statistical analysis

Data were statistically analyzed using JMP 7 software (SAS Institute, Cary, North Carolina, USA). The statistical significance of intergroup differences was assessed using the *t*-test for quantitative scales, Pearson's χ^2 test; $p < 0.05$ was considered significant.

Results

I. Backgrounds and characteristics of patients

A total of 32,068 patients (mean age, 63.5 ± 13.9

Table 1 Annual trends of JR-NET data

	2005	2006	2007	2008	2009	Total
Total number	n = 5,040	n = 6,174	n = 6,690	n = 6,758	n = 7,406	n = 32,068
Age	64.0+/–13.8	63.4+/–12.9	64.1+/–13.7	64.6+/–13.3	64.4+/–13.8	63.5+/–13.9
Female	2,341 (46.4%)	2,921 (47.3%)	3,109 (46.5%)	3,131 (46.3%)	3,495 (47.2%)	14,997 (46.8%)
mRS before treatment	0.7	0.7	0.7	0.6	0.6	0.7
Procedures	n = 4,500	n = 5,457	n = 6,466	n = 6,503	n = 7,232	n = 30,158
Aneurysm treatment	1,777 (39.5%)	2,396 (43.9%)	2,725 (42.1%)	2,668 (41.0%)	3,112 (43.0%)	12,678 (40.5%)
Dome embolization, ruptured	751 (16.7%)	963 (17.7%)	1,073 (16.6%)	1,091 (16.8%)	1,254 (17.3%)	5,132 (17.0%)
Dome embolization, unruptured	883 (19.6%)	1,105 (20.3%)	1,373 (21.2%)	1,302 (20.0%)	1,597 (22.1%)	6,260 (20.8%)
Dissection/parent artery occlusion	143 (3.2%)	328 (6.0%)	279 (4.3%)	275 (4.2%)	261 (3.6%)	1,439 (4.8%)
Angioplasty/stenting	1,476 (32.8%)	1,734 (31.2%)	2,275 (35.2%)	2,363 (36.3%)	2,438 (33.7%)	10,286 (34.1%)
Carotid artery	1,042 (23.2%)	1,281 (23.5%)	1,717 (26.6%)	1,855 (28.5%)	1,926 (26.6%)	7,821 (25.9%)
Vertebral/subclavian artery	203 (4.5%)	230 (4.2%)	281 (4.4%)	282 (4.3%)	254 (3.5%)	1,250 (4.1%)
Intracranial artery	231 (5.1%)	223 (4.1%)	277 (4.3%)	226 (3.5%)	258 (3.6%)	1,215 (4.0%)
Brain & spinal AVM embolization	217 (4.8%)	281 (5.1%)	204 (3.2%)	213 (3.3%)	259 (3.6%)	1,174 (3.9%)
DAVF embolization	317 (7.0%)	424 (7.8%)	468 (7.2%)	464 (7.1%)	525 (7.3%)	2,198 (7.3%)
Tumor embolization	347 (7.7%)	373 (6.8%)	317 (4.9%)	319 (4.9%)	382 (5.3%)	1,738 (5.8%)
Acute stroke treatment	366 (8.1%)	249 (4.6%)	277 (4.3%)	266 (4.1%)	281 (3.9%)	1,439 (4.8%)
Physicians in charge	n = 4,935	n = 5,988	n = 6,690	n = 6,758	n = 7,406	n = 31,777
Senior trainer, board certified	3,139 (63.6%)	3,573 (59.7%)	3,097 (46.3%)	3,277 (48.5%)	3,624 (48.9%)	16,710 (52.6%)
Specialist, board certified	1,355 (27.5%)	1,801 (30.1%)	3,103 (46.4%)	3,044 (45.0%)	3,358 (45.3%)	12,661 (39.8%)
Non-specialist	438 (8.9%)	617 (10.3%)	462 (6.9%)	375 (5.5%)	405 (5.5%)	2,297 (7.2%)

AVM: arteriovenous malformation, DAVF: dural arteriovenous fistula, mRS: modified Rankin Scale.

years; female, 46.8%) were registered in this study (Table 1), which involved 200 and 256 board-certified physicians at 122 and 150 centers in JR-NET[11] and in JR-NET2, respectively (Appendix). Figure 1 shows the proportions of treated patients within various age groups. Although patients aged between 40 years and 70 years were the main recipients of treatment, the rate of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009 ($p < 0.001$). In contrast, the ratio of younger patients (< 40 years) remained constant ($p = 0.361$; Fig. 1).

II. Procedures

Among a total of 32,068 neuroendovascular procedures implemented between 2005 and 2009, angioplasty and treatment for aneurysms accounted for 34.1% and 40.5%, respectively. Embolization of brain and spinal arteriovenous malformations (AVMs), dural arteriovenous fistulae (dAVF), tumors, and treatment for acute stroke accounted for 3.9%, 7.3%, 5.8%, and 4.8% of procedures, respectively. Carotid artery stenting (CAS) accounted for 25.9% of all procedures (Table 1). The proportions of treatments remained relatively constant, except for CAS, which slightly increased from 23.2% in 2005 to 26.6% in 2009 ($p < 0.001$; Fig. 2).

Elective or emergency procedures: The total numbers of elective and emergency procedures increased annually, but the rate of emergency treatment remained relatively constant between 28% and 30% throughout the study period (Fig. 3).

Physicians in charge: Senior trainers certified by JSNET were in charge of 63.6% and 48.9% of procedures during 2005 and in 2009 (Table 1), respectively. The total number of treatment procedures with JSNET senior trainers and specialists in charge increased annually, but the rate of procedures supervised by JSNET senior trainers gradually decreased, although the difference did not reach significance. However, treatment delivered with JSNET non-specialist in charge decreased from 8.9% in 2005 to 5.5% in 2009 ($p = 0.029$).

mRS scores before and after treatment: Figure 4A and 4B shows the overall proportions of mRS scores before and after treatment. Before treatment, ≥90% of patients were in relatively good condition, with mRS scores of 0–2 (Fig. 4A). At 30 days after undergoing procedures, >80% of patients maintained mRS scores of 0–2 (Fig. 4B).

mRS scores after each type of procedure: Figure 5 shows the outcomes of each type of treatment

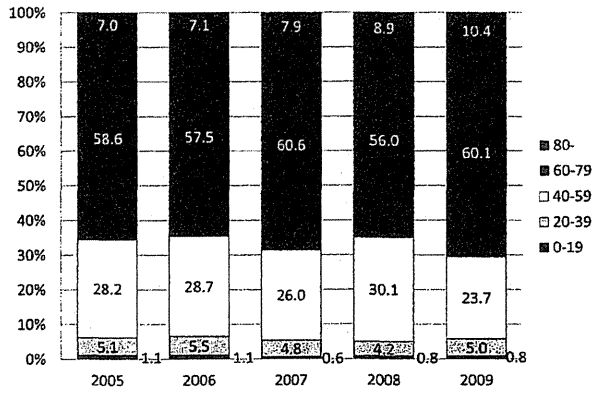

Fig. 1 Annual changes in patients' age during JR-NET1&2. Rates of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009 ($p < 0.001$), whereas the ratio of younger patients (< 40 years) remained constant ($p = 0.361$). JR-NET1&2: Japanese Registry of Neuroendovascular Therapy 1 and 2.

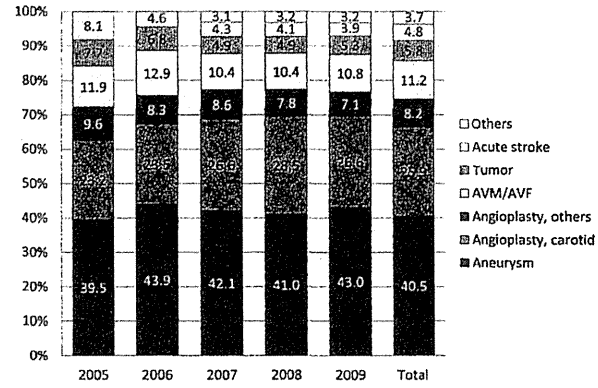

Fig. 2 Annual changes in the types of procedures. The proportion of treatments remained relatively constant, but carotid artery stenting (CAS) slightly increased from 23.2% in 2005 to 26.6% in 2009 ($p < 0.001$).

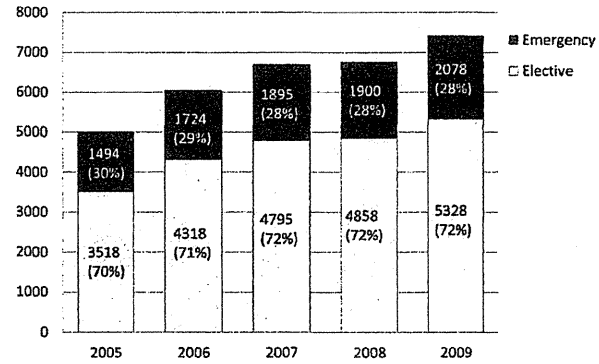

Fig. 3 Number of elective and emergency procedures. The total numbers of elective and emergency procedures increased annually, although the overall rate of emergency treatment remained between 28% and 30% throughout the period.

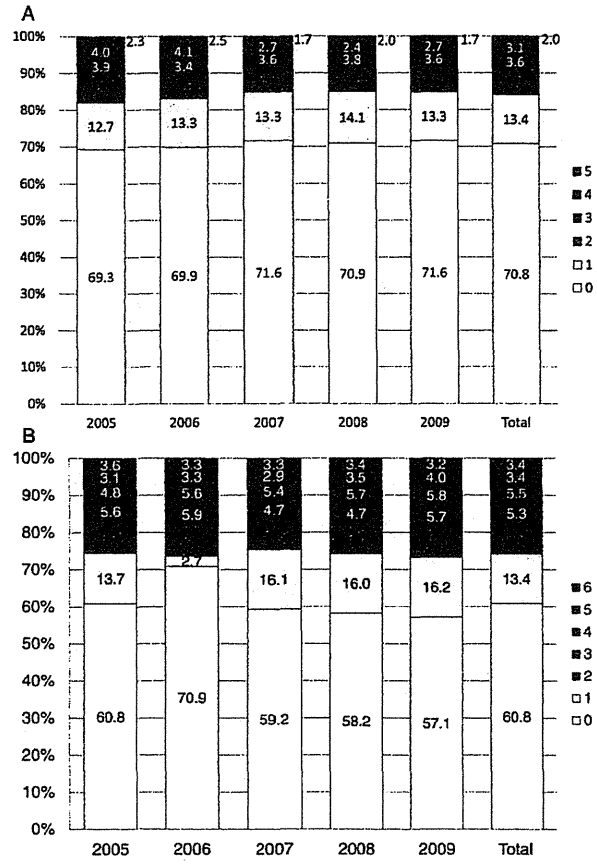

Fig. 4 Proportions of modified Rankin scale (mRS) scores before and after procedures. Ratio of patients with mRS 0–2 was ≥90% before therapeutic procedures (A), decreased at 30 days thereafter (B), but remained >80%.

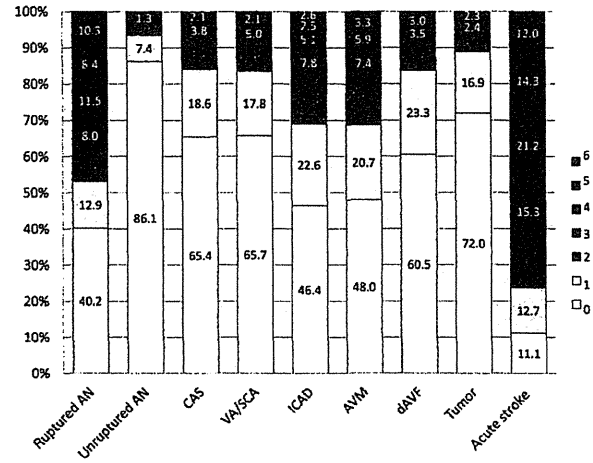

Fig. 5 Proportions of modified Rankin scale (mRS) scores at 30 days after various procedures. Outcomes were favorable (mRS 0–2) for 61.7% and 96.3% of patients with ruptured and unruptured aneurysms respectively. Ratios of favorable outcomes of carotid artery stenting (CAS), vertebral artery (VA)/SCA (subclavian artery), dural arteriovenous fistula (dAVF), and tumor embolization were >90%. On the other hand, the ratios of favorable outcomes were 82.0%, 81.9%, and only 37.2% in intracranial artery disease (ICAD), arteriovenous malformation (AVM) and acute stroke, respectively.

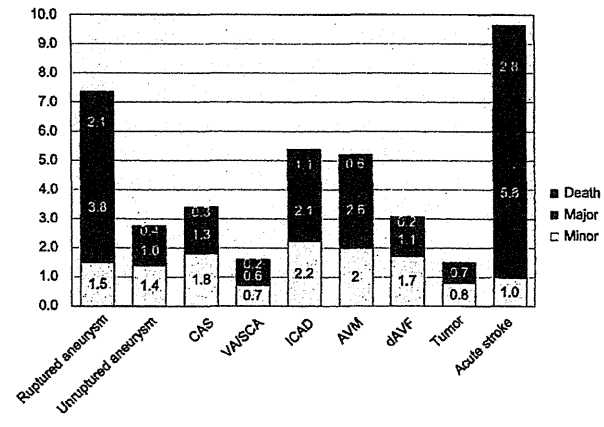

Fig. 6 Complications associated with each procedure. Complication rates were higher after procedures for ruptured aneurysm (7.4%) and acute stroke (9.5%), but less frequent for those that treated unruptured aneurysms (2.8%), VA/SCA (1.5%), and tumor embolization (1.5%).

according to mRS scores. Outcomes were favorable for 61.7% and 96.3% of patients with ruptured and unruptured aneurysms, respectively, (mRS 0–2) and for ≥90% those after CAS, VA/SCA, dAVF, and tumors. On the other hand, 82.0%, 81.9%, and 37.2% of those treated for intracranial artery disease (ICAD), in AVM, and acute stroke had favorable outcomes.

Procedural complications of each treatment: Figure 6 shows the frequency of procedural complications after each type of treatment. Death, major and minor procedural complications occurred in 7.4% and 2.8% of patients treated for ruptured and unruptured aneurysms, respectively. Among angioplasties, procedural complications occurred in 3.4%, 1.5%, and 5.4% in the carotid artery, the VA/SCA and in ICAD, respectively. Among arteriovenous shunt diseases, complications developed in 5.2% and 3.0% of those treated for AVM and dAVF, respectively. The rate of complications of tumor embolization was 1.5%, and none of the patients died of procedure-related complications. On the other hand, complications developed at a rate of 9.6% in patients treated for acute stroke, including 2.8% who died.

Discussion

The present study investigated recent trends in neuroendovascular therapy through analyses of 32,608 patients registered in the nationwide JR-NET1&2 surveys. The number of procedures constantly increased from 5,040 in 2005 to 7,406 in 2009, and the rate of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009. The proportion of treatments remained relatively constant, but angioplasty/stenting for carotid diseases slightly increased from 23.2% in 2005 to 26.6% in 2009. More procedural complications were associated with acute stroke (9.5%), ruptured aneurysm (7.4%), ICAD (5.4%), and AVM (5.2%).

The number of annual neuroendovascular procedures increased by 46.9% (from 5,040 to 7,406). The annual numbers of procedures required to treat intracranial aneurysms and angioplasty/stenting for atherosclerotic disease between 2005 and 2009 increased by 75.1% (from 1,777 to 3,112) and 65.2% (1,476 to 2,438), respectively. The mRS scores after procedures remained favorable in >80% of the patients each year. Clinical outcomes and complication rates significantly differed among procedures. Rates of favorable outcomes of procedures to treat ruptured aneurysms and acute stroke were around 60% and < 40%, respectively, and more procedural complications were also associated with these conditions. However, whether complications were major or minor was sometimes difficult to judge in emergency patients under general anesthesia or sedation, and in patients with poor neurological status. Thus, procedural complications in these two groups might have been over- or underestimated.

Several reports have described nationwide trends in neuroendovascular therapies.[12–19] Some of them are analyses of a national healthcare database in the United States.[12–15,17,20] For example, Huang et al. reported trends in the management of unruptured cerebral aneurysms in the United States.[15] They analyzed the length of hospital stay, in-hospital mortality rates, the number of hospitalizations, and total national charges related to inpatient treatment. Their findings provide valuable information regarding trends, but obtaining clinical data about neurological status, neuroendovascular procedures, and follow-up results might be difficult. Detailed evaluations and analyses could be achieved if areas or centers were selected. Higashida et al. described endovascular treatment for unruptured intracranial aneurysms in 18 of 47 states in the United Staes during 2007.[21] Qureshi et al. described how class I evidence (ISAT) from a nationwide impact survey impacted clinical practice. Their database was derived from stratified sampling at 20% of US hospitals.[20] In that regard, data from the nationwide JR-NET1&2 surveys are valuable because the study collected precise information regarding not only patient's characteristics, but also neurological status, types of treatment, devices, complications, and follow-up at 30 days after procedures.

This study has some limitations. Although JR-NET 1&2 provided a robust amount of patient information including clinical details, particularly information related to neuroendovascular therapies, it covered only about 35% of all procedures performed in Japan, which was calculated according to annual reports of training facilities of the Japan neurosurgical society (unpublished). This was a significant drawback in terms of avoiding selection bias. This shortcoming might be improved in a new nationwide survey (JR-NET 3), which is collecting information between 2010 and 2013 in a similar setting to that of JR-NET 1&2.

Conclusion

Data from this study suggest an increasing trend towards neuroendovascular treatment in Japan. The rate of neuroendovascular intervention is increasing annually and clinical outcomes seem acceptable. Details about each treatment or disease will be assessed in sub-analyses of this database.

Acknowledgments

The authors express their special thanks to the study group members: The JR-NET Study Group: Principle investigator, N. Sakai; Investigators: A. Hyodo, S. Miyachi, Y. Nagai, C. Sakai, T. Satow, W. Taki, T. Terada, M. Ezura, T. Hyogo, S. Matsubara, K. Hayashi; Co-investigators; T. Fujinaka, Y. Ito, S. Kobayashi, M. Komiyama, N. Kuwayama, Y. Matsumaru, Y. Matsumoto, Y. Murayama, I. Nakahara, S. Nemoto, K. Satoh, K. Sugiu S. Yoshimura and the specialists certified by the Japanese Society for Neuroendovascular Therapy listed in the Appendix. This study was supported by research grants for cardiovascular diseases (17C-1, 20C-2) from the Ministry of Health, Labor, and Welfare of Japan.

Conflicts of Interest Disclosure

All authors who are members of The Japan Neurosurgical Society (JNS) have registered self-reported COI disclosure statements through the website for JNS members.

This manuscript has not been published or presented elsewhere in part or in entirety, and is not under consideration by another journal.

Appendix

Participants, their hospitals, and the number of registered patients in JR-NET2 are listed when >100 patients were registered; names of investigators are listed when < 100 patients were registered. This information has already been reported for JR-NET1.[11]

Y Matsumoto, R Kondo, E Kondo, Y Matsumori, Kohnan Hp., 913; N Sakai, H Adachi, Y Ueno, H Imamura, H Yamagami, Y Kuramoto, Kobe City Med. Ctr General Hp., 809; I Nakahara, Y Watanabe, Kokura Memorial Hp., 586; T Abe, M Hirohata, Kurume Univ., 535; K Sugiu, K Tokunaga, Okayama Univ., 485; M Ezura, S Nishimura, N Kimura, I Suzuki, Sendai Med. Ctr, 471; M Nakamura, Hyogo Brain and Heart Ctr at Himeji, 448; T Suyama, M Nagashima, Tominaga Hp., 427; K Goto, S Ota, Brain Attack Ctr Ota Memorial Hp., 409; S Yamazaki, Tsuchiura Kyodo Hp., 348; T Nakazawa, Shiga Med. Univ., 347; Y Matsumaru, W Tsuruta, M Hayakawa, Toranomon Hp., 344; K Kazekawa, M Tsutsumi, H Aikawa, T Kodama, Fukuoka Univ. Chikushi Hp., 334; W Taki, H Sakaida, N Toma, F Asakura, Mie Univ. 324; E Kobayashi, N Hayasaka, Chiba Univ., 322; S Yoshimura, Y Enomoto, Gifu Univ., 290; K Iihara, T Satow, N Nakajima, Y Takenobu, National Cardiovascular Ctr, 289; M Kawanishi, A Shindo, K Kawakita, T Yano, Kagawa Univ., 276; H Shibuya, Sagamihara Kyodo Hp., 262; C Sakai, N Sakai, Institute of BioMed. Research and Innovation, 258; N Fukui, Kochi Med. Ctr, 258; T Hyogo, T Kataoka, Nakamura Memorial Hp., 230; I Naito, T Iwai, M Takatama, N Miyamoto, Geriatrics Research Institute and Hp., 228; T Ueda, T Takada, Y Otsuka, St. Marianna Univ. Toyoko Hp., 222; N Kuwayama, N Eiraku, N Akioka, Toyama Univ., 217; H Ishihara, Yamaguchi Univ., 214; T Nonaka, A Takahashi, Shiroishi Neurosurgical Hp., 213; T Hatano, M Murakami, Kyoto Med. Ctr, 205; T Hashimoto, Tokyo Med. Univ., 201; D Sato, Aizawa Hp, 200; A Nakahara, R Ogami, M Hp., 200; T Ichihashi, Fukuroi Municipal Hp., 196; T Fujinaka, M Hirata, M Sakaguchi, T Nishida, Osaka Univ., 196; M Komiyama, T Ishiguro, Osaka City General Hp., 193; Y Kiura, T Okazaki, S Sakamoto, Hiroshima Univ., 193; Y Akiyama, Tenri Hp., 186; H Sato, Tokyo Police Hp.,185; A Ishii, A Morizane, Kyoto Univ., 182; K Takayama, Ishinkai Yao Hp., 181; M Imaoka, Aso General Hp., 177; J Hamada, N Uchiyama, M Mori, Kanazawa Univ., 173; H Abe, Tachikawa General Hp., 170; A Nishio, Y Mitsuhashi, T Kawakami, Osaka City Univ., 170; S Iwabuchi, M Hayashi, Toho Med. Univ. Ohashi Hp., 162; M Nagahata, N Shimamura, Hirosaki Univ., 159; T Kubota, Hakodate Neurosurgical Hp., 158; K Imai, T Takeshita, Kyoto First Red Cross Hp., 153; H Sakai, Toyohashi Med. Ctr, 150; K Fujimoto, Osaka General Med. Ctr, 150; T Higa, Tokyo Women's Med. Univ., 147; K Harada, Fukuoka Wajiro Hp., 145; S Kobayashi, N Koguchi, T Yamauchi, Chiba Emergency Med. Center, 144; N Ikeda, Ube Kosan Central Hp.; H Hiramatsu, Hamamatsu Med. Univ., 142; J Satomi, Tokushima Univ.,139; H Ota, I Ikushima, Miyakonojo Med. Association Hp., 138; H Tenjin, Y Kosaka, Kyoto Second Red Cross Hp.,134; K Akaji, Mihara Memorial Hp., 128; S Aketa, Osaka Police Hp., 124; K Hayashi, M Morikawa, N Horie, K Hiu, Nagasaki Univ., 121; H Morishima, St. Marianna Univ. School of Medicine, 111; F Oya, Nagano Municipal Hp., 111; A Hyodo, K Suzuki, Dokkyo Med. Univ. Koshigaya Hp., 109; Y Arai, Fukui Univ., 106; M Sakamoto, Tottori Univ., 103; J-H Son, Shinmatsudo Chuo General Hp., 101; K Hayasaki, Saiseikai Ibaraki Hp., 101; S Tamatani, S Yamamoto, Dokkyo Med. Univ., 100; M Yasuda, Y Fumoto, Kano Hp., 100.

K Haraguchi, H Manabe, M Hayashi, O Kikuchi, S Iihoshi, K Miyata, J Sakurai, S Yamauchi, A Takahashi, N Tamagawa, J Moroi, A Shimada, K Asakura, H Shimaguchi, O Miyagi, M Matsumoto, A Kojima, T Takahashi, S Ishihara, S Kohyama, F Yamane, T Dembo, R Kanazawa, K Nakai, M Katayama, S Kittipong, M Tanaka, Y Numaguchi, M Fujimoto, A Uemura, T Saguchi, O Tone, Y Sato, K Shigeta, Y Yoshida, T Ohashi, K Amari, Y Sakata, S Tateshima, Y Ito, T Sorimachi, S Inagawa, K Morita, K Kitazawa, M Arai, N Minamide, Y Hirota, Y Takabatake, K Kanemaru, J Yamada, H Kitajima, S Fukazawa, T Okamoto, T Nakano, A Tsurumi, T Kojima, M Negoro, A Sadato, M Hayakawa, T Watanabe, K Irie, T Tanaka, T Hattori, N Kobayashi, A Tsuji, M Kawanishi, M Yamada, M Hirai, K Owada, M Ohashi, T Ota, K Maeno, S Sakamoto, T Kuroiwa, K Murao, K Nakazawa, J Kobayashi, N Nakagawa, T Fukawa, A Fujita, K Matsumoto, Y Yoshida, I Yamaura, A Masuda, H Minami, K Uchida, M Shirakawa, H Nakagawa, I Nakagawa, H Takeuchi, S Kawada, A Handa, M Koyanagi, K Yoshida, S Matsubara, T Mizogami, K Migita, H Yasuda, S Kato, K Satoh, M Hanaoka, N Hayashi, K Yoshino, A Nishida, T Shiraishi, O Nishizaki, M Iwanaga, T Higashi, M Iwaasa, M Okawa, K Nakahara, T Yoshioka, M Kaji, Y Hori, T Asano, M Okahara, A Kashiwagi, H Kiyosue, S Tanoue, T Kubo, and H Yonaha.

References

1) Bertog SC, Grunwald IQ, Kühn AL, Franke J, Vaskelyte L, Hofmann I, Id D, Hornung M, Sievert H: Complications during carotid artery stenting. *J Cardiovasc Surg (Torino)* 54: 67–82, 2013

2) Fiorella D, Albuquerque FC, Woo HH, McDougall CG, Rasmussen PA: The role of neuroendovascular therapy for the treatment of brain arteriovenous malformations. *Neurosurgery* 59: S163–177; discussion S3–13, 2006
3) McConnell KA, Tjoumakaris SI, Allen J, Shapiro M, Bescke T, Jabbour PM, Rosenwasser RH, Nelson PK: Neuroendovascular management of dural arteriovenous malformations. *Neurosurg Clin N Am* 20: 431–439, 2009
4) Naggara ON, White PM, Guilbert F, Roy D, Weill A, Raymond J: Endovascular treatment of intracranial unruptured aneurysms: systematic review and meta-analysis of the literature on safety and efficacy. *Radiology* 256: 887–897, 2010
5) Setacci C, de Donato G, Setacci F, Sirignano P, Galzerano G, Borrelli MP, Cappelli A: Carotid artery stenting in recently symptomatic patients. *J Cardiovasc Surg (Torino)* 54: 61–66, 2013
6) Shutze W, Gierman J, McQuade K, Pearl G, Smith B: Treatment of proximal vertebral artery disease. *Vascular* Epub 2013 Mar 21
7) Taki W: Memorial review celebrating the 50th year of publication of NMC—neuroendovascular therapy. *Neurol Med Chir (Tokyo)* 50: 809–823, 2010
8) Yamada R, Anderson MB, Guimaraes M, Schönholz C: Carotid stenting in asymptomatic patients: how to identify patients without symptoms and at high risk for neurologic events. *J Cardiovasc Surg (Torino)* 54: 55–59, 2013
9) Samaniego EA, Dabus G, Linfante I: Avoiding complications in neurosurgical interventional procedures. *J Neurosurg Sci* 55: 71–80, 2011
10) Wong JM, Ziewacz JE, Panchmatia JR, Bader AM, Pandey AS, Thompson BG, Frerichs K, Gawande AA: Patterns in neurosurgical adverse events: endovascular neurosurgery. *Neurosurg Focus* 33: E14, 2012
11) Sakai N, Taki W, Ezura M, Sato K, Terada T, Nagai Y, Hattori I, Fukuda H, Hygo T, Hyodo A, Matsubara S, Miyachi S, Murao S, Sakai C, Nagai Y, Research Group for Cardiovascular Diseases (17C-1): Expert consensus document of neuroendovascular therapy 2009. *JNET* 3(Supple 1): 1–78, 2009
12) Giles KA, Hamdan AD, Pomposelli FB, Wyers MC, Schermerhorn ML: Stroke and death after carotid endarterectomy and carotid artery stenting with and without high risk criteria. *J Vasc Surg* 52: 1497–1504, 2010
13) Grigoryan M, Chaudhry SA, Hassan AE, Suri FK, Qureshi AI: Neurointerventional procedural volume per hospital in United States: implications for comprehensive stroke center designation. *Stroke* 43: 1309–1314, 2012
14) Hoh BL, Rabinov JD, Pryor JC, Carter BS, Barker FG: In-hospital morbidity and mortality after endovascular treatment of unruptured intracranial aneurysms in the United States, 1996–2000: effect of hospital and physician volume. *AJNR Am J Neuroradiol* 24: 1409–1420, 2003
15) Huang MC, Baaj AA, Downes K, Youssef AS, Sauvageau E, van Loveren HR, Agazzi S: Paradoxical trends in the management of unruptured cerebral aneurysms in the United States: analysis of nationwide database over a 10-year period. *Stroke* 42: 1730–1735, 2011
16) Sakai N, Taki W, Yoshimura S, Hyogo T, Ezura M, Matsumoto Y, Ito Y, Abe H, Sonobe M, Kobayashi S, Nemoto S, Murayama Y, Matsumaru Y, Oishi H, Kuwayama N, Miyachi S, Terada T, Komiyama M, Fujinaka T, Sugiu K, Sato K, Nakahara I, Kazekawa K, Hirohata M, Hyodo A, Sakai C; RESAT Study Group: Retrospective survey of endovascular treatment for ruptured intracranial aneurysm in Japan: Retrospective Endovascular Subarachnoid Aneurysm Treatment (RESAT) study. *Neurol Med Chir (Tokyo)* 50: 961–965, 2010
17) Siddiq F, Chaudhry SA, Tummala RP, Suri MF, Qureshi AI: Factors and outcomes associated with early and delayed aneurysm treatment in subarachnoid hemorrhage patients in the United States. *Neurosurgery* 71: 670–677; discussion 677–678, 2012
18) Taki W; PRESAT group, Sakai N, Suzuki H: Factors predicting retreatment and residual aneurysms at 1 year after endovascular coiling for ruptured cerebral aneurysms: Prospective Registry of Subarachnoid Aneurysms Treatment (PRESAT) in Japan. *Neuroradiology* 54: 597–606, 2012
19) Yoshimura S, Egashira Y, Sakai N, Kuwayama N; Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism-Japan retrospective survey group: Retrospective nationwide survey of acute stroke due to large vessel occlusion in Japan: a review of 1,963 patients and the impact of endovascular treatment. *Cerebrovasc Dis* 32: 219–226, 2011
20) Qureshi AI, Vazquez G, Tariq N, Suri MF, Lakshminarayan K, Lanzino G: Impact of International Subarachnoid Aneurysm Trial results on treatment of ruptured intracranial aneurysms in the United States. Clinical article. *J Neurosurg* 114: 834–841, 2011
21) Higashida RT, Lahue BJ, Torbey MT, Hopkins LN, Leip E, Hanley DF: Treatment of unruptured intracranial aneurysms: a nationwide assessment of effectiveness. *AJNR Am J Neuroradiol* 28: 146–151, 2007

Address reprint requests to: Nobuyuki Sakai, MD, DMSc, Department of Neurosurgery, Kobe City Medical Center, 2-1-1 Minatojima Minaminachi, Chuo, Kobe, Hyogo 650-0047, Japan.
e-mail: n.sakai@siren.ocn.ne.jp

短　報

抗血栓療法で良好に維持している左心室腔内血栓症の犬の1例

船山麻理菜　　寺崎絵里　　小宮山絵梨　　上地正実†

日本大学生物資源科学部（〒252-0880　藤沢市亀井野1866）

(2011年7月19日受付・2012年8月28日受理)

要　　約

犬の血栓塞栓症はまれである．われわれは，末梢性動脈血栓塞栓症及び左心室腔内における血栓形成が疑われる犬に遭遇した．症例はボーダー・コリー，避妊雌，4歳9カ月齢，両後肢の起立困難，肢端の冷感が突然認められたことから末梢性動脈血栓塞栓症が疑われた．また，心臓超音波検査にて左心室腔内心尖部に突出した腫瘤（20.6×18.5mm）が認められ，その経過から左心室腔内血栓を疑い，ダルテパリンナトリウム及び塩酸オザグレルの投与を行った．投与後7日で腫瘤は13.1×4.9mmまで縮小し，第58病日から歩行可能となり，第79病日に腫瘤は消失した．血栓の確定診断は，外科的除去による病理学的検査が必要だが，内科療法により短期間で消失したことから，腫瘤は血栓であると判断した．本症例では抗血栓療法による血栓形成の抑制により血栓を溶解に導くことができたと考えられた．

——キーワード：低分子ヘパリン，心筋梗塞，塩酸オザグレル，血栓症．

日獣会誌　66，52～56（2013）

血栓塞栓症は心臓内や血管内で形成された血栓により血流が遮断される疾患である．人においては血栓症の発症要因としてVirchowの3要因，すなわち①血管壁の性状変化，②血液成分の変化，③血流の変化が提唱されている［1］．血栓塞栓症は猫における発生が多く［2］，犬における血栓塞栓症はまれである．犬における血栓塞栓症の危険因子として，感染性心内膜炎が一般的であるが，副腎皮質機能亢進症，免疫介在性溶血性貧血，敗血症，蛋白漏出性腎症または蛋白漏出性腸症に併発する傾向がある［3, 4］．治療方法は，直接血栓を除去する外科療法，ヘパリン，ワルファリンなどの抗血栓療法，組織型プラスミノーゲンアクチベーター（t-PA）製剤などの血栓溶解療法がある［5, 6］．しかし，各治療法の問題点として，①外科療法は麻酔の危険性及び手術侵襲，②抗血栓療法は非侵襲的ではあるが効果が不十分なこと，③血栓溶解療法は虚血再灌流障害による高カリウム血症や代謝性アシドーシスなどを起こして死亡することが挙げられる［7, 8］．このため，人及び犬において標準的な治療指針はいまだ確立されていない．

われわれは，原疾患が明らかでない犬における左心室腔内血栓症及び末梢性動脈血栓塞栓症を経験した．抗血栓療法のみで症状の改善が認められ，良好な経過を観察しているのでその概要を報告する．

症　　例

症例は，ボーダー・コリー，避妊雌，4歳9カ月齢，

表1　第6病日から第420病日までの血液検査

病　日		6	13	22	30	79	100	420
RBC	($10^4/\mu l$)	389	287	521	501	550	601	734
WBC	($10^2/\mu l$)	328	488	202	176	132	116	56
Hct	(%)	28	23	38	36	40	41	44
PLT	($10^4/\mu l$)	7.5	40.4	34.5	41.8	47.2	39.3	36.0
CRP	(mg/dl)	6.2	5.2	5.7	7.7	3.1	0.0	0.1
総蛋白	(g/dl)	5.4	7.0	8.2	7.6	7.3	6.8	7.0
ALB	(g/dl)	1.1	1.6	2.2	2.3	2.4	2.7	3.4
ALKP	(IU/l)	244	243	322	263	205	166	79
ALT	(IU/l)	296	59	25	16	<10	<10	35
AST	(IU/l)	67	41	7	24	11	39	27
BUN	(mg/dl)	22	20	20	16	18	208	18
CREA	(mg/dl)	0.8	0.7	0.7	0.8	0.8	0.8	1.0
CK	(IU/l)	270	—	—	—	—	61	60
PT	(秒)	10.2	—	—	—	10.1	—	—
APTT	(秒)	24.2	—	—	—	<15	—	—
Fibrinogen	(mg/dl)	246	—	—	—	443	—	—
AT	(%)	56	—	—	—	87	—	—
FDPs	(μg/ml)	10	—	—	—	—	—	—

基準範囲：PT 6～9秒，APTT 15～21秒，
Fibrinogen 200～400 mg/dl，AT 75～135%，
FDP 4 μg/ml 以下
—：検査実施せず

† 連絡責任者：上地正実（日本大学生物資源科学部獣医内科学研究室）
〒252-0880　藤沢市亀井野1866　☎・FAX 0466-84-3481　E-mail：uechi.masami@cardiovets.jp

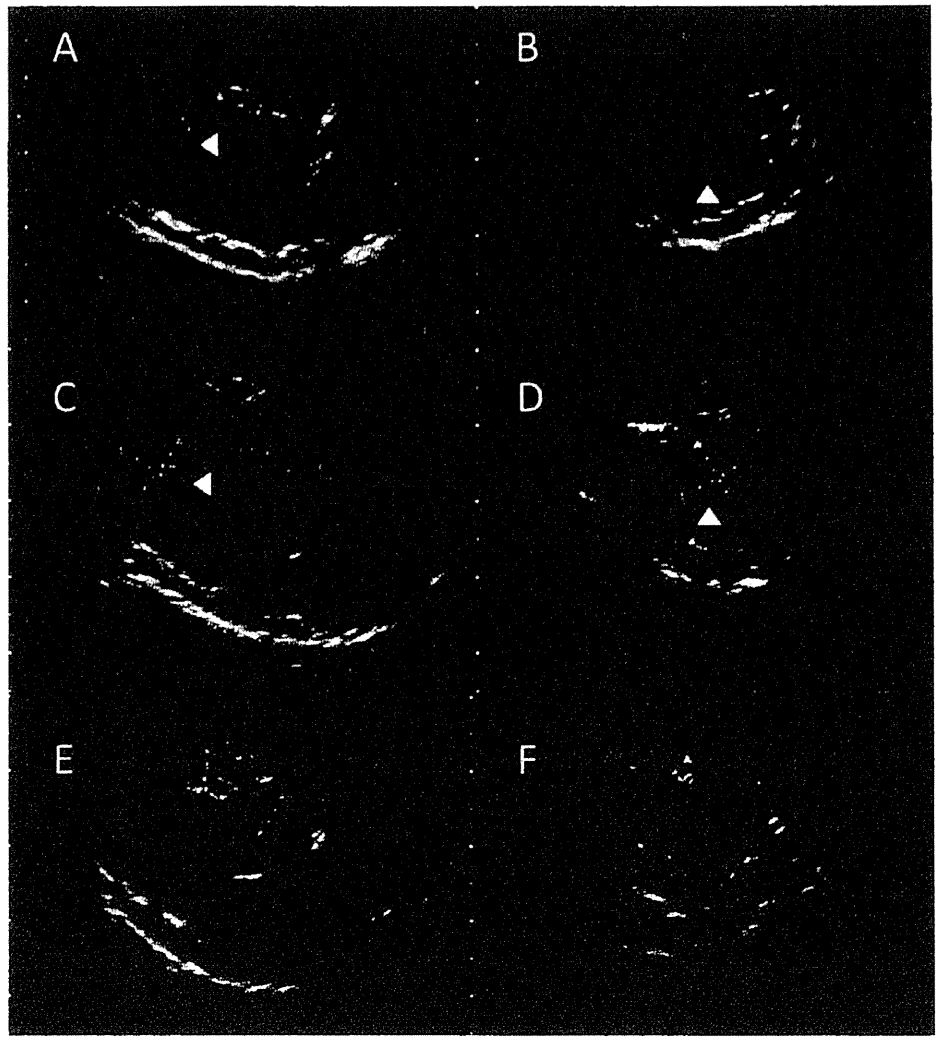

図1　心臓超音波検査所見
第6病日（A, B），第30病日（C, D），第79病日（E, F）の心臓超音波検査所見を示す．第79病日で腫瘤状エコー病変部（白矢頭）が消失した．A, C, Eは右側傍胸骨長軸四腔断面像，B, D, Fは右側傍胸骨短軸断面像乳頭筋レベルである．

体重14.5kg．2010年8月上旬に近医にて左後肢前十字靱帯損傷のためメロキシカム及びフィロコキシブが投与されていた．投薬24日目に総白血球数（34,900/μl）増加，投与27日目（第0病日）に突然の両後肢起立困難となり，股動脈圧の触知不可，爪床及び肉球の蒼白及び排尿排便困難が認められた．臨床徴候より末梢性動脈血栓塞栓症を疑った．ヘパリン，ジピリダモール，グリチルリチン酸モノアンモニウム，グルタチオン，シルデナフィルクエン酸塩が投与され，輸液として乳酸リンゲルが処置された．第6病日に日本大学付属動物病院循環器科に紹介された．

来院時の一般検査では，元気消失，起立不能，両後肢の疼痛，浮腫及び冷感があった．股動脈圧は微弱だが触知可能であった．血液検査では，総白血球数32,800/μl，C反応性蛋白濃度（CRP）6.2mg/dl，クレアチニンキナーゼ270IU/lは高値を示し，ヘマトクリット値28％，血小板数75,000/μl，アルブミン値1.1g/dlは低値を示した（表1）．また，線溶系及び血液凝固検査ではプロトロンビン時間（PT）10.2秒，活性化部分トロンボプラスチン時間（APTT）24.2秒，血漿フィブリノーゲン濃度246mg/dl，アンチトロンビン（AT）56％，フィブリン分解産物（FDP）10μg/mlであった．SpO_2は右後肢が96％，左後肢が95％であり，心電図検査（α6000 AX-D，フクダ エム・イー工業㈱，東京）にて不整脈は認められなかった．胸部X線検査にて心拡大は認められず（椎骨心計測比：10.5v，心胸郭比：63.7％），肺野

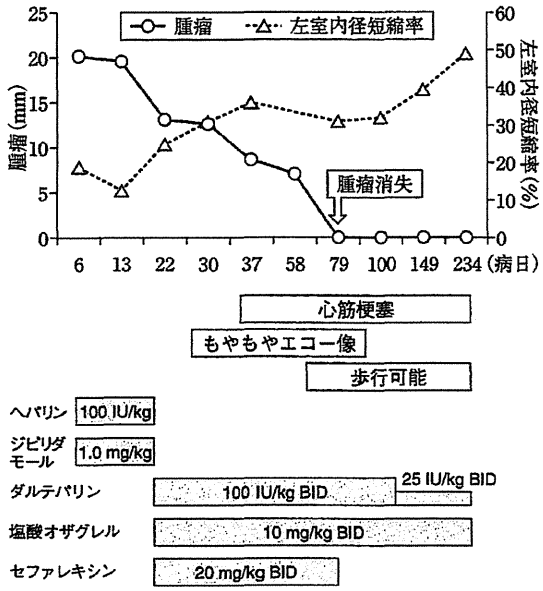

図2　腫瘤サイズ及び左室内径短縮率の推移．左縦軸は腫瘤サイズを，右縦軸は左室内径短縮率を示す．

に異常は認められなかった．心臓超音波検査（APLIO SSA-770A，東芝メディカルシステムズ㈱，栃木）では，左室内径短縮率は18.8％，左心房/大動脈比は1.46であり，心室中隔壁の高エコー性及び左心室腔内においてもやもやエコー像が認められた．また，左心室腔内心尖部に突出した高エコー性の腫瘤（20.6×18.5mm）が認められた．本腫瘤は左心室腔内心尖部に有茎状に付着し，血流に伴う可動性が確認された．心臓腫瘤の確定診断には外科的生検あるいは除去による病理学的検査が必要であるが，侵襲性が高い手技を選択しなければならない．そのため，本症例では心臓超音波検査及び血液検査の結果から心臓腫瘍あるいは血栓と仮診断した．

また，本症例では両後肢の疼痛，蒼白，股動脈圧消失，不全麻痺及び運動麻痺が認められたことから，末梢性動脈血栓塞栓症の発症も疑われた．末梢性動脈血栓の診断は超音波検査もしくは造影検査が必要であるが，本症例では臨床徴候から末梢性動脈血栓塞栓症と仮診断した．また，末梢性動脈血栓塞栓症の確定診断は，外科的除去術による病理学的検査が必要であるが，本症例では診断的治療として内科療法を選択した．

第13病日まで，ヘパリン加生理食塩水輸液，ジピリダモール，グリチルリチン酸モノアンモニウム，グルタチオン，シルデナフィルクエン酸塩の処置を継続したが，臨床徴候の改善は認められず，努力性呼吸が認められた．また，心臓超音波検査にて左室内径短縮率は12.6％，ヘマトクリット値は23％まで低下した．第14病日に輸血300m*l*を行い，ヘマトクリット値は33％まで上昇した．さらに，投薬内容をダルテパリンナトリウム注射液（100IU/kg, SC, BID），塩酸オザグレル（10mg/kg, PO, BID），セファレキシン（20mg/kg, PO, BID）に変更した．第22病日に呼吸状態は改善し，ヘマトクリット値は38％まで上昇した．血液検査では総白血球数20,200/μlが低下し，アルブミン値2.2g/d*l*は上昇した．また，心臓超音波検査にて，腫瘤は13.1×4.9mmに縮小したが，左心室腔内にもやもやエコー像が認められた．第30病日に心室中隔心尖部領域の運動性低下及び非薄化が認められた．

本症例は第58病日から歩行可能となった．第79病日に左心室腔内に腫瘤は認められなくなり，第79病日の線溶系及び血液凝固検査ではPT 10.1秒，APTT＜15秒，血漿フィブリノーゲン濃度443mg/d*l*，AT87％であった．第95病日に左心室腔内のもやもやエコー像は消失した（図1，2）．第234病日までダルテパリンナトリウム（25IU/kg, SC, BID）及び塩酸オザグレル（10mg/kg, PO, BID）の投与は継続された．現在，第420病日が経過しているが，一般状態は良好で左心室腔内に腫瘤は認められず，心室中隔壁に大きな変化はない．血液検査の異常及びその他心臓に異常は認められない．

考　　察

本症例は，左心室腔内に腫瘤及び末梢性動脈血栓塞栓症を発症したが，抗血栓療法により両疾患ともに改善が認められた．

本症例では，第6病日に左心室腔内に腫瘤が確認され，心臓腫瘍あるいは血栓の可能性が考えられた．左心室腔内の高エコー性腫瘤は，粘液腫または血栓である可能性が高い．しかし，両者に超音波検査における診断的特徴はなく，確定診断には病理学的検査を必要とする［9］．心臓腫瘍であった場合は外科的除去術が有効であるが，侵襲が高い．血栓であった場合は内科的治療により改善する可能性もあるため，今回は外科的除去術を選択しなかった．また，組織型プラスミノーゲンに選択的に作用し血栓を特異的に分解するt-PA製剤などの血栓溶解療法は，出血傾向及び血栓溶解後に生じる虚血再灌流障害の発生率が高いことが報告されている［8］．特に獣医領域での血栓塞栓症は血流障害の発現から治療を開始するまで長時間経過している場合が多く，虚血再灌流障害を惹起する可能性が高い．このため本症例ではt-PA製剤などによる血栓溶解療法を実施しなかった．

本症例で選択した薬剤は，トロンボキサンA_2合成酵素阻害薬及び低分子ヘパリンである．血管内皮に接着した血小板は，トロンビン，トロンボキサンA_2，アドレナリンなどを遊離し，付近の血小板を凝集させるため［7］，血小板凝集抑制及び血管拡張作用を示すトロンボキサンA_2合成酵素阻害薬［10, 11］を選択した．また，APTT

を延長させずに第Xa因子を阻害する低分子ヘパリン[12]は，未分画ヘパリンに比較して作用が緩徐であり，腎不全，過体重，妊娠動物を除き，薬効モニタリングの必要性が低い利点がある．これら両薬剤の併用は持続性のトロンビン産生を抑制することが知られている[13]．本症例では左心室腔内の腫瘤が短期間で退縮したことから，腫瘤は血栓であったと考えられた．

左心室腔内血栓症に関連する疾患は，心筋梗塞，感染性心内膜炎の報告があるが，発症の原因はいまだ解明されていない[9]．本症例では起立困難を呈する（第0病日）前に総白血球数が増加し，第6病日に血小板数の低値，APTTの延長，ATの低値及びFDPの高値を示したことから播種性血管内凝固症候群（DIC）であったと考えられた．人において敗血症による感染性心内膜炎及びDICが，血行動態と微小血管の機能不全を誘引し，急性の冠状動脈血栓症を引き起こす[14]．また，犬においては感染性心内膜炎に続発する冠状動脈の敗血症性塞栓症が知られている．本症例では第6病日に左心室の可動性低下，第6病日から第13病日までに左室内径短縮率の低下，第22病日に左心室内もやもやエコー像，第30病日に心室中隔部の局所的な運動性低下，心室壁の非薄化及び高エコー性所見が認められたことから敗血症による感染性心内膜炎により，冠状動脈の血栓塞栓症が生じ，急性心筋梗塞が生じたと示唆された．心筋梗塞後，心筋の局所的な運動性低下[15-17]が左心室腔内血栓症を誘引した．第30病日までに冠状動脈側副路の発達により冠状血流量が増加し心筋梗塞部位が縮小するとともに[18]，左室内径短縮率が改善したと考えられた．

また，犬の末梢性動脈血栓塞栓症はまれな疾患であり，好発犬種，雌雄差は認められない[19]．発症の原因はいまだ解明されていないが，敗血症による蛋白異化亢進は低アルブミン血症を誘引し，末梢性動脈血栓塞栓症の原因となる[20, 21]．さらに第0病日前に投与されていた選択的シクロオキシゲナーゼ-2阻害薬の投与は血管壁の性状変化及び血小板の活性化を誘引することで血栓塞栓症のリスク因子となる[22]．また末梢性動脈血栓塞栓症の基礎疾患として，血液粘稠度の亢進，血管炎などの炎症性疾患の存在を考慮する必要がある．本症例では心筋梗塞による左心室腔内の血液うっ滞，敗血症による血管内皮からの組織因子産生，抗凝固性蛋白であるトロンボモジュリンの発現及び血管内皮由来のプラスミノーゲンアクチベーターの産生抑制[23]，DIC，選択的シクロオキシゲナーゼ-2阻害薬などにより末梢性動脈血栓塞栓症を引き起こしたと考えられた．

本症例では，抗血栓療法により左心室腔内の血栓と思われる腫瘤を溶解させることができた．獣医療では，血栓塞栓症の標準的な治療法はいまだ確立されていないため，今後さらなる検討が必要である．

引用文献

[1] Catherine NB, Roopen A : Virchow and his triad : a question of attribution, Br J Haematol, 143, 180-190 (2008)

[2] Laste NJ, Harpster NK : A retrospective study of 100 cases of feline distal aortic thromboembolism : 1977-1993, J Am Anim Hosp Assoc, 31, 493-500 (1995)

[3] Goncalves R, Penderis J, Chang YP, Zoia A, Mosley J, Andersong TJ : Clinical and neurological characteristics of aortic thromboembolism in dogs, J Small Anim Pract, 49, 178-184 (2008)

[4] Sykes JE, Kittleson MD, Chomel BB, Macdonald KA, Pesavento PA : Clinicopathologic findings and outcome in dogs with infective endocarditis : 71 cases (1992-2005), J Am Vet Med Assoc, 228, 1735-1747 (2006)

[5] Dunn ME : Thrombectomy and thrombolysis : the interventional radiology approach. J Vet Emerg Crit Care (San Antonio), 21, 144-150 (2011)

[6] Clare AC, Kraje BJ : Use of recombinant tissue-plasminogen activator for aortic thrombolysis in a hypoproteinemic dog, J Am Vet Med Assoc, 212, 539-543 (1998)

[7] Konecny F : Thromboembolic conditions, aetiology diagnosis and treatment in dogs and cats, Acta Vet Brno, 79, 497-508 (2010)

[8] Welch KM, Rozanski EA, Freeman LM, Rush JE : Prospective evaluation of tissue plasminogen activator in 11 cats with arterial thromboembolism, J Feline Med Surg, 12, 122-128 (2009)

[9] Yadava OP, Yadav S, Juneja S, Chopra VK, Passey R, Ghadiok R : Left ventricular thrombus sans overt cardiac pathology, Ann Thorac Surg, 76, 623-625 (2003)

[10] Nakazawa M, Iizuka K, Ujiie A, Hiraku S, Ohki S : Research and development of Ozagrel, a highly selective inhibitor of TXA2 synthase, Yakugaku Zasshi, 114, 911-933 (1994) (in Japanese)

[11] Naito J, Komatsu H, Ujiie A, Hamano S, Kubota T, Tsuboshima M : Effects of thromboxane synthetase inhibitors on aggregation of rabbit platelets, Eur J Pharmacol, 91, 41-48 (1983)

[12] Weitz JI : Low-molecular-weight heparins, N Engl J Med, 337, 688-698 (1997)

[13] Andreotti F, Testa L, Biondi-Zoccai GG, Crea F : Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes : an updated and comprehensive meta-analysis of 25,307 patients, Eur Heart J, 27, 519-526 (2006)

[14] Yamauchi T, Yamamoto S, Fukumoto M, Oyama N, Nakano A, Nakayama T, Iwasaki H, Shimizu H, Tsutani H, Lee JD, Okada K, Ueda T : Early manifestation of septic shock and disseminated intravascular coagulation complicated by acute myocardial infarction in a patient suspected of having Legionnaires' disease, Kansenshogaku Zasshi, 72, 286-292 (1998)