



Serum Sulfatide Levels across Atheromatous Plaques are Significantly Affected by Plaque Injury Caused by Percutaneous Coronary Intervention

Akihito Kudo¹ · Tetsuya Ishikawa¹ · Hidehiko Nakamura¹ · Kota Yamada¹ · Shiro Nakahara¹ · Isao Taguchi¹ · Teruo Inoue² · Ken-ichi Sako³ · Mamoru Kyogashima⁴

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Abstract

Sulfatides might accelerate atherothrombosis. Therefore, this study aimed to monitor serum sulfatide levels in coronary arteries across atheromatous plaques during percutaneous coronary intervention (PCI) with either drug-eluting stents or drug-coated balloons. From every patient, we collected blood from points 1 and 2 before PCI, and points 3 and 4 15 min after PCI, where odd numbered points were proximal and even numbered points were distal to a stenotic lesion. Patients were separated into two groups on the basis of the requirement of a pre-balloon dilation technique (pre-BD) before collecting samples at point 2. This was because of difficulty in passing a microcatheter through narrowed lumens around atheromatous lesions. In patients without pre-BD ($n = 23$), mean serum sulfatide levels at points 2 (4.60 ± 4.04 nmol/mL), 3 (4.35 ± 3.76 nmol/mL), and 4 (4.53 ± 3.26 nmol/mL) were significantly higher than those at point 1 (2.49 ± 1.11 nmol/mL; all $p < 0.05$). Patients with pre-BD ($n = 18$) required additional time (15–20 min) for collecting samples at points 2 to 4 compared with those without pre-BD, but there was no significant difference between the groups. The reason for this lack of significance is not known but may be due (at least in part) to diffusion of sulfatides in the circulation caused by the extra time needed for collection. These results suggest that accumulated sulfatides in stenotic plaques evoke atherothrombosis because of the thrombogenic property of sulfatides under pathological conditions.

Keywords Sulfatide · Coronary artery disease · Plaque injury · Atherothrombosis

Introduction

Sulfatides, which are sulfuric esters of galactosylceramides (galactocerebrosides), are a group of sulfated glycosphingolipids [1]. They are located primarily on the

plasma membrane, especially the myelin sheath. From the late 1980s, our team, as well as other research groups, have focused on the role of sulfatides in thrombosis and hemostasis [2, 3]. In 1987, Hara and Taketomi observed high amounts of sulfatides in serum lipoproteins, including low-density lipoprotein from Watanabe hyperlipidemic rabbits [4], and their accumulation in atheromatous aortae [5]. We previously reported that sulfatides induced large thrombi if they were injected into rats with intensely damaged vessels [6, 7]. Furthermore, we also demonstrated that sulfatides play a major role in inflammation in vascular injury and initiate neointimal thickening after bare-metal stent implantation [8]. Recently, Li *et al.* reported high peripheral serum sulfatide levels in patients with ST segment elevation myocardial infarction (STEMI) [9]. These observations suggest that sulfatides in sera and in atheromatous plaques in humans could contribute to the pathogenesis of acute coronary syndrome.

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✉ Mamoru Kyogashima
mkyogashi@nichiyaku.ac.jp

¹ Department of Cardiology, Dokkyo Medical University Saitama Medical Center, Koshigaya, Saitama 343-8555, Japan

² Department of Cardiovascular Medicine, Dokkyo Medical University, Mibu-machi, Tochigi 321-0293, Japan

³ Clinical Pharmacological Educational Center, Nihon Pharmaceutical University, Ina-machi, Saitama 362-0806, Japan

⁴ Division of Microbiology and Molecular Cell Biology, Nihon Pharmaceutical University, 10281 Komuro, Ina-machi, Saitama 362-0806, Japan

In this study, we directly measured sulfatide levels proximal and distal to a stenotic lesion before and after percutaneous coronary intervention (PCI) in patients with stable atherosclerotic coronary artery disease. This study aimed to determine whether plaque rupture affects local sulfatide levels across plaques.

Methods

Study Design

We included patients with stable atherosclerotic coronary artery disease who underwent planned single coronary stent implantation or balloon angioplasty alone using a drug-coated balloon (with the exception of three patients; see Table 1) from October 2014 to December 2015. In all of the patients (one-vessel disease, 27/41 (65.9%); two-vessel disease, 8/41 (19.5%); three-vessel disease, 6/41 (14.6%)), the target lesion was a type A or B lesion according to the American College of Cardiology/American Heart Association lesion classification [10] in the proximal left anterior descending artery. To reduce the heterogeneity of the study population, we excluded patients with chronic kidney disease (CKD) stage G3b or higher [11]. All of the patients received oral medications, including antiplatelet agents,

statins, beta-blockers, renin–angiotensin system inhibitors, long-acting nitrates, or calcium channel blockers (Table 1).

The sampling procedure is shown in Fig. 1. Blood was sampled at four points in each patient. Before the procedure, point 1 was sampled proximal to the stenotic lesion and point 2 was sampled distal to the lesion. Point 3 was sampled proximally 15 min after the procedure and point 4 distally 15 min after the procedure. A microcatheter was used to sample blood distal to the lesion. All patients were divided into two groups according to the requirement for pre-balloon dilation (pre-BD) before sampling blood at point 2 because of an incapability to pass the microcatheter through the lesion.

Intravenous heparin was administered to maintain an activated clotting time of 200–250 s during the procedure. The blood samples were run off at one time in a blinded fashion. At each sampling point, whole blood was immediately collected into a plain tube or a tube containing acid citrate dextrose.

Measurement of Sulfatides

Sulfatides were extracted from 50 μ L of serum with a ratio of *n*-hexane/isopropanol of 3:2 (v/v). Sulfatides were then analyzed as lyso forms using a matrix-assisted laser desorption/ionization time-of-flight mass spectrometer (Autoflex™; Bruker Daltonik, Bremen, Germany) in the negative ion mode [12].

Measurement of Coagulative, Fibrinolytic, and Coronary Atherosclerosis Markers

Thrombin–antithrombin complex (TAT), plasmin– α 2-plasmin inhibitor complex (PIC), and high-sensitivity C-reactive protein (hs-CRP) levels were analyzed at SRL, Inc. (Tokyo, Japan) using a chemiluminescent enzyme immunoassay, latex photometric immunoassay, and nephelometry, respectively. Diacron-reactive oxygen metabolite (d-ROM) testing for oxidative stress was performed at Dokkyo Medical University Saitama Medical Center laboratory as previously described [13]. The results of the d-ROM test are expressed in arbitrary units (Caratelli Units [U.CARR]), where 1 U.CARR corresponds to 0.08 mg/100 mL H₂O₂.

Statistical Analysis

Values are expressed as the mean \pm SD. Variables were evaluated by repeated-measures analysis of variance for intragroup comparison. For comparison between values at point 1 from different groups, the unpaired *t* test was used. A *p* value < 0.05 was considered to be significant. Analyses were performed using KaleidaGraph, version 4.5 (Synergy Software, Reading, PA, USA).

Table 1 Characteristics of patients undergoing PCI

Age, years	42–79 (66 \pm 11)
Men/women	31/10
Risk factor	
Diabetes (%)	13 (32)
Hypertension (%)	36 (88)
Triglyceride (mg/ml)	55–250 (133 \pm 62)
LDL-cholesterol(mg/ml)	52–180 (100 \pm 32)
HDL-cholesterol(mg/ml)	31–81 (51 \pm 14)
Medication	
Statin (%)	38 (93)
ACEI/ARB (%)	28 (68)
PCI	41
DCB	28
DCB + BMS	1
DES	10
BMS	1
POBA	1
Pre-BD (–)	23
Pre-BD (+)	18

ACEI angiotensin converting enzyme inhibitors, ARB angiotensin blocker, BMS bare-metal stent, DCB drug-coated balloon, DES drug-eluting stent, PCI percutaneous coronary intervention, POBA percutaneous old balloon angioplasty, pre-BD pre-balloon dilation

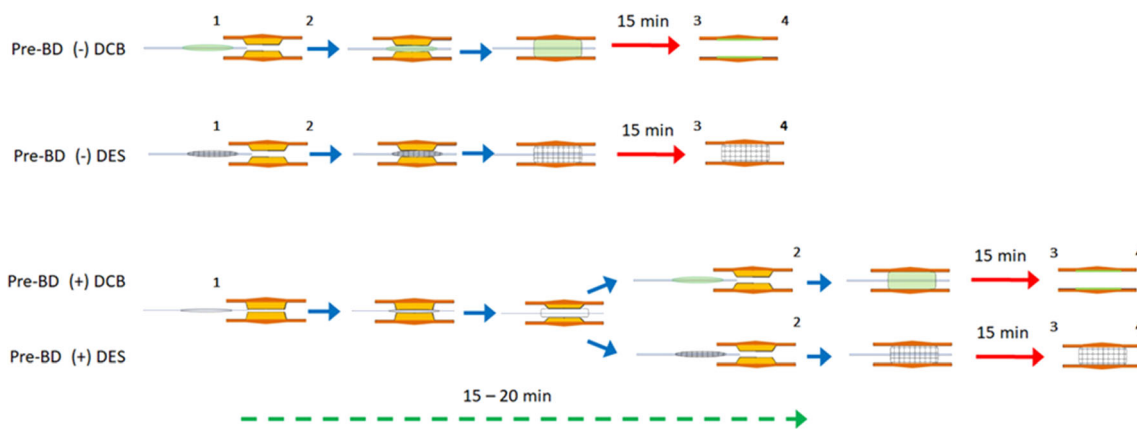


Fig. 1 Summary of PCI procedures. Blood was sampled at four points in each patient. Points 1 and 2 were sampled proximally and distally, respectively, to the stenotic lesion before the procedure. Points 3 and 4 were sampled proximally and distally, respectively, to the stenotic lesion 15 min after the procedure. Patients were principally treated by either a DES or DCB. All patients were divided into two groups according to the

requirement for pre-BD before sampling blood at point 2 because of the inability to pass a microcatheter through the lesion. According to this additional procedure, the sampling time at point 2 was delayed approximately 15–20 min in the pre-BD (+) group compared with the pre-BD (-) group. DCB, drug-coated balloon; DES, drug-eluting stent; pre-BD, pre-balloon dilation

Results

Sulfatide Levels from Four Different Sampling Points

Serum sulfatide levels that were obtained from the four different sampling points are shown in Fig. 2. In the group without

balloon dilation before PCI [(pre-BD (-)] (Fig. 2, left), mean sulfatide levels at points 2 (4.60 ± 4.04 nmol/mL), 3 (4.35 ± 3.76 nmol/mL), and 4 (4.53 ± 3.26) were significantly higher than that at point 1 (2.49 ± 1.11 nmol/mL) (vs point 2, $p < 0.02$; vs point 3, $p < 0.03$; vs point 4, $p < 0.03$). In contrast, in the group with pre-BD [pre-BD (+)] (Fig. 2, right),

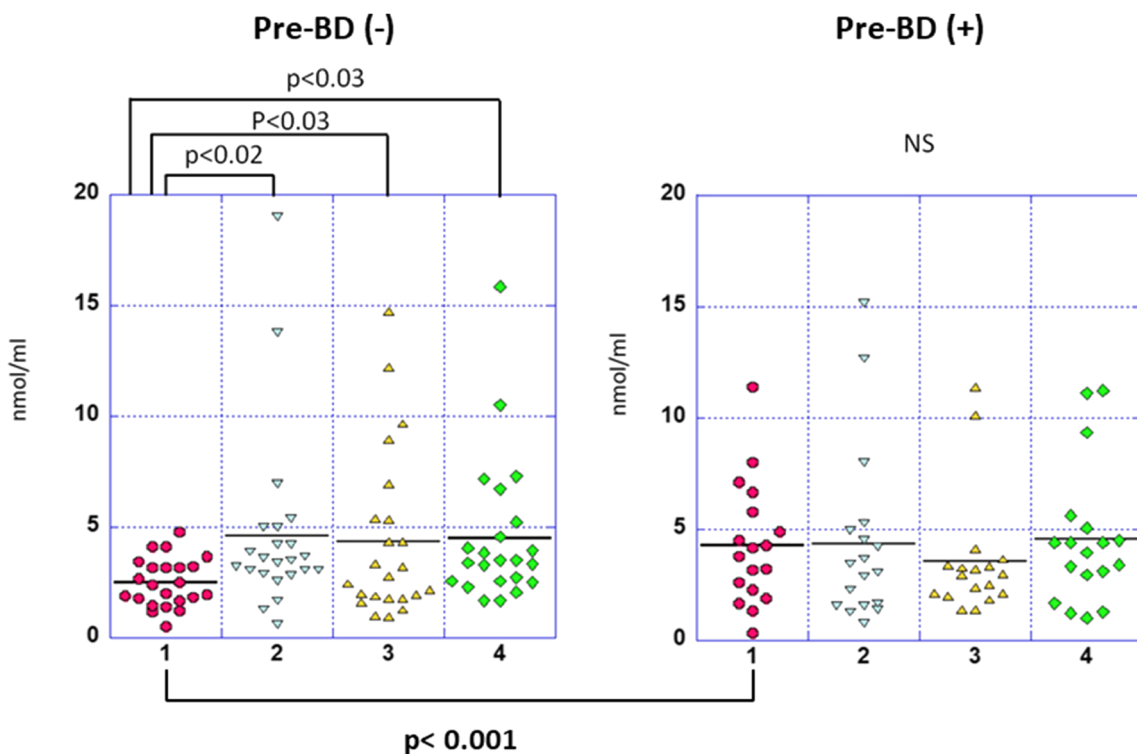


Fig. 2 Changes in sulfatide levels caused by PCI. In the pre-BD (-) group (left), mean sulfatide levels at points 2 (4.60 ± 4.04 nmol/mL), 3 (4.35 ± 3.76 nmol/mL), and 4 (4.53 ± 3.26 nmol/mL) were significantly higher than that at point 1 (2.49 ± 1.11 nmol/mL; vs point 2, $p < 0.02$; vs point 3, $p < 0.03$; vs point 4, $p < 0.03$). In the pre-BD (+) group (right), there was

no significant difference in mean sulfatide among the sampling points. The mean sulfatide level in the pre-BD (+) group (right) was significantly higher than that in the pre-BD (-) group (left) at sampling point 1 ($p < 0.001$). NS, no significant difference; pre-BD, pre-balloon dilation

there was no significant difference in mean sulfatide levels between each sampling point (point 1, 4.29 ± 2.74 nmol/mL; point 2, 4.35 ± 3.97 nmol/mL; point 3, 3.57 ± 2.73 nmol/mL; and point 4, 4.55 ± 3.09 nmol/mL). These results suggested that the PCI procedure induced elevation of sulfatides across plaques and that the pre-BD procedure affected this change. Sulfatide levels at sampling point 1 were the most likely to be unaffected by the PCI procedure and showed the baseline value at this point. The mean sulfatide level in the pre-BD (+) group was significantly higher than that in the pre-BD (-) group at sampling point 1 ($p < 0.001$) (Fig. 2).

Levels of TAT, PIC, Hs-CRP, and d-ROMs

TAT and PIC are parameters that indicate coagulative and fibrinolytic states [14], respectively, while hs-CRP and d-ROM levels indicate vascular inflammation [15, 16]. Sequential changes in these variables during the observation period were not observed (Table 2), regardless of whether there was a pre-BD procedure. However, mean values of PIC and d-ROMs tended to be higher in the pre-BD (+) group than in the pre-BD (-) group. There was no correlation between the sulfatide level and these parameters at each corresponding point.

Discussion

In our study, we measured serum sulfatide levels at the proximal (points 1 and 3) and distal (points 2 and 4) sites of atheromatous plaques before and after PCI. Patients in the pre-BD (-) group had a significantly lower mean sulfatide level at point 1 compared with the other points. This finding indicated that elevated sulfatide levels were probably derived from atheromatous plaques themselves, consistent with the finding of accumulated sulfatides in rabbit aortae [5]. In contrast, such an elevation in sulfatide levels in patients in the pre-BD (+) group was not observed. This finding is probably because of technical difficulty in collecting sulfatides from coronary arteries. These results suggest that a substantial elevation in sulfatide levels in PCI from plaques is caused by mechanical stimuli, such as chafing or injuring of vessels, rather than continuous production from sites. Released sulfatides from plaques because of the pre-BD procedure may have been diluted in the circulation before sample collection because of the longer sampling time (Fig. 1). Further exploration of sulfatides in the coronary circulation has yet to be undertaken. In general, until now, studies of glycosphingolipids (including sulfatides) have focused mainly on the plasma membranes of animal cells for their development and differentiation [17]. Therefore, information regarding the origins and metabolism of glycosphingolipids in body fluids is very limited.

In experiments using WHHL rabbits, sulfatides were accumulated in the aorta and these were assumed to come from serum lipoproteins. This situation could be applicable in humans. In support of this assumption, a positive correlation between serum sulfatide levels and carotid intima-media thickness in patients with familial hypercholesterolemia was reported previously [18]. In our study, the mean sulfatide level in the pre-BD (+) group was significantly higher than that in the pre-BD (-) group at sampling point 1. This finding suggests that higher serum sulfatide levels cause a higher plaque burden, resulting in promotion of atheromatous plaque formation.

We measured TAT, PIC levels in our study. Coagulation and fibrinolysis are causally associated with cardiovascular events [14]. Levels of hs-CRP are a biomarker for coronary atherosclerosis [15] and d-ROMs indicate oxidative stress, which damages vessels [16]. However, in our study, these variables showed no sequential changes within the observation period, emphasizing the significance of sulfatides.

Because of the adequate use of heparin, thrombotic incidents with the procedure are unusual. There were no significant changes in TAT and PIC levels in our study during the procedure. However, once a vulnerable plaque ruptures in the absence of adequate antithrombotics, sulfatides that are released from the site may make a powerful contribution to inducing plaque thrombosis. In the early 1980s, sulfatides were reported to activate blood coagulation factor XII (FXII) *in vitro*, suggesting a possible role of sulfatides in promoting coagulation [19]. The physiological importance of FXII was disputed until a recent report in which FXII was shown to participate in plaque thrombus formation in a mouse model [20]. Furthermore, sulfatides enhance aggregation of activated platelets [21]. These results suggest the possible contribution of sulfatides in plaques for not only enhancing atherosclerosis but also accelerating thrombosis under injured endothelium. Indeed, Li *et al.* reported high peripheral serum sulfatide levels in patients with STEMI [9].

While sulfatides probably promote atherothrombosis, their role in other conditions is controversial. Sulfatides have been contradictorily reported to show anticoagulant properties, including prolongation of the clotting time and bleeding time, probably disturbing fibrin formation by binding to fibrinogen [2, 3, 22, 23]. Cardiovascular disease (CVD) is a critical complication of chronic kidney disease (CKD) [11, 24]. We previously found a negative correlation between serum sulfatide levels and a high incidence of CVD in patients in the terminal stage of CKD, with end-stage renal failure (ESRF), who were treated with hemodialysis [25]. Such patients were excluded from this study. CVD in CKD comprises atheromatous and non-atheromatous diseases (heart failure, cardiac dysrhythmia, valvular diseases, etc.) [26]. Additionally, the pathological condition of patients with CVD and a terminal stage of CKD, especially in those with ESRF treated by hemodialysis,

Table 2 TAT, PIC, hs-CRP, and d-ROM levels from four different sampling points

	Pre-BD (-)				Pre-BD (+)			
	Point 1	Point 2	Point 3	Point 4	Point 1	Point 2	Point 3	Point 4
TAT, ng/ml	2.0522 ± 1.096	1.8391 ± 0.7976	2.2261 ± 1.2567	1.9609 ± 0.9746	2.0222 ± 1.2786	1.7944 ± 0.6975	2.3444 ± 1.2849	2.2278 ± 1.4385
PIC, mg/ml	0.7913 ± 0.2778	0.7913 ± 0.2746	0.8044 ± 0.3111	0.8522 ± 0.3591	0.9611 ± 0.5457	0.9833 ± 0.5586	0.9722 ± 0.5160	1.0000 ± 0.5477
hs-CRP, ng/ml	3214.4 ± 7201	3187.3 ± 7070	3030.2 ± 6606	3132.6 ± 6926	2435.8 ± 6015	2502.0 ± 6060	2353.1 ± 5669	2431.3 ± 5998
d-ROM, CARR U	297.87 ± 53.84	306.48 ± 53.55	295.43 ± 54.52	302.39 ± 52.06	321.00 ± 55.26	332.83 ± 59.62	325.50 ± 59.98	329.78 ± 60.82

Point 1, sample collected proximal to a stenotic lesion; point 2, sample collected distal to the lesion; point 3, sample collected proximally 15 min after the procedure; point 4, sample collected distally 15 min after the procedure.

d-ROM diacron-reactive oxygen metabolite, hs-CRP high-sensitivity C-reactive protein, PIC plasmin- α 2-plasmin inhibitor complex, pre-BD pre-balloon dilation, TAT thrombin-antithrombin complex

is different from that in patients in our study [27]. In fact, serum lipid quality and arteriosclerosis in patients with ESRF is distinct from those in patients with typical cardiac atherosclerosis without CKD [10, 27–29]. Therefore, serum sulfatides may be incorporated differently in lipoproteins in patients with ESRF, and their thrombotic activity may be modified. These issues remain to be clarified in further studies.

Conclusion

On the basis of our finding of changes in serum sulfatide levels throughout the PCI procedure, we speculate that sulfatides are rapidly released from ruptured atheromatous plaques, probably accelerating atherothrombogenesis. Sulfatides are candidate molecules targeted for exploration, both for their thrombotic as well as their atherosclerotic properties.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval The study protocol was approved in accordance with the Declaration of Helsinki by the review boards of Dokkyo Medical University Saitama Medical Center and Nihon Pharmaceutical University.

Informed Consent Written informed consent was obtained from each patient.

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