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Detection of the "Midband" Lipoprotein in Patients with Coronary Artery Spasm

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Summary

Background: Dyslipidemia in patients with coronary vasospasm has been characterized by a low level of high-density lipoprotein (HDL) cholesterol without elevation of low-density lipoprotein (LDL) cholesterol, distinct from patients with organic coronary artery disease.

Hypothesis: Disordered triglyceride-rich lipoprotein metabolism may be linked to the genesis of coronary artery spasm.

Methods: The incidence of the "midband" lipoprotein observed between very low-density lipoprotein (VLDL) and LDL bands in the polyacrylamide disc gel electrophoretic analysis was determined in 48 patients with coronary spastic angina (CSA), in 50 patients with stable effort angina and a significant fixed coronary stenosis (SEA), and in 40 control subjects without coronary artery disease (Control).

Results: The incidence was significantly ($p<0.05$) higher in CSA (71%) than in SEA (50%) and Control (25%). Smoking was significantly ($p<0.05$) more prevalent in CSA (77%) than in SEA (50%) and Control (50%). In SEA, serum levels of triglyceride and apoproteins C-II, C-III, and E were all significantly higher, and the serum level of HDL cholesterol was significantly lower in the midband-positive than in the midband-negative subgroup. In CSA, no significant differences were found in these serum levels between the midband-positive and -negative subgroups, except for a significantly ($p<0.05$) lower level of HDL cholesterol in the former. However, a significantly ($p<0.05$) higher incidence of diabetes mellitus or impaired glucose tolerance was noted in the midband-positive (41%) than in the midband-negative subgroup (7%) in CSA. The incidence of the detected midband lipoprotein was significantly decreased in the blood samples obtained from 20 of CSA after a >6-month angina-free period (70 → 25%, $p<0.05$).

Conclusions: The midband lipoprotein was frequently detected in patients with coronary vasospasm, suggesting that dyslipidemia with disordered triglyceride-rich lipoprotein metabolism may be linked to the genesis of coronary artery spasm.

Key words: coronary vasospasm, coronary spastic angina, midband lipoprotein, triglyceride-rich lipoprotein, high-density lipoprotein cholesterol

Introduction

Coronary artery spasm has been established as an important cause of ischemic episodes in a wide variety of coronary heart diseases, including variant angina, rest angina, some exertional anginas, unstable angina, myocardial infarction, and sudden death.[1,2] However, the precise underlying mechanisms of coronary spasm or exaggerated vasoconstriction remain to be clarified. Lipid disorders have been recognized to be an important risk factor for atherosclerotic coronary artery disease.[3,4] Recent studies emphasized that the concentrations of low-density lipoprotein (LDL) correlate positively and high-density lipoprotein (HDL) negatively with coronary artery disease.[3–5] Dyslipidemia in patients with coronary vasospasm has been characterized by a low level of HDL cholesterol as well as apolipoprotein (apo) A-I without elevation of LDL cholesterol, distinct from patients with organic coronary artery disease.[6–8] Also, increased oxidative susceptibility of LDL has been recently demonstrated in patients with variant angina.[9,10] An increase in the total mass of HDL is suggested to be coupled with the process of degradation or lipolysis of triglyceride-rich lipoproteins, and an inverse relationship between HDL cholesterol and triglyceride levels has been observed frequently.[11] However, an association between triglyceride-rich lipoprotein metabolism and coronary vasospasm remains to be elucidated.

Most of the plasma triglycerides are carried in very low-density lipoprotein (VLDL) and are degraded by endothelial lipoprotein lipase to intermediate-density lipoproteins (IDL)

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or VLDL remnants, which are hydrolyzed further by hepatic triglyceride lipase to LDL. Gofman *et al.* were the first to implicate IDL in the development of coronary vascular disease.[12] High levels of IDL cholesterol and a more frequent occurrence of "midband" lipoprotein, which is observed between LDL and VLDL by polyacrylamide gel electrophoresis, have been reported in populations of survivors of myocardial infarction in Japan and Italy and also in subjects with angiographically documented coronary artery disease.[13, 14] A lower incidence of hypercholesterolemia and higher incidence of coronary spasm than in Western countries are known to be characteristic of Japanese cases with coronary artery disease.[13, 15] In the present study, we tried to clarify whether the midband lipoprotein is linked to the genesis of coronary artery spasm by determining the incidence of the detection of this lipoprotein on polyacrylamide gel in Japanese patients with coronary spastic angina.

Methods

Study Patients

Consecutive 48 patients (38 men, 10 women, mean age 59 ± 11 years; range 29–73 years) with coronary spastic angina (CSA) who had at least one episode of angina in the preceding week, in whom electrocardiographic (ECG) ST-segment deviation (≥0.1mV) was confirmed during anginal attacks, were subjected to serum lipoprotein electrophoretic analysis. In all patients, coronary artery spasm was angiographically demonstrated in at least one of the major coronary arteries during spontaneous or induced attacks by intracoronary injection of acetylcholine. None of them had a significant (>75% luminal narrowing) organic coronary arterial stenosis, although mild lesions or irregularity were angiographically detected in most cases. Another 50 patients (37 men, 13 women, mean age 60 ± 10 years; range 36–73 years) with stable effort angina and a significant organic narrowing of either coronary artery documented by coronary angiographic study, who had a positive treadmill exercise stress test but were free of rest angina (SEA), were also subjected to the study. For control, 40 age- and gender-matched subjects (30 men, 10 women, mean age 58 ± 12 years; range 28–71 years) without significant systemic disease, who had negative treadmill exercise stress test results with the standard Bruce protocol (Control), were selected. Patients receiving antioxidative agents, such as vitamins E and C or probucol, as well as patients receiving 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors were excluded from the study. Clinical and angiographic characteristics of the study groups are listed in Table I. Written informed consent was obtained from all study patients and the study protocol was approved by the ethics committee of our institute.

Serum Analysis

A venous sample was obtained in the fasting state. The total cholesterol was measured directly in the serum, and HDL cholesterol was measured after precipitation of VLDL cholesterol and LDL cholesterol with dextran sulfate-magnesium chloride by an enzymatic method. The concentration of triglyceride in serum was determined by measuring glycerol after an enzymatic hydrolysis with lipase-esterase. The LDL cholesterol concentration was calculated according to the following formula: LDL cholesterol = (total cholesterol) − (HDL cholesterol) − (triglyceride/5). The concentrations of apoA-I, apoA-II, apoB, apoC-II, apoC-III, and apoE were determined by immunoturbidimetry.

Lipoprotein electrophoretic analysis: Blood samples were drawn into a tube after overnight fasting and sera were immediately separated by low-speed centrifugation and stored at −20°C for a few days before the electrophoretic analysis. For the separation of lipoprotein fractions, 3% disc gels (Lipophor™, Quantimetrix Co., Hawthorne, Calif., USA) were used. Serum (25 µl) was applied to each gel tube. Loading gel (200 µl) containing 0.36 mg/l Sudan Black B was added to the top of the tube and mixed with the specimen. After 30 min of photopolymerization, the loading gel tubes were placed into an electrophoretic chamber (Model 1500, Quantimetrix Co.). The electrolyte buffer consisted of trisaminomethane 66.1% w/w and boric acid 33.9% w/w, pH 8.2–8.6. Electrophoresis was conducted at a constant current of 3mA per each tube for 30 min. The various prestained lipoproteins and subfractions were separated on the basis of molecular size. Then the gels were scanned directly in the glass tube at a wave length of 610 nm using the Densitron 20-HR (Jokoh Co., Ltd., Tokyo, Japan). The band observed between pre ß-band and ß-band was called a "midband" as reported by Mead and Dangerfield.[16]

Assessment of Coronary Risk Factors

Current smoking was considered to be a factor if the patient had smoked in the year preceding the procedure. Diabetes mellitus was diagnosed either clinically or by 75 g oral glucose tolerance test. Impaired glucose tolerance was diagnosed by

TABLE I Clinical and angiographic characteristics of the study groups

Characteristic	Control	CSA	SEA
No. of patients	40	48	50
Age	58 ± 12	59 ± 11	62 ± 10
Male/female	30/10	38/10	37/13
Previous MI (%)	0 (0)	10 (21)	32 (64)[a]
Hypertension (%)	0 (0)	14 (29)	25 (50)[b]
Smoking (%)	20 (50)	37 (77)[c]	25 (50)
Diabetes mellitus (%)	0 (0)	8 (17)	19 (38)[b]
Body mass index > 25 (%)	7 (18)	11 (23)	9 (18)

[a] $p < 0.01$ vs. CSA.
[b] $p < 0.05$ vs. CSA.
[c] $p < 0.05$ vs. Control and SEA.
Abbreviations: CSA = coronary spastic angina, SEA = stable effort angina, MI = myocardial infarction.

75 g oral glucose tolerance test, based on World Health Organization (WHO) diagnostic guidelines.[17] Hypertension was defined as a persistent resting blood pressure exceeding 140 (systolic) or 90 (diastolic) mmHg. Body mass index was calculated as weight (kg)/height (m)^2.

Follow-Up Study

Patients with coronary spastic angina were followed up with medication, including a sufficient dosage of calcium entry blockers to prevent the occurrence of anginal attacks. As a rule, smoking cessation, a reduction in body weight, and an increase in physical activity were recommended to all patients. Blood samples were obtained again in 20 patients if they had had no angina for > 6 months.

Statistical Analysis

Values are presented as mean ± standard deviation. Comparisons of serum lipid levels and age among the three groups were performed with one-way analysis of variance (ANOVA), followed by Scheffe's test. The clinical characteristics and electrophoretic profiles of the study groups were compared by a chi-square test with Yates' correction. The paired Student's *t*-test was used to determine the significance of the changes during the follow-up in the serum lipid levels in CSA. The level of significance was set as $p < 0.05$.

TABLE II Serum lipid profiles and apolipoprotein levels in study patients

	Control	CSA	SEA
No. of patients	40	48	50
Total cholesterol (mg/dl)	188 ± 33	190 ± 38	196 ± 37
Triglyceride (mg/dl)	107 ± 60	125 ± 66	129 ± 56[a]
LDL cholesterol (mg/dl)	119 ± 34	123 ± 36	133 ± 37[a]
HDL cholesterol (mg/dl)	48 ± 12	42 ± 14[a]	37 ± 12[b]
ApoA-I (mg/dl)	126 ± 17	110 ± 26[a]	98 ± 22[b]
ApoA-II (mg/dl)	31 ± 5	30 ± 6	28 ± 6[b]
ApoB (mg/dl)	89 ± 21	102 ± 27	110 ± 26[a]
ApoC-II (mg/dl)	3.3 ± 1.3	3.2 ± 1.7	3.4 ± 1.7
ApoC-III (mg/dl)	8.6 ± 2.9	8.9 ± 4.2	8.2 ± 3.3
ApoE (mg/dl)	4.5 ± 1.7	4.9 ± 1.5	4.6 ± 1.3
Midband (+) (%)	10 (25)	34 (71)[c]	25 (50)[a]

[a] $p < 0.05$ vs. Control.
[b] $p < 0.01$ vs. Control and $p < 0.05$ vs. CSA.
[c] $p < 0.01$ vs. Control and $p < 0.05$ vs. SEA.
Abbreviations: LDL = low-density lipoprotein, HDL = high-density lipoprotein, Apo = apolipoprotein. Other abbreviations as in Table I.

Results

Results are summarized in Tables I–III and in Figure 1. As shown in Table I, smoking was found to be significantly ($p < 0.05$) more prevalent in CSA (77%) than in Control (50%) and SEA (50%). The prevalences of previous myocardial

TABLE III Comparative data of risk factors and serum lipid profiles in study patients with and without "midband" lipoprotein

	CSA		SEA	
Midband	(+)	(−)	(+)	(−)
No. of patients	34	14	25	25
Age	60 ± 11	57 ± 10	63 ± 9	60 ± 12
Male/female	27/7	11/3	19/6	18/7
Hypertension (%)	8(24)	6(43)	14(56)	11(44)
DM (%)	7(21)	1(7)	7(28)	12(48)
IGT (%)	7(21)	0(0)	7(28)	3(12)
DM or IGT (%)	14(41)[a]	1(7)	14(56)	15(60)
Smoking (%)	26(76)	11(79)	17(68)	18(72)
Body mass index	23 ± 2	23 ± 3	23 ± 2	24 ± 3
Total cholesterol (mg/dl)	192 ± 39	185 ± 33	201 ± 36	190 ± 38
Triglyceride (mg/dl)	129 ± 69	117 ± 60	153 ± 57[b]	105 ± 31
LDL cholesterol (mg/dl)	126 ± 36	113 ± 36	137 ± 37	128 ± 37
HDL cholesterol (mg/dl)	40 ± 11[a]	48 ± 17	33 ± 10[a]	41 ± 13
ApoA-I (mg/dl)	108 ± 25	114 ± 28	92 ± 17	104 ± 26
ApoA-II (mg/dl)	31 ± 7	28 ± 5	27 ± 5	29 ± 8
ApoB (mg/dl)	106 ± 28	91 ± 20	115 ± 24	105 ± 28
ApoC-II (mg/dl)	3.3 ± 2.0	3.1 ± 0.8	3.8 ± 1.9[a]	2.9 ± 1.2
ApoC-III (mg/dl)	9.0 ± 4.9	8.5 ± 2.1	9.2 ± 3.5[b]	7.1 ± 2.5
ApoE (mg/dl)	4.9 ± 1.7	4.8 ± 1.0	5.1 ± 1.4[b]	4.1 ± 1.1

[a] $p < 0.05$ vs. Midband (−).
[b] $p < 0.01$ vs. Midband (−).
Abbreviations: DM = diabetes mellitus, IGT = impaired glucose tolerance. Other abbreviations as in Tables I and II.

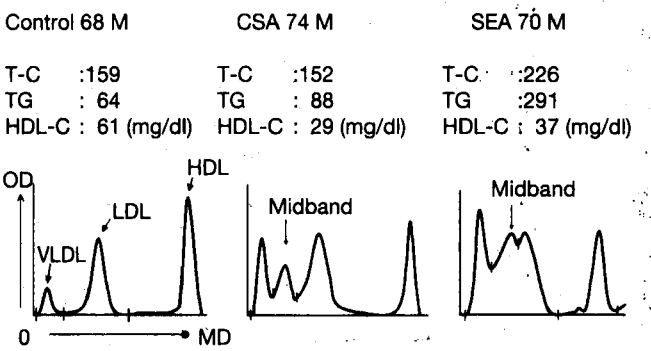

FIG. 1 Examples of densitometric profiles of 3% polyacrylamide disc gel electrophoretic assay in study patients. Left: The normal pattern in a 68-year-old male subject of Control. Note three prominent peaks corresponding to VLDL, LDL and HDL. Right: A significant peak (arrow) of midband lipoprotein is noted in a hypertriglyceridemic 70-year-old male patient with SEA. Center: Note a prominent peak (arrow) of midband lipoprotein in a 74-year-old male patient with CSA without hypertriglyceridemia. CSA = coronary spastic angina, SEA = stable effort angina, T-C = total cholesterol, TG = triglyceride, HDL-C = high-density lipoprotein cholesterol, LDL = low-density lipoprotein, VLDL = very low-density lipoprotein, MD = migration distance, OD = optic density.

infarction, diabetes mellitus, and hypertension were all significantly higher in SEA than in CSA, although the incidence of body mass index >25 did not differ significantly between CSA and SEA.

Serum Lipid Levels

Serum lipid profiles and apolipoprotein levels in study patients are shown in Table II. Compared with Control, both serum HDL cholesterol and apoA-I levels were significantly lower in CSA. No significant differences were noted in serum total cholesterol, LDL cholesterol, or triglyceride levels between CSA and Control. Serum triglyceride, calculated LDL cholesterol, and apoB levels were all significantly ($p < 0.05$) higher in SEA than in Control. Significantly lower levels of HDL cholesterol, apoA-I, and apoA-II were found in SEA than in Control ($p < 0.01$) and in CSA ($p < 0.05$).

Lipoprotein Electrophoretic Analysis

The pattern of midband in polyacrylamide gel electrophoresis is shown in Figure 1. Usually, three prominent peaks corresponding to VLDL, LDL, and HDL were clearly identified in the densitometric analysis of the 3% polyacrylamide disc gel electrophoresis. When a lipoprotein band with >25% of the densitometric peak of LDL after the baseline correction was observed in the intermediate portion between VLDL and LDL bands, or as a shoulder of the VLDL peak, the midband was considered to be positive. The band as a shoulder of the LDL peak was not included in the "midband" in the present study. When the midband was positive, the observed LDL band was generally rather broad with a greater dispersion. As shown in Table II, the prevalence of midband was significantly ($p < 0.05$) higher in CSA (71%) than in Control (25%) ($p < 0.01$) and also in SEA (50%) ($p < 0.05$). Also, the prevalence of midband was significantly ($p < 0.05$) higher in SEA than in Control. In CSA, the prevalence was not significantly different between the smoking (84%, n = 37) and the nonsmoking subgroups (73%, n = 11).

Comparison between Subjects with and without Midband

As shown in Table III, the midband-positive subgroup had significantly higher serum triglyceride, apoC-II, apoC-III, and apoE levels and a lower HDL cholesterol level than the midband-negative subgroup in SEA. The incidence of diabetes mellitus or impaired glucose tolerance by 75 g oral glucose tolerance test was comparable between the midband-positive (56%) and -negative (60%) subgroups in SEA. In CSA, no significant differences were found in the serum lipid levels between the subgroups, except for a significantly ($p < 0.05$) lower level of HDL cholesterol in the midband-positive subgroup. Diagnosis of either diabetes mellitus or impaired glucose tolerance was noted significantly ($p < 0.05$) more often in the midband-positive subgroup (41%) than in the midband-negative subgroup (7%) in CSA. Even after the patients with diabetes mellitus were excluded from the analysis, the serum triglyceride level was still significantly ($p < 0.01$) higher in the midband-positive subgroup (158 ± 63 mg/dl, n = 18) than in the midband-negative subgroup (98 ± 27 mg/dl, n = 13) in SEA, and the level was still comparable between the midband-positive (125 ± 63 mg/dl, n = 27) and midband-negative (120 ± 59 mg/dl, n = 13) subgroups in CSA.

Follow-Up Study

Blood samples were again obtained in 20 patients of CSA after at least 6 months of angina-free period under medication with calcium entry blockers. The prevalence of midband was significantly decreased after the follow-up (70 → 25%, $p < 0.05$). The prevalence of smoking significantly decreased (75 → 10%, $p < 0.05$) and the HDL cholesterol level significantly increased (38 ± 4 → 44 ± 4 mg/dl, $p < 0.05$) after follow-up. In contrast, in another eight patients who still had anginal attacks during the last month after the 6-month follow-up while receiving calcium entry blockers, the prevalence of midband failed to decrease (63 → 75%, not significant).

Discussion

The present study clearly demonstrated that the prevalence of a kind of dysbetalipoproteinemia, characterized by the appearance of midband in polyacrylamide disc gel electrophoresis for lipoproteins, was high among Japanese patients with coronary vasospasm. The intermediate products of VLDL catabolism, represented by IDL and VLDL remnants, may constitute midband lipoproteins, although it remains to be

elucidated what the midband lipoprotein detected in the present study is. Significantly higher serum triglyceride, apoC-II, apoC-III, and apoE levels, as well as lower HDL cholesterol levels were noted in the midband-positive subgroup than in the midband-negative subgroup in the patients with stable effort angina. In contrast, in the patients with coronary spasm, no significant differences were found in the serum lipid levels between the subgroups, except for a significantly lower level of HDL cholesterol in the midband-positive subgroup. Instead, the incidence of either diabetes mellitus or impaired glucose tolerance diagnosed by oral glucose loading test was significantly higher in the midband-positive subgroup than in the midband-negative subgroup in the patients with coronary spasm. Thus, the appearance of the midband lipoprotein was frequently associated with impaired glucose metabolism in patients with coronary spastic angina, while it seemed to be dependent mainly on the presence of hypertriglyceridemia in the patients with stable effort angina. Disordered triglyceride-rich lipoprotein metabolism not always characterized by hypertriglyceridemia but concomitant with glucose metabolic disorder, appeared to be implicated in the genesis of the midband lipoprotein observed in the majority of coronary vasospastic patients, suggesting that such a dyslipidemic state may be intimately related to the pathogenesis of coronary artery spasm. Of importance is the fact that the incidence of the midband lipoprotein detected in the active stage of spasm decreased after the disappearance of angina in patients with coronary spasm.

Disordered Triglyceride-Rich Lipoprotein Metabolism

Triglyceride-rich lipoproteins are hydrolyzed by lipoprotein lipase and then hepatic triglyceride lipase. The major role of apoC-II appears to be as a necessary activator for lipoprotein lipase.[18] ApolipoproteinC-III is a marker of triglyceride-rich lipoprotein metabolism and is known to inhibit lipoprotein lipase activity and also hepatic triglyceride lipase activity.[19] As the endocytosis of triglyceride-rich lipoproteins by hepatocytes occurs via the interaction of apoE with receptors present on these cells, overexpression of dysfunctional apoE mutants leads to accumulation of VLDL and remnant particles in the plasma.[20] Elevations of apoC-II, apoC-III, and apoE levels concomitant with lower HDL cholesterol levels were generally observed in association with hypertriglyceridemia in the present study.

Midband Lipoprotein with Smoking and Impaired Glucose Metabolism

Disordered triglyceride-rich lipoprotein metabolism is frequently associated with cigarette smoking and glucose intolerance.[13, 14, 21] Elevation of IDL cholesterol concentration in diabetic patients might be responsible for their higher incidence of coronary and peripheral vascular disease. Cigarette smokers have a high level of IDL cholesterol as well as a low level of HDL cholesterol.[13] Topping *et al.* reported that clearance of remnant in smokers would be delayed and their concentrations would rise concomitantly;[22] smoking is known to be a major risk factor for coronary spasm.[21] It has been reported that an elevation of the serum HDL cholesterol level, attainable by smoking cessation, is important to reduce the incidence of cardiovascular accidents in patients with coronary vasospasm.[7]

Recent reports demonstrated that patients with vasospastic angina exhibited a high incidence of impaired glucose tolerance with late hypersecretion of insulin.[23, 24] Insulin stimulates hepatic VLDL cholesterol secretion, whereas peripheral insulin resistance causes a reduced breakdown of triglyceride-rich lipoprotein and a decrease in HDL cholesterol synthesis. Also an increase in atherogenic small, dense LDL has been demonstrated in association with insulin resistance.[25] Oxidative susceptibility was shown to be increased in small, dense, and triglyceride-rich LDL.[26] Dyslipidemia secondary to diabetes mellitus, hyperinsulinemia, or glucose intolerance causes impairment of catabolism of triglyceride-rich lipoprotein, lowers lipoprotein lipase activity, and increases remnant lipoprotein levels.

Midband Lipoprotein in the Pathogenesis of Coronary Artery Spasm

Triglyceride-rich lipoproteins were bound to arterial endothelium, where lipoprotein lipase would then initiate triglyceride hydrolysis and decrease the size of the adhering particles, leading to production of remnant lipoproteins, so that they could enter the deeper structure of the arterial wall.[27] The inhibition of lipoprotein lipase-activated lipolysis by VLDL-associated apoC-III may prolong the residence time of VLDL and, therefore, increase the exposure time of the arterial wall to this atherogenic particle.[27] Recently, remnants of chiromicron and VLDL have been shown to impair endothelium-dependent arterial relaxation in rabbit aortic preparations.[28] Furthermore, remnant lipoprotein levels were reported to be independently associated with abnormal endothelium-dependent vasomotor function in humans, suggesting that triglyceride-rich lipoprotein metabolic disorder may cause endothelial dysfunction.[29] Remnant lipoproteins may be oxidatively modified in the arterial intima and cause an increase in the susceptibility of coronary endothelium to oxidative stress, leading to coronary endothelial dysfunction. It is suggested that there is a deficiency in endothelial nitric oxide activity in spasm arteries, which leads to the supersensitivity of the artery to the vasoconstrictor effect of agonists.[30] As vascular smooth muscle hypercontraction based on endothelial dysfunction or damage is postulated as the pathogenesis of coronary artery spasm, dyslipidemia with abnormal triglyceride-rich lipoprotein metabolism causing enhancement of coronary tone, via endothelial dysfunction, may predispose patients to coronary spasm.[30]

Although it is possible that IDL or triglyceride-rich lipoprotein remnants play a key role as a substrate for oxygen–free radical reactions in the pathogenesis of coronary artery spasm, it cannot be excluded that impaired triglyceride-rich lipoprotein metabolism may be caused by the lipid oxidative stress from the frequently repeated spasm-induced ischemia/reper-

fusion. It is also conceivable that midband lipoproteins may represent some form of acute phase reaction and that they may be just a bystander or a modulator of endothelial function rather than the cause of coronary spasm. Further studies with a large population of patients for multivariate analysis are needed to clarify the causal relation between the midband lipoprotein and coronary vasospasm. The hypothesis that free radical reaction may play a key role in the genesis of coronary spasm needs to be further investigated.

Conclusion

Although precise mechanisms by which disordered triglyceride-rich lipoprotein metabolism relates to the genesis of coronary spasm remain to be elucidated, the "midband" lipoprotein is frequently detected in patients with coronary spasm and seems to be intimately related to the disease activity of coronary spasm.

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