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The presence of metabolic syndrome is independently associated with elevated serum CD40 ligand and disease severity in patients with symptomatic coronary artery disease

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Abstract

Nontraditional atherosclerotic risk factors have become the focus of attention in recent years. In addition, metabolic syndrome is gaining recognition as another multiplex cardiovascular risk factor. However, to date, no studies have investigated the effect of metabolic syndrome on circulating soluble CD40 ligand (sCD40L), monocyte chemoattractant protein 1, cellular adhesion molecules, and disease severity in patients with symptomatic coronary artery diseases. This study was conducted to address this issue. Patients with stable angina who received percutaneous coronary interventions for significant ($\geq$70% diameter stenosis) de novo lesions between January 1999 and January 2004 and had preprocedural serum samples were enrolled. Metabolic syndrome was defined by the National Cholesterol Education Program criteria with waist criterion modified into body mass index of more than 25 kg/m^2. The serum samples were thawed and analyzed for circulating sCD40L, monocyte chemoattractant protein 1, adhesion molecules, and high sensitivity C-reactive protein (hs-CRP). Coronary severity was assessed by a modified version of Gensini scoring system. A total of 313 patients, 248 males and 65 females, were studied. Among them, 222 (70.9%, 170 males and 52 females) had metabolic syndrome. Patients with metabolic syndrome had higher serum creatinine level and lower low-density lipoprotein cholesterol despite higher triglyceride concentration. In multivariate analysis, patients with metabolic syndrome had higher sCD40L (6057 $\pm$ 275 vs. 5051 $\pm$ 423 pg/mL, P = .037) and more hs-CRP in higher tertiles (P = .005) than patients without, but similar levels of intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and P selectin. Metabolic syndrome was also significantly associated with multiple coronary vessel involvements with 70% or higher diameter stenosis (36.5% double-vessel and 14% triple-vessel diseases vs 30.8% double-vessel and 5.5% triple-vessel diseases, P = .026) and multiple coronary segment involvements with 50% or higher diameter stenosis (P = .014) in multivariate analysis. In conclusion, the presence of metabolic syndrome is independently associated with elevated sCD40L, hs-CRP, and coronary disease severity in patients with coronary artery disease requiring interventional treatment of stable angina.

1. Introduction

Coronary artery disease (CAD) is among the leading causes of death and imposes a great burden on health care expenditure worldwide. Nontraditional atherosclerotic risk factors have become the focus of attention in recent years. Among them, CD40 ligand (CD40L), a member of the tumor necrosis factor (TNF) family, is expressed by major cellular players in atherosclerosis [1]. Elevated soluble CD40L (sCD40L) has been found in diabetes mellitus, hypercholesterolemia, and unstable angina [2,3], and has strong independent prognostic value in healthy individuals and in patients with acute coronary syndrome (ACS) [4,5].

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Cipollone et al [6] reported that preprocedural sCD40L level is predictive of restenosis after coronary angioplasty. Clinical studies also showed increased release of monocyte chemoattractant protein 1 (MCP-1), a chemokine downstream to CD40L, in ACS and elevated MCP-1 predicted prognosis [7]. Furthermore, cellular adhesion molecules also have been shown to participate in the initiation and progression of atherosclerosis [8]. Intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) were both shown to be associated with coronary artery and peripheral artery diseases [9,10]. Moreover, both CD40L and MCP-1 are linked to expression of cellular adhesion molecules [1,11].

Recently, metabolic syndrome has gained recognition as a multiplex risk factor for atherosclerotic cardiovascular diseases [12,13]. Metabolic syndrome is associated with higher incidence of cardiovascular diseases and events [14-16], and increased mortality from coronary heart disease, cardiovascular disease, and all causes [17,18]. Subjects with metabolic syndrome present a prothrombotic and pro-inflammatory state [19,20]. However, to date, no studies have investigated the effect of metabolic syndrome on circulating inflammatory CD40L, MCP-1, and cell adhesion molecules in patients with cardiovascular diseases. Furthermore, few studies have reported the relationship between metabolic syndrome and coronary disease severity [21,22]. Therefore, this study was conducted to explore the association of metabolic syndrome with circulating CD40L, MCP-1, cell adhesion molecules, and coronary disease severity in patients with symptomatic CADs.

2. Methods

2.1. Study population

A Windows 2000–based cardiac catheterization report data bank has recently been established in this institute. It uses the hospital-information-system data stored in the mainframe computer and contains all the angiographic report data from the past 12 years. In addition, a serum data bank, consisting of all the samples from patients who underwent different types of cardiac catheterization, were willing to donate blood samples for research use, and gave informed consent, has been in operation since March 1999. This study is part of a joint cardiology–endocrinology-and-metabolism research program that uses these 2 resources to investigate unresolved and challenging cardiovascular issues.

The current study is a substudy of an original protocol that investigated the association of inflammation-linked markers with postcoronary intervention restenosis. During the study period from March 1999 to January 2004, consecutive patients with stable angina who had angiographic follow-ups after initial percutaneous coronary interventions (PCIs) for de novo native lesions were queried for recruitment. Patients who met the catheterization inclusion criteria (coronary lesions $\geq$70% diameter stenosis and associated with objective evidence of ischemia) were subsequently queried in the serum data bank for preprocedural blood samples at the index PCI. All subjects with interventions for restenotic native or stented lesions were excluded from recruitment. Patients who presented with ischemic cardiomyopathy or ACS with or without cardiogenic shock for PCI were also excluded. In addition, patients with acute infection, systemic inflammation disorders such as connective tissue disease, severe heart failure, advanced renal insufficiency, cerebrovascular events, or who had undergone surgery in the past 2 months before index PCI were also excluded. The relevant clinical demographic data were retrieved from the database and completed by thoroughly reviewing the medical chart records. This study protocol was approved by the institutional review board for human research of this hospital.

2.2. Definition of metabolic syndrome

The metabolic syndrome was defined by the National Cholesterol Education Program criteria with modification of waist criterion into body mass index (BMI) of more than 25 kg/m^2 [13,17]. High blood pressure criterion was defined as systolic pressure of more than 130 or diastolic pressure of over more than 85 mm Hg after multiple measurements in sitting position at rest or being already on antihypertensive medication(s). The impaired fasting glucose was defined by fasting blood glucose of more than 110 mg/dL on 2 occasions or being already on oral hypoglycemic agents or insulin shot. Low high-density lipoprotein cholesterol (HDL-C) was defined as that less than 40 mg/dL in men or 50 mg/dL in women. Hypertriglyceridemia was defined as fasting triglyceride of more than 150 mg/dL. Those who met 3 or more of these 5 criteria were classified as having metabolic syndrome.

2.3. Angiographic measurements and coronary severity scoring

The angiographic measurements were made on a viewing workstation with software for quantitative analysis of angiograms (Philips Inturis Suite, R2.2, Philips Medical Systems, Eindhoven, Netherlands). The angiographic characteristics (lesion location and percentage stenosis) of major coronary lesions in the index coronary angiogram were obtained by reviewing the session cine thoroughly. The CAD vessel numbers were defined as the number(s) of the 3 major coronary vessels with 70% or higher diameter stenosis. A modified version of Gensini scoring system was used to calculate the coronary disease severity [23]. Only lesions with 50% or higher diameter stenosis were measured to simplify the calculation. This system consists of lesion location (segments) and obstructive severity scores, and the total scores equal the sum of location score times severity score of all diseased segments. For the location scores, 5 points were given for left main lesion; 2.5 for proximal left anterior descending (LAD) or left circumflex (LCX) artery; 1.5 for midsegment LAD and LCX; 1 for distal segment of LAD and LCX, first diagonal branch, first obtuse marginal branch, right coronary artery,

posterior descending artery, and intermediate artery; 0.5 for second diagonal and second obtuse marginal branches; and 0.25 for third diagonal and third obtuse marginal branches. For the Gensini obstructive severity scores, 4 points were given for lesions 50% to 75% stenotic, 8 for lesions up to 90% stenotic, 16 for lesions 99% stenotic, and 32 for lesions totally occluded.

2.4. Fasting blood glucose, lipid profile, and insulin

All serum samples were stored at −70°C till use. These blood samples were drawn from the antecubital vein from 7:00 to 8:00 AM after overnight fasting and before angiographic procedures. The adequately sized aliquots of serum samples were thawed and analyzed in a single batch for blood glucose and lipid profiles. Plasma glucose was measured by the glucose oxidase–peroxidase method (Wako Diagnostics, Tokyo, Japan). Serum triglyceride and cholesterol concentrations were assayed by an enzymatic method using commercial kits (WAKO, Tokyo, Japan). The HDL-C level was determined in the supernatant of plasma after magnesium chloride–phosphotungstic precipitation of apolipoprotein B–containing lipoproteins. The low-density lipoprotein cholesterol (LDL-C) concentration was estimated by the formula of Friedewald et al [24]. Serum insulin was determined by a commercially available assay kit (IMMULITE, I-2000, EURO/Diagnostic Products Cooperation, Gwynedd, UK). The inter- and intra-assay coefficients of variation for insulin were 4.3% and 5.4%, respectively.

Homeostasis model assessment (HOMA) insulin resistance index (fasting glucose mg/dL × fasting insulin [μU/mL]/405) was calculated in patients without preexisting diabetes mellitus or impaired fasting glucose [25]. Insulin resistance was defined as HOMA index in the top quartile of the study patients, impaired fasting glucose (>110 mg/dL), or diabetes.

2.5. Measurements of sCD40L, MCP-1, cell adhesion molecules, and high sensitivity C-reactive protein

The adequately sized aliquots of serum samples of all enrolled patients were also thawed and analyzed for sCD40L, circulating MCP-1, ICAM-1, VCAM-1, P selectin, and high sensitivity C-reactive protein (hs-CRP) in a single batch. Soluble CD40L and MCP-1 were measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). The intra- and interassay coefficients of variation for sCD40L were 5.00% and 6.20%, respectively, with a sensitivity of less than 10.0 pg/mL. The intra- and interassay coefficients of variation for MCP-1 were 5.80% and 5.70%, respectively, with a sensitivity of less than 5.0 pg/mL. Serum hs-CRP was determined by particle-enhanced immunoturbidimetry (Latex microparticles sensitized with duck anti-CRP IgY kit, provided by Good Biotech, Taichung, Taiwan). The intra- and interassay coefficients of variance were 1.4% and 1.42%, respectively, with a sensitivity of 0.06 mg/dL. ICAM-1, VCAM-1, and P selectin were also measured by enzyme-linked immunosorbent assay (R&D Systems).

2.6. Statistical analysis

All data of continuous variables are expressed as mean ± SEM. As the cutoff HOMA index for the top quartile of nondiabetic patients in this study was 3.58, a value more than 3.58 was defined as insulin resistance. As the detecting limit of hs-CRP measuring kit used in the current study was 0.06 mg/dL, statistical analysis of hs-CRP was made in tertiles with trichotomy points arbitrarily set at 0.104 and 0.438 mg/dL, respectively. Univariate analysis for between-group differences in means was performed by unpaired student's t test and nonparametric Mann-Whitney U test (fasting plasma glucose, serum triglyceride, HDL-C, and VCAM-1) when appropriate. Differences in categorical variables were measured by χ^2 test. Multivariate analyses for between-group differences in means of vascular inflammatory markers were performed by the general linear model and in hs-CRP tertiles by multinomial logistic regression analysis, with predicting factors including metabolic syndrome, sex, hypertension, diabetes, smoking, age, serum cholesterol, and triglyceride. Statistical analyses were performed by SPSS for Windows, release 10.0.1 (SPSS, Chicago, IL). A 2-tailed P value of less than .05 was considered statistically significant.

3. Results

3.1. Baseline demographics

A total of 313 patients, 248 males and 65 females, were studied. Among them, 222 (70.9%; 95% confidence interval, 65.9%-76.0%), 170 males and 52 females, aged 65.3 ± 0.7 years, had metabolic syndrome. The demographic characteristics of both groups are presented in Table 1. Metabolic syndrome patients had higher serum insulin concentration (11.59 ± 0.70 vs 8.24 ± 0.49 μU/mL, $P < .001$) and HOMA index (3.44 ± 0.26 vs 1.90 ± 0.15, $P < .001$). These patients also had higher serum creatinine level (1.3 ± 0.1 vs 1.2 ± 0.1 mg/dL, $P = .035$), but lower LDL-C level (117 ± 2 vs 126 ± 3 mg/dL, $P = .035$), despite higher triglyceride concentration. Patients with metabolic syndrome tended to be female (52/222 vs 13/91, P = .070) and younger (65.3 ± 0.7 vs 67.6 ± 1.1 years, $P = .068$). Patients with and without metabolic syndrome did not differ in the systolic or diastolic blood pressure, or use of statins, angiotensin-converting enzyme inhibitors, or aspirin.

3.2. Inflammatory cytokines, cell adhesion molecules, and hs-CRP

In univariate analysis, patients with metabolic syndrome presented higher sCD40L, ICAM-1, VCAM-1, and P selectin than, but similar circulating MCP-1 to those without metabolic syndrome (Table 2). However, only sCD40L (6057 ± 275 vs 5051 ± 423 pg/mL, $P = .037$) was significantly elevated in patients with metabolic syndrome in multivariate analysis. Patients presenting with metabolic syndrome also had more hs-CRP in higher tertiles (35.5%

Table 1
Baseline demographic data of patients with CAD with and without metabolic syndrome

	Metabolic syndrome	No metabolic syndrome	*P*
	n = 222	n = 91	
Sex (M/F)	170/ 52	78/ 13	.070
Age (y)	65.3 ± 0.7	67.6 ± 1.1	.068
Diabetes mellitus, n (%)	76 (34.2)	11 (12.1)	<.001
Smoking	110 (49.5)	45 (49.4)	.971
Hypertension, n (%)	180 (81.1)	51 (56.7)	<.001
BH (cm)	162 ± 1	163 ± 1	.616
BW (kg)	69.5 ± 0.7	62.3 ± 0.8	<.001
BMI (kg/m^2)	26.4 ± 0.3	23.4 ± 0.2	<.001
Fasting glucose (mg/dL) (median)	139 ± 4 (119)	103 ± 4 (96)	<.001[a]
Insulin (μU/mL)[b]	11.59 ± 0.70	8.24 ± 0.49	<.001
HOMA index[b]	3.44 ± 0.26	1.90 ± 0.15	<.001
Creatinine (mg/dL)	1.3 ± 0.1	1.2 ± 0.1	.035
Triglyceride (mg/dL) (median)	160 ± 6 (142)	104 ± 4 (99)	<.001[a]
HDL-C (mg/dL) (median)	31 ± 1 (32)	38 ± 1 (37)	<.001[a]
Cholesterol (mg/dL)	181 ± 3	185 ± 3	.427
LDL-C (mg/dL)	117 ± 2	126 ± 3	.035
BP, systolic (mm Hg)	129 ± 1	128 ± 2	.637
BP, diastolic (mm Hg)	72 ± 1	70 ± 1	.351
Use of statin, n (%)	75 (33.8)	23 (25.3)	.168
Use of ACEI, n (%)	128 (57.7)	49 (53.8)	.665
Use of aspirin, n (%)	213 (95.9)	88 (96.7)	.920

BH indicates body height; BP, blood pressure; ACEI, angiotensin-converting enzyme inhibitor.
[a] Mann-Whitney *U* test.
[b] In nondiabetic patients only.

[78/220] vs 27% [24/89] in the middle tertile and 37.7% [83/220] vs 25.8% [23/89] in the upper tertile) in both univariate (P = .002) and multivariate (P = .005) analyses.

Table 2
Differences in inflammatory cytokines, adhesion molecules, and hs-CRP tertile distribution between patients with CAD with and without metabolic syndrome

	Metabolic syndrome	No metabolic syndrome	P^a	P^b
	n = 222	n = 91		
sCD40L (pg/mL)	6057 ± 275	5051 ± 423	.049	.037
MCP-1 (pg/mL)	335 ± 12	354 ± 51	.621	.834
ICAM-1 (ng/mL)	244 ± 7	217 ± 8	.024	.248
VCAM-1 (ng/mL) (median)	1117 ± 34 (1009)	998 ± 35 (991)	.017[c]	.597
P selectin (ng/mL)	86 ± 3	73 ± 3	.003	.505
Hs-CRP, n (%)	220 (99.1)	89 (97.8)		
≤0.104 mg/dL, n (%)	59 (26.8)	42 (47.2)	.002	.005
0.105-0.438 mg/dL, n (%)	78 (35.5)	24 (27.0)		
>0.438 mg/dL, n (%)	83 (37.7)	23 (25.8)		

[a] Univariate analysis.
[b] Multivariate analysis with predicting factors including metabolic syndrome, sex, hypertension, diabetes, smoking, age, serum cholesterol, and triglyceride.
[c] Mann-Whitney *U* test.

Table 3
Differences in coronary involvements and disease severity between patients with and without metabolic syndrome

	Metabolic syndrome	No metabolic syndrome	P^a	P^b
	n = 222	n = 91		
Coronary lesions, n (%)[c]				
LAD	159 (71.6)	58 (63.7)	.017	.140
LCX	104 (46.8)	32 (35.2)	.058	.349
Right coronary artery	100 (45.0)	39 (42.9)	.724	.550
Intermediate	3 (1.4)	0	.265	
CAD vessel numbers[c]	1.6 ± 0.0	1.4 ± 0.1	.007	.368
CAD, n (%)[c]				
Single vessel	110 (49.5)	58 (63.7)	.042	.026
Double vessel	81 (36.5)	28 (30.8)		
Triple vessel	31 (14.0)	5 (5.5)		
Gensini segment numbers[d]	2.0 ± 0.1	1.7 ± 0.1	.005	.168
Gensini diseased segments, n (%)[d]				
One segment	83 (37.4)	47 (51.6)	.091	.014
Two segments	68 (30.6)	29 (31.9)		
Three segments	55 (24.8)	12 (13.2)		
Four segments	13 (5.9)	2 (2.2)		
Five segments	2 (0.9)	1 (1.1)		
Six segments	1	0		
Lesion location scores	2.9 ± 0.1	2.5 ± 0.2	.073	.273
Total Gensini scores	20.9 ± 1.7	18.4 ± 2.2	.356	.506

[a] Univariate analysis.
[b] Multivariate analysis with predicting factors including metabolic syndrome, sex, hypertension, diabetes, smoking, age, serum cholesterol, and triglyceride.
[c] Includes vessels with diameter stenosis of 70% or more.
[d] Includes only lesions with diameter stenosis of 50% or more.

3.3. Coronary involvement and severity scores

In univariate analysis, the presence of metabolic syndrome was associated with significantly more coronary vessel involvements, which have at least 70% diameter stenosis (CAD vessel numbers 1.6 ± 0.0 vs 1.4 ± 0.1, P = .007; Table 3), with more patients presenting with triple-vessel disease (14.0% [31/222] vs 5.5% [5/91]) or double-vessel disease (36.5% [81/222] vs 30.8% [28/91]) (P = .042). Patients with metabolic syndrome showed a tendency toward more LCX involvement. Regarding the Gensini CAD severity scoring, patients with metabolic syndrome had more diseased segments with at least 50% diameter stenosis (2.0 ± 0.1 vs 1.7 ± 0.1, P = .005) despite similar total scores. In multivariate analysis, metabolic syndrome was significantly associated with multiple coronary vessel involvements with 70% or higher diameter stenosis (P = .026, Table 3) and multiple segment involvements (Gensini scoring) with 50% or higher diameter stenosis (P = .014).

4. Discussion

In summary, we found in this study that the presence of metabolic syndrome is independently associated with elevated sCD40L and hs-CRP, but not circulating MCP-1 or cell adhesion molecules in patients with angiographically docu-

mented CAD requiring interventional treatment of stable angina. Secondly, the existence of metabolic syndrome in these patients with CAD was associated with more extensive coronary involvements and more severe lesion stenoses.

4.1. Metabolic syndrome and inflammation

The metabolic syndrome consists of a constellation of factors that altogether raise the risk for CVD more than its individual components [18]. Because waist circumference measures were not available, we used BMI instead to classify individuals with obesity in the current study. This modification was adopted in the study by Malik et al [17], and BMI was reported to have identification and prognostic values similar to those for waist circumference [15]. Since the publication of the Adult Treatment Panel III that identified the metabolic syndrome as a grouped risk entity, clinicians have become more aware of the existence of and need to treat this syndrome. The prevalence of metabolic syndrome is about 5% to 40% [14,26,27]. In the current study consisting of patients undergoing repetitive coronary angiography after index PCI for symptomatic CAD, the incidence of metabolic syndrome was 70%, arguing for the magnitude of metabolic syndrome in established CAD.

Insulin resistance has been consistently identified to be a central pathophysiologic process in metabolic syndrome [12,28]. It has been proposed that innate immunity and inflammation, modified by environmental stimuli, might be possible causes for insulin resistance. Therefore, it is interesting to explore the inflammatory features associated with metabolic syndrome, even in patients with existing cardiovascular diseases. Integration of inflammatory considerations with the components of metabolic syndrome may enhance the clinical and prognostic values of this syndrome and help guide clinical management. Subjects with metabolic syndrome were reported to present a prothrombotic and proinflammatory state [19,20]. Among the surrogated markers, CRP was the most commonly studied and consistently found to be elevated [29,30] and has provided prognostic information on cardiovascular risk in patients with metabolic syndrome but do not have CAD [31]. Hemostatic factors were also reported to be increased in non-CAD metabolic syndrome [29]. C-reactive protein, interleukin 6, and fibrinogen were further found to be elevated in patients with metabolic syndrome who have CAD [32]. However, to date, no studies have directly investigated the effect of metabolic syndrome on sCD40L, MCP-1, or cell adhesion molecules in patients with established CAD.

CD40 is a 50-kd integral membrane protein of the TNF receptor family, whereas CD40L is a 39-kd member of the TNF family. Studies have shown that ligation of CD40 on atheroma-associated cells mediates expression of cell adhesion molecules, cytokines, chemokines, growth factors, matrix metalloproteinases, and procoagulants, all involved in atherogenesis and subsequent complications [1,33-35]. Elevated CD40L was found in patients with CAD [3,4]. In addition, cellular adhesion molecules were reported to be increased in atherosclerotic cardiovascular diseases [9,10]. Intercellular adhesion molecule 1 is further reported to act more as a marker for cardiovascular events in healthy people and VCAM-1 as a risk predictor for patients with CAD [10]. To our knowledge, this study is the first to clearly document that the presence of metabolic syndrome is independently (by multivariate analysis) associated with elevated serum sCD40L and hs-CRP, but not MCP-1, ICAM-1, VCAM-1, or P selectin in patients with stable angina requiring PCI for angiographically documented CAD.

4.2. Metabolic syndrome and coronary disease severity

Increasing severity of metabolic syndrome was associated with increasing prevalence of coronary calcification in patients without clinical CAD [15]. Patients with this syndrome were also reported to be at increased risk for progressive carotid atherosclerosis [36]. Metabolic syndrome was associated with advanced vascular damage (carotid intima-media thickness, ankle brachial pressure index, and albuminuria) in patients with existing cardiovascular diseases [37]. Increasing coronary disease severity and clinical consequences as well as treatment of CAD in association with increasing metabolic syndrome scores was reported in one study [21]. One recently published study stated that metabolic syndrome was associated with the extent of CAD in patients with non–ST-elevation ACS [22]. Another study showed that the metabolic syndrome increased the cardiovascular risk in women with angiographic CAD [27]. Our study lends more support to the imperative pathogenic role of metabolic syndrome even in symptomatic patients with CAD in whom the consequences of metabolic syndrome may be mediated by enhanced chronic systemic inflammation (sCD40L and hs-CRP).

In terms of study limitation, the current findings were limited to patients with stable angina requiring PCI for significant coronary diseases. Whether our results could be generalized to patients with CAD in general awaits further study. Secondly, the coronary severity scoring system used here did not take into account lesions with less than 50% diameter stenosis to simplify the measurements. Although this underestimated the real atherosclerotic burden, it was a straightforward and simplified measure of clinically significant coronary severity, whereas the real atherosclerotic extent is not easy to evaluate despite intravascular ultrasound studies.

In conclusion, we found that, in this study, the presence of metabolic syndrome is independently associated with elevated sCD40L, hs-CRP, and disease severity in patients with CAD requiring PCI treatment of stable angina. Our study results confirm the clinical importance of metabolic syndrome in patients with well-developed CAD.

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