CASE SERIES

Diabetes mellitus and carotid artery plaques exhibiting high-intensity signals on MR angiography are related to increased platelet reactivity after carotid artery stenting

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Received 30 March 2016
Revised 7 June 2016
Accepted 15 June 2016
Published Online First 1 July 2016

ABSTRACT

Background Increased platelet reactivity after carotid artery stenting (CAS) may cause thromboembolic complications.

Objective This study aimed to investigate the incidence of increased platelet reactivity after CAS and to determine the factors related to it.

Methods Patients who underwent CAS were recruited prospectively. They received pre-procedural antiplatelet therapy comprising some combination of aspirin (100 mg/day), clopidogrel (75 mg/day), and/or cilostazol (200 mg/day) for a minimum of 7 days. ADP- and collagen-induced platelet aggregation were measured before and 4 days after CAS. Changes in platelet reactivity were reported as changes in the categorized platelet reactivity grade based on the effective dose 50%. Clinical characteristics of patients with and without increased platelet reactivity were compared.

Results Among 38 consecutive patients who underwent CAS, 18 (47%) exhibited increased platelet reactivity. Diabetes mellitus (OR 15.0; 95% CI 2.1 to 106.5; p=0.007) and carotid artery plaques exhibiting high-intensity signals (HIS) on time-of-flight MR angiography (TOF-MRA) (OR 25.2; 95% CI 2.0 to 316.2; p=0.013) were independently associated with increased platelet reactivity in a multivariate analysis.

Conclusions Increased platelet reactivity occurred in nearly half of the studied patients subjected to CAS and was independently associated with diabetes mellitus and carotid artery plaques exhibiting HIS on TOF-MRA.

INTRODUCTION

Despite the designation of carotid endarterectomy (CEA) as the gold standard management for internal carotid artery stenosis according to multiple large randomized controlled clinical trials,[1–3] the use of carotid artery stenting (CAS) as an appropriate alternative therapy is increasing. Two randomized controlled clinical trials of CEA and CAS have demonstrated comparable levels of procedural safety and stroke prevention efficacy,[4 5] and other randomized controlled clinical trials have failed to reveal the non-inferiority of CAS.[6–8] Ischemic events are the most common CAS-related complications, and a meta-analysis of several randomized clinical controlled trials found that the rate of ischemic stroke within 30 days was 7.0% among patients treated with CAS compared with only 3.5% among those treated with CEA.[9] Accordingly, the importance of dual antiplatelet therapy as standard pretreatment has been emphasized for patients undergoing CAS.[10–12]

Increasing concerns regarding poor responses to antiplatelet therapy have been raised in the fields of neurovascular and cardiology.[13–16] Recent reports involving the point-of-care assay have demonstrated intra-individual changes in measured platelet reactivity from before to after neurovascular stenting.[17 18] Although the point-of-care assay, which uses single concentrations of specific agonists, is a fairly simple and convenient tool for detecting insufficient platelet inhibition, the induction of platelet aggregation at a fixed single concentration is a crucial issue. More appropriately, the concentration of agonist used to induce platelet aggregation should be optimized to reflect individual differences in platelet reactivity after antiplatelet therapy.[19 20]

Light transmittance aggregometry (LTA), which allows the use of several agonists at specific concentrations, is considered the gold standard for platelet aggregation measurement. Platelet reactivity tends to exhibit an active sigmoid dose–response curve[21] in which changes in reactivity appear as a curve shift.[22] The effective dose 50% (ED_{50}) is widely used to evaluate reactivity in this type of dose response; specifically, a change in the ED_{50} indicates a change in reactivity. Therefore, platelet aggregation should be evaluated using multiple concentrations of the agonist because the ED_{50} is determined based on the results of these tests.

In this study we used LTA to investigate changes in platelet reactivity from before to after CAS and identified factors related to increased platelet reactivity.

METHODS

Patients

Between October 2013 and September 2015, all patients admitted with a diagnosis of internal carotid artery stenosis and treated with CAS at the Department of Neurosurgery, Gifu University Hospital were investigated prospectively. Clinical demographic information such as age, sex, previous atherosclerosis-related history, and perioperative medical conditions was recorded. The indication criterion for CAS was stenosis >80% in asymptomatic lesions and/or >50% in symptomatic lesions, in accordance with the North American

To cite: Tsujimoto M, Enomoto Y, Kokuzawa J, *et al. J NeuroIntervent Surg* 2017;**9**:106–110.

Symptomatic Carotid Endarterectomy Trial (NASCET) protocol. Patients were treated with antiplatelet therapy comprising some combination of aspirin (100 mg/day), clopidogrel (75 mg/day), and/or cilostazol (200 mg/day) for a minimum of 7 days before the procedure; these agents were selected at the discretion of the attending physicians. Patients continued to receive the same antiplatelet therapy for at least 3 months after CAS. The experimental protocol was approved by the institutional ethics committee and informed consent was obtained from all patients.

Blood sampling and preparation of human platelet-rich plasma

Blood samples were collected before and 4 days after CAS to avoid the effects of heparin or catecholamine, which was used during or after CAS. Blood samples were drawn into a 1/10 volume of 3.2% sodium citrate. Platelet-rich plasma (PRP) was obtained from blood samples by centrifugation at 155*g* for 12 min at room temperature. Platelet-poor plasma (PPP) was prepared from residual blood by centrifugation at 1400*g* for 5 min.

ADP and collagen induction of light transmittance platelet aggregation

Aggregation of platelets in citrated PRP was conducted at 37°C in a light transmittance aggregometer (PA-200 Kowa, Tokyo, Japan) with a stirring speed of 800 rpm. ADP (Sigma-Aldrich, St Louis, Missouri, USA) and collagen (Takeda Austria, Linz, Austria) were used to induce aggregation. Platelets were preincubated for 1 min; subsequently, aggregation was monitored for 4 min after the addition of the agonist. The PRP and corresponding PPP transmittance percentages were recorded as 0% and 100%, respectively, and aggregation was expressed as a percentage of the maximum transmittance. Each agonist was tested at three concentrations: ADP 3, 10, and 20 μM and collagen 3, 10, and 20 μg/mL.

The ED_{50} was defined as the concentration required to induce >50% platelet aggregation transmittance; a low ED_{50} value indicates high platelet reactivity. We used the ED_{50} to classify platelet reactivity to ADP stimulation as follows: high reactivity, ED_{50} ≤3 μM; medium to high reactivity, 3.1–10 μM; medium to low reactivity, 10.1–20 μM; and low reactivity, >20 μM. Similarly, reactivity to collagen stimulation was classified as follows: high reactivity, ED_{50} ≤3 μg/mL; medium to high reactivity, 3.1–10 μg/mL; medium to low reactivity, 10.1–20 μg/mL; and low reactivity, >20 μg/mL (figure 1). We defined an increase in platelet reactivity as a shift to a higher reactivity category over serial assessments. Patients who exhibited increased platelet reactivity to ADP stimulation, collagen stimulation, or both were categorized as activated.

MRI analysis

All patients underwent preoperative MRI screening followed by digital subtraction angiography to ascertain the suitability of their lesions for CAS. Previous reports identified carotid artery plaques exhibiting high-intensity signals (HIS) on time-of-flight magnetic resonance angiography (TOF-MRA), as observed on sagittal oblique maximum intensity projection images, as an independent risk factor for ischemic complications in patients subjected to CAS.[23] We therefore recorded this sign during plaque evaluation.

In all patients, baseline diffusion-weighted imaging (DWI) was performed after diagnostic angiography and before CAS. A second DWI was performed within 72 hours after CAS, at which time only newly appearing lesions were regarded as ischemic lesions after CAS. MRI findings were evaluated by blinded neuroradiologists.

CAS procedures

All CAS procedures were performed under local anesthesia via the percutaneous transfemoral route. All procedures were performed by a single neurointerventional team. A 100 U/kg heparin bolus was administered immediately before the procedure to increase the activated clotting time to a minimum of

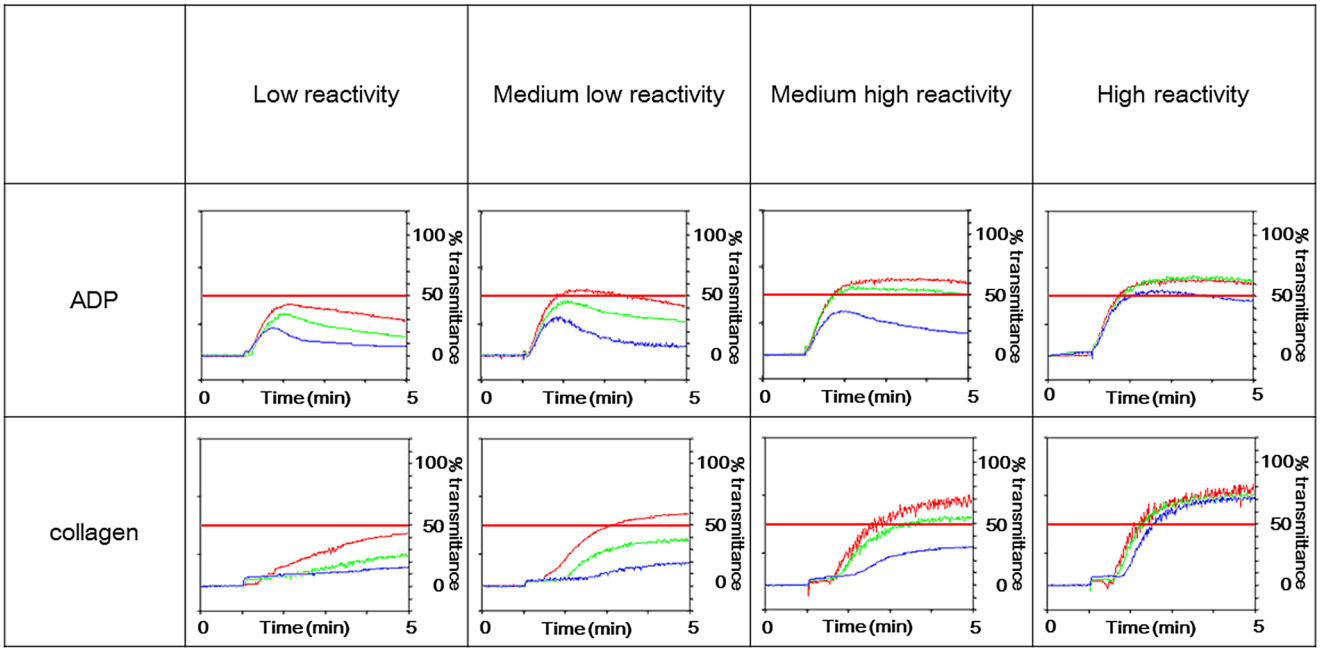

Figure 1 Platelet reactivity grade categorization based on effective dose 50% (ED_{50}) values. Representative platelet aggregation curves of each platelet reactivity grade are shown. Blue lines indicate 3 μM ADP and 3 μg/mL collagen, green lines indicate 10 μM ADP and 10 μg/mL collagen, and red lines indicate 20 μM ADP and 20 μg/mL collagen.

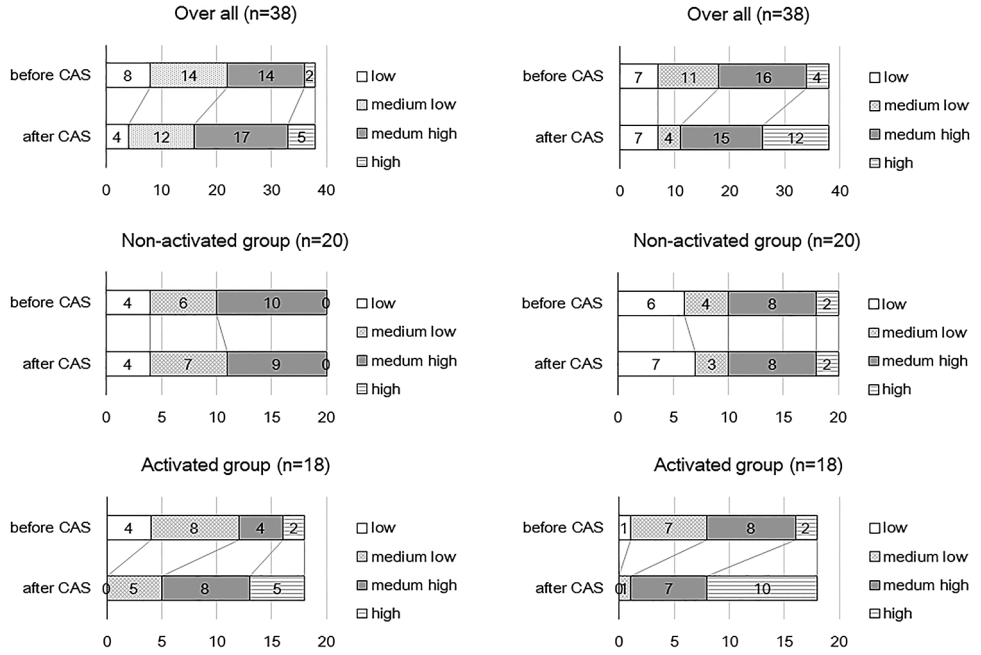

Figure 2 Distribution of categorized platelet reactivity grades based on effective dose 50% (ED_{50}) values. The numbers of patients are shown in each cell according to the platelet reactivity category. Platelet reactivity grades were classified as follows: high reactivity, ED_{50} ≤3 μM; medium to high reactivity, 3.1–10 μM; medium to low reactivity, 10.1–20 μM; and low reactivity, >20 μM for ADP stimulation (A), and high reactivity, ED_{50} ≤3 μg/mL; medium to high reactivity, 3.1–10 μg/mL; medium to low reactivity, 10.1–20 μg/mL; and low reactivity, >20 μg/mL for collagen stimulation (B).

250 s. Two types of embolic protection devices were used: distal balloon protection via a Guardwire (Medtronic AVE, Santa Rosa, California, USA; n=16) or proximal balloon protection via an Optimo (Tokai Medical Products, Aichi, Japan) and Guardwire (n=22). Two types of stents were placed in the stenotic lesions: an open cell stent such as Precise (Johnson & Johnson, Cordis, Minneapolis, Minnesota, USA; n=32) or Protage (Covidien, Mansfield, Massachusetts, USA; n=2), or a Wallstent (Boston Scientific, Natick, Massachusetts, USA; n=4) closed cell stent. Stroke neurologists performed neurological assessments 24 hours after CAS.

Statistical analysis

Values are presented as means±SD. Categorical variables were analyzed using the χ^2 or Fisher's exact test as appropriate. Continuous variables with normal distributions were analyzed using the Student's t-test or the paired t-test; those with non-normal distributions were analyzed using the Mann-Whitney U test or Wilcoxon signed-rank test as appropriate. Univariate and multivariate logistic regression analyses were performed to determine which factors correlated with increased platelet reactivity after CAS. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using PASW Statistics software, V.18 (SPSS Japan, Tokyo, Japan).

RESULTS

A total of 38 consecutive patients who underwent CAS during the study period were included. All procedures were successfully completed and yielded adequate angiographic results. Among the 38 patients, 20 (53%) and 18 (47%) were categorized as non-activated and activated, respectively. ADP- and collagen-induced changes in categorized platelet reactivity grades are shown in figure 2A and B, respectively. The characteristics of patients in the non-activated and activated groups are shown in table 1.

Platelet reactivity before CAS did not differ significantly between the groups; in contrast, platelet reactivity after CAS was significantly higher in the activated group than in the non-activated group at all concentrations of ADP and collagen (table 2). In the univariate analysis, a significantly larger number of patients in the activated group presented with diabetes mellitus (DM) compared with the non-activated group (13/18 (72%) vs 3/20 (15%); p<0.001). The level of glycated hemoglobin (HbA1c) was also significantly higher in the activated group than in the non-activated group (6.5±0.7 mg/dl vs 5.9±0.7 mg/dl; p=0.02). Furthermore, HIS was observed significantly more frequently on TOF-MRA evaluations of patients in the activated group (10/18; 56%) than in the non-activated group (1/20; 5%; p=0.001).

After CAS, the incidence of ischemic lesions on DWI did not differ significantly between the groups (5/20 (25%) in the non-activated group vs 6/18 (33%) in the activated group; p=0.64). One patient in the non-activated group experienced an ipsilateral symptomatic stroke during CAS (1/20; 5%); no symptomatic strokes occurred in the activated group (p=0.53). No other thromboembolic complications occurred within 30 days after CAS in either group.

Only variables with p values <0.20 in the univariate analysis were included in the multivariate logistic regression model; these included DM, hyperlipidemia, HIS on TOF-MRA, triglyceride concentration, and HbA1c concentration. DM (OR 15.0; 95% CI 2.1 to 106.5; p=0.007) and the presence of HIS on TOF-MRA (OR 25.2; 95% CI 2.0 to 316.2; p=0.013) were found to be independent factors related to increased platelet reactivity after CAS (table 3).

DISCUSSION

In this study we found that nearly half of the studied patients developed increased platelet reactivity after CAS, and that DM and the presence of carotid artery plaques exhibiting HIS on

Table 1 Baseline characteristics among patients in the present study subgroups

	All (n=38)	Non-activated group (n=20)	Activated group (n=18)	p Value
Age, years	71.9±8.0	71.0±9.0	73.0±6.8	0.44
Male sex	32 (84)	18 (90)	14 (78)	0.28
History				
Diabetes mellitus	16 (42)	3 (15)	13 (72)	<0.001
Hypertension	31 (82)	16 (80)	15 (83)	0.56
Hyperlipidemia	25 (66)	11 (55)	14 (78)	0.14
Symptomatic stenosis	17 (45)	9 (45)	8 (44)	0.97
Medication				
Aspirin	32 (84)	18 (90)	14 (78)	0.28
Clopidogrel	37 (97)	20 (100)	17 (94)	0.47
Cilostazole	13 (34)	5 (25)	8 (44)	0.21
Statins	24 (63)	11 (55)	13 (72)	0.27
Plaque evaluation MRI/MRA				
HIS on TOF-MRA	11 (29)	1 (5)	10 (56)	0.001
CAS procedure				
Protection				0.7
Distal balloon protection	16 (42)	9 (45)	7 (39)	
Proximal balloon protection	22 (58)	11 (55)	11 (61)	
Stent				0.34
Open cell	34 (89)	17 (85)	17 (94)	
Closed cell	4 (11)	3 (15)	1 (6)	
Periprocedural ischemic symptoms	1 (3)	1 (5)	0 (0)	0.53
Postoperative ischemic lesions on DWI	11 (29)	5 (25)	6 (33)	0.64
Laboratory parameters				
Triglycerides, mg/dL	117.0±53.5	100.5±42.0	134.5±60.0	0.09
HDL cholesterol, mg/dL	61.1±30.0	64.3±33.9	57.1±23.7	0.5
LDL cholesterol, mg/dL	104.2±41.7	112.2±48.0	93.9±30.4	0.21
C-reactive protein, mg/dL	0.5±1.4	0.7±1.9	0.3±0.6	0.34
Hemoglobin A1c, mg/dL	6.2±0.8	5.9±0.7	6.5±0.7	0.02
Platelets, $\times 10^4/mm^3$	22.6±4.5	22.3±4.1	23.0±4.9	0.72

Values are shown as mean±SD or n values (%).
CAS, carotid artery stenting; DWI, diffusion-weighted imaging; HDL, high-density lipoprotein; HIS, high-intensity signal; LDL, low-density lipoprotein; TOF-MRA, time-of-flight magnetic resonance angiography.

Table 2 Maximum aggregation values

	Non-activated group (n=20)	Activated group (n=18)	p Value
Before CAS			
ADP			
3 μM	31.2±11.7	29.7±12.8	0.70
10 μM	45.1±13.4	44.7±12.8	0.62
20 μM	51.4±12.9	51.9±13.6	0.93
Collagen			
3 μg/mL	30.9±17.4	27.4±18.5	0.63
10 μg/mL	47.9±20.9	49.3±19.4	0.82
20 μg/mL	59.1±22.4	61.6±15.4	0.87
After CAS			
ADP			
3 μM	32.3±10.4	41.0±14.3	0.037
10 μM	46.6±11.1	57.5±8.5	0.002
20 μM	53.5±12.6	63.8±8.4	0.031
Collagen			
3 μg/mL	30.5±17.6	49.3±19.4	0.003
10 μg/mL	48.5±19.5	67.6±12.7	0.001
20 μg/mL	61.6±18.0	77.0±10.5	0.022

Values are shown as mean±SD.
CAS, carotid artery stenting.

TOF-MRA were independently associated with increased platelet reactivity after CAS. To our knowledge, this study is the first to conduct an LTA-based investigation of factors associated with increased platelet reactivity after CAS.

Following the placement of a stent within a vessel, platelet-rich thrombi form in response to the foreign material.[24] In addition, the exposed subendothelium—a consequence of cracking and dislodging of the plaque due to balloon angioplasty or stent deployment—interacts with platelets and induces additional thrombogenic reactions. In a previous report we noted that carotid artery plaques that exhibited HIS on TOF-MRA indicated the presence of plaques containing fragile components.[23] Such plaques are at risk of rupture during CAS procedures, which could lead to increased platelet activation in the affected patients.

Among patients subjected to CAS, previously reported risk factors for stroke or death after CAS included DM and age >75 years;[25] however, the mechanism underlying these associations was not clarified. Several mechanisms have been suggested to explain the enhanced platelet function characteristic of DM, among which metabolic alterations, oxidative stress, and endothelial dysfunction appear to play crucial roles.[26] In patients with DM, amplified platelet reactivity to several agonists and insufficient suppression of activated platelets consequent to endothelial dysfunction might promote platelet reactivity after CAS. Our observation of increased platelet

Table 3 Multivariate logistic regression analysis of independent predictive factors associated with increased platelet reactivity after CAS

	OR	95% CI	p Value
Diabetes mellitus	15.0	2.10 to 106.5	0.007
HIS on TOF-MRA	25.2	2.00 to 316.2	0.013

CAS, carotid artery stenting; HIS, high-intensity signal; TOF-MRA, time-of-flight magnetic resonance angiography.

reactivity might explain the poor outcomes of patients with DM after CAS.

Several studies have reported the occurrence of thromboembolic complications both within and beyond 24 h after CAS,[27 28] and meta-analyses of randomized controlled clinical trials have reported relatively high incidence rates of thromboembolic complications within 30 days after CAS.[9] Despite improvements in the devices used to protect against embolic barrage during CAS, the prevention of post-procedural thromboembolic complications is a critical issue that should be addressed to improve the outcomes of patients undergoing CAS. Continuous intensive antiplatelet therapy during the periprocedural period, which aims to reduce the number of thromboembolic complications, is an advantage of CAS relative to CEA; however, the increased platelet reactivity associated with the former procedure might counteract this advantage.

This study has several limitations. First, this was a single-center study of a small number of patients and therefore we could not draw any definitive conclusions regarding the relationship between changes in platelet reactivity after CAS and thromboembolic events. Second, the method used to classify patients as activated or non-activated could not be used to evaluate changes in platelet reactivity in all patients because, once a patient had been categorized as highly reactive, further increases in platelet reactivity could not be identified. In the present study, no patients were categorized as highly reactive to both ADP- and collagen-induced platelet aggregation, and therefore increased platelet reactivity to at least one agonist could be determined. To resolve these limitations, future analyses should include platelet functioning tests involving multiple concentrations of multiple agonists and larger numbers of patients to ensure the accurate recognition of changes in platelet reactivity after CAS.

CONCLUSIONS

This study observed increased post-procedural platelet reactivity in nearly half of patients subjected to CAS. In addition, DM and the presence of carotid artery plaques exhibiting HIS on TOF-MRA were found to be independently associated with increased platelet reactivity after CAS.

Acknowledgements The authors thank Dr Takayuki Kato and Dr Yasuhiko Kaku for their advice on editing the manuscript.

Funding This study was supported by Grants-in-Aid for Scientific Research Grant Number 25861267 and 16K20001 from the Japan Society for the Promotion of Science.

Competing interests None declared.

Ethics approval Ethics approval was obtained from the Committee of Ethics in Gifu University Graduate School of Medicine.

Provenance and peer review Not commissioned; externally peer reviewed.

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