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Different Clinical and Coronary Angiographic Findings According to Ratios of Total Cholesterol to High-Density Lipoprotein Cholesterol During the Acute Phase of Myocardial Infarction

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Abstract

Objectives. Several pathological studies have shown that a higher ratio of the serum total cholesterol concentration to the high-density lipoprotein cholesterol concentration (TC/HDL-C ratio) is associated with plaque rupture in patients with acute coronary syndromes. We examined the relationship between the serum total cholesterol concentration and the TC/HDL-C ratio, and clinical and angiographic findings in patients with first acute myocardial infarction.

Methods. Two hundred eighty patients were classified into quartiles according to the TC/HDL-C ratio measured within 24 hr from symptom onset: 70 patients in the first quartile (group L: mean TC/HDL-C ratio, 3.0), 140 in the second and third quartiles (group M: mean TC/HDL-C ratio, 4.6), and 70 in the fourth quartile (group H: mean TC/HDL-C ratio, 7.5).

Results. There were no differences among the three groups with regard to sex, diabetes mellitus or hypertension. Patients in group L were older (66 ± 9 vs 60 ± 11, 56 ± 10 years, $p < 0.01$) and had a higher incidence of stable angina before acute myocardial infarction (26% vs 14%, 10%, $p < 0.05$) than in patients groups M and H. Although coronary angiograms revealed no difference in the number of diseased vessels among the three groups, extent index indicating the proportion of each coronary segment that appears angiographically abnormal was lowest in group L (0.7 ± 0.5), followed by group M (1.3 ± 0.6), and high-

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est in group H(1.7 ± 0.6, $p < 0.01$). The number of segments with calcification and the incidence of calcification in the culprit lesion were higher in group L than in groups M and H.

Conclusions. Our findings suggest that the clinical presentations and angiographic appearances differ according to the TC/HDL-C ratio in the acute phase of acute myocardial infarction.

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Key Words

■**Myocardial infarction, pathophysiology (acute)** ■**Lipoproteins, HDL**
■**Cholesterol** ■**Angiography**

INTRODUCTION

Plaque rupture is generally considered to be the most common mechanism of acute coronary syndromes. However, plaque erosion without plaque rupture has been recognized as another important cause[1–3]. Recently, several pathological studies have shown that the ratio of the serum total cholesterol concentration to the high-density lipoprotein cholesterol concentration (TC/HDL-C ratio) is higher in patients with acute coronary syndromes who have plaque rupture than in those who have plaque erosion[3–5]. This study tested the hypothesis that clinical features differ according to the TC/HDL-C ratio at the onset of acute myocardial infarction. We examined the relationship of the TC/HDL-C ratio to clinical and angiographic findings in patients with first acute myocardial infarction.

SUBJECTS AND METHODS

Study patients

Two hundred eighty consecutive patients (mean age 61 ± 10 years, 223 men and 57 women) fulfilled the following inclusion criteria and were enrolled in our study: 1) no previous history of myocardial infarction; 2) admission within 12 hr from symptom onset; 3) typical chest pain for at least 30 min; 4) ST-segment elevation of ≥ 1 mm in at least 2 limb leads or ≥ 2 mm in at least 2 contiguous precordial leads; 5) an increase in the serum creatine kinase level to more than twice the upper limit of normal; 6) Thrombolysis in Myocardial Infarction (TIMI)[6] grade 3 flow in the infarct-related artery confirmed by coronary angiography immediately after admission and at discharge; and 7) measurement of lipid and lipoprotein levels within 24 hr from symptom onset. Patients receiving lipid-lowering therapy were excluded. Patients were classified into quartiles according to the TC/HDL-C ratio measured within 24 hr from symptom onset: 70 patients in the first quartile (group L: mean TC/HDL-C ratio, 3.0), 140 in the second and third quartiles (group M: mean TC/HDL-C ratio, 4.6), and 70 in the fourth quartile (group H: mean TC/HDL-C ratio, 7.5).

Blood samples

Blood samples for measurement of peripheral white blood cell counts were taken on admission. Blood samples for measurement of serum creatine kinase were taken on admission, every 3 hr during the first 24 hr, every 6 hr for the next 2 days, and then daily until discharge. Serum samples were analyzed for total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and total triglyceride within 24 hr from symptom onset.

Coronary angiography

Coronary angiography was performed with the Judkins technique immediately after admission and at discharge. Recanalization was defined as TIMI grade 3 flow. Stenosis was considered significant if the lumen diameter was narrowed by ≥ 75% in any projection. The allocation of recanalization therapy was left to the discretion of the physician in charge. Predischarge all coronary angiograms were evaluated according to the criteria of Bogaty *et al.*[7] by two independent observers blinded to clinical variables. The extent of angiographically abnormal segments was quantified by means of a score that was normalized to an extent index. This was done simply and visually by assigning a score of 0 to 3 per segment of the coronary arterial tree. The culprit lesion was excluded from this analysis, because this study included some patients who underwent coronary angioplasty. Angiographical abnormality was defined as narrowing, irregularity, or both. A segment was scored as below;

A score of 0: no abnormality was apparent,

A score of 1: any abnormality was confined to 10% or less of the segment length,

A score of 2: the abnormality affected more than 10% up to 50% of the segment length,

A score of 3: the abnormality affected more than 50% of the segment length.

The extent index was the extent score divided by the number of segments that could be properly visualized on antegrade flow. Angiographic calcification was defined as readily apparent radiopacities noted without cardiac motion before contrast injection within the vascular wall[8]. Angiographic ulceration was defined as a small crater consisting of a discrete luminal widening with luminal irregularity in the culprit lesion[9].

Statistical analysis

Data were analyzed using SPSS (Release 10, SPSS Inc.). Continuous data were expressed as mean ± standard deviation and categorical data as percentage. Analysis of variance was used for continuous variables. If significance was indicated by analysis of variance, a Bonferonni correction was used as a post-hoc test for multiple comparisons. Chi-square analysis was used to compare categorical variables. Multivariate logistic regression analysis was used to examine the determinants of diffuse angiographically detectable coronary atherosclerosis as indicated by extent index of ≥ 1.7 in patients of the highest quartile. Odds ratios and 95% confidence intervals were calculated. Differences were considered significant at $p < 0.05$.

RESULTS

Baseline characteristics

The baseline characteristics of the three groups are summarized in **Tables 1** and **2**. There were no differences among the three groups with regard to sex, diabetes mellitus, hypertension, or a family history of cardiac disease, time from symptom onset to admission, method of recanalization. Patients in group L were older and had a lower body mass index, a higher incidence of stable angina and a lower peripheral white blood cell count on admission than patients in groups M and H. Patients in Group H had a higher incidence of any history of cigarette smoking than patients in groups L and M. The levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol were lowest in group L, followed by group M, and highest in group H. The level of high-density lipoprotein cholesterol was highest in group L, followed by group M, and lowest in group H.

Angiographic findings and infarct size (Table 1)

Involvement of the left anterior descending coronary artery was significantly higher and involvement of the right coronary artery was lower in group L, as compared with groups M and H. There was a slightly but not significantly lower peak creatine kinase level in group L than in group H. Although coronary angiograms revealed no difference in the number of diseased vessels among the three groups, extent index was lowest in group L, followed by group M, and highest in group H (**Fig. 1**). Number of segments with calcification and incidence of calcification in the culprit lesion were higher in group L than in groups M and H (**Fig. 2**). Among 100 patients in whom recanalization occurred spontaneously or after thrombolysis, ulceration in the culprit lesion, considered as angiographic findings of plaque rupture[9] on follow-up coronary angiography performed at discharge (15 ± 4 hospital days), was present in none of 26 in group L, 6 of 50 patients (12%) in group M and 7 of 24 patients (29%) in group H ($p < 0.001$).

Multivariate predictors of diffuse angiographical coronary atherosclerosis (Table 3)

Multivariate analysis identified TC/HDL-C as an independent predictor of diffuse angiographically detectable coronary atherosclerosis as indicated by extent index of ≥ 1.7. The other variables examined, including age, body mass index, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides and smoking, were not significant determinants of diffuse angiographically detectable coronary atherosclerosis.

DISCUSSION

Our study demonstrated different clinical presentations and angiographic appearances according to the TC/HDL-C ratio measured within 24 hr from the onset of acute myocardial infarction. Patients with a low TC/HDL-C ratio had a higher incidence of stable angina before acute myocardial infarction and more severe angiographic coronary calcification. In contrast, patients with a high TC/HDL-C ratio had a higher incidence of smoking and more diffuse angiographically detectable coronary atherosclerosis and more frequent ulceration in the culprit lesion, considered to be an angiographic finding of plaque rupture[9]. These findings suggest that the mechanism of acute myocardial infarction may

Table 1 Baseline characteristics

	Group L (n=70)	Group M (n=140)	Group H (n=70)
Age (yr)	66±9	60±11**	56±10**#
Male	51(73)	111(79)	61(87)
Height (cm)	160±8	162±8	164±8*
Weight (kg)	58±7	65±11**	69±11**#
Body mass index (kg/m^2)	21±2	24±3**	25±3**
Preinfarction angina	53(76)	84(60)	41(59)
Stable angina	18(26)	19(14)*	7(10)*
Unstable angina	35(50)	65(46)	34(49)
Smoking	41(59)	94(67)	56(80)**
Diabetes mellitus	22(31)	33(24)	20(29)
Hypertension	37(53)	64(46)	30(43)
Family history of coronary artery disease	23(33)	39(28)	12(17)
Medication before acute myocardial infarction			
Aspirin	9(13)	14(10)	6(9)
Nitrates	7(10)	8(6)	2(3)
Beta-blockers	3(4)	4(3)	2(3)
Calcium antagonists	15(21)	21(15)	8(11)
Angiotensin-converting enzyme inhibitors	2(3)	6(4)	2(3)
Time from symptom onset to admission (hr)	2.5±3.0	2.3±2.4	2.6±3.1
White blood cell count on admission (/mm^3)	10,126±2,760	11,315±3,825*	12,103±3,317**
Method of recanalization (angioplasty)	44(63)	90(64)	46(66)
Peak creatine kinase (mU/ml)	3,094±2,047	3,228±1,907	3,772±2,806
Infarct-related artery			
Right coronary artery	19(27)	60(43)*	35(50)**
Left circumflex artery	4(6)	17(12)	5(7)
Left anterior descending coronary artery	47(67)	63(45)**	30(43)**
	[n=35]†	[n=50]†	[n=22]†
Time from symptom onset to recanalization†	3.6±1.5	3.7±1.7	3.7±1.8
Culprit lesion (segment 6)†	19(54)	31(62)	15(68)
Method of recanalization (angioplasty)†	29(83)	33(66)	14(64)
Collateral circulation†	14(40)	16(32)	6(27)
Peak creatine kinase (mU/ml)†	3,654±2,462	4,237±2,038	4,710±3,015*
Multivessel disease	11(16)	29(21)	12(17)
Number of segments with calcification	2.4±2.5	1.5±1.6**	0.9±1.5**
Calcification in the culprit lesion	33(47)	31(22)**	16(23)**
Ulceration	0/26(0)	6/50(6)**	7/24(29)**##
Extent index	0.7±0.5	1.3±0.6**	1.7±0.6**##

Continuous values are mean±SD. ( ): %. *p<0.05, **p<0.01 vs group L. #p<0.05, ##p<0.01 vs group M.
†Only patients with initial Thrombolysis in Myocardial Infarction grade 0 or 1 flow of the left anterior descending coronary artery, consisting of 35 patients in group L, 50 patients in group M and 22 patients in group H.

differ between patients with a low TC/HDL-C ratio and those with a high TC/HDL-C ratio.

Several pathological studies have shown that patients with acute coronary syndromes who have plaque rupture have a higher TC/HDL-C ratio than those who have plaque erosion[3–5]. Farb *et al.*[10] have recently reported that abnormal cholesterol levels correlate with plaque rupture but not with plaque erosion. Because lipid-lowering therapy has been convincingly developed, the significance of

Table 2 Serum cholesterol

	Group L (n=70)	Group M (n=140)	Group H (n=70)
TC(mg/d*l*)	169±33	198±34**	217±34**##
HDL-C(mg/d*l*)	57±12	43±8**	31±7**##
LDL-C(mg/d*l*)	99±24	134±28**	153±30**##
TC/HDL-C ratio	3.0±0.4	4.6±0.6**	7.5±2.5**##
Serum triglyceride(mg/d*l*)	73±43	101±56*	172±21**##

Values are mean±SD. *p<0.05, **p<0.01 vs group L. ##p<0.01 vs group M.
TC=total cholesterol; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TC/HDL-C ratio=ratio of TC to HDL-C.

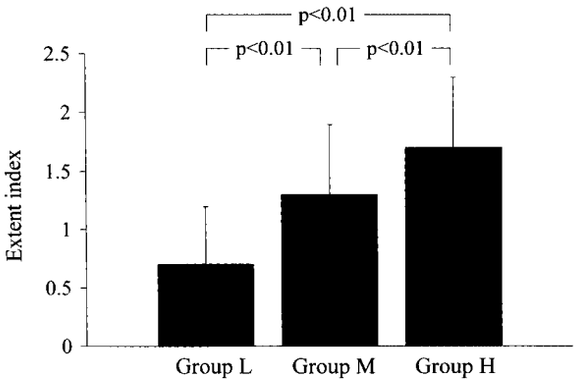

Fig. 1 Bar graphs comparing the extent index
Bar graphs showing the comparison of extent index, indicating the proportion of each coronary segment that appears angiographically abnormal, in the three groups. Extent index was highest in group H, followed by group M, and lowest in group L.

TC/HDL-C ratio in coronary artery disease should be elucidated not only in the pathological studies but also in the clinical setting. However, to our knowledge, there is no report concerning angiographic findings according to TC/HDL-C ratio. Previous studies have shown that lipid and lipoprotein levels change dramatically after acute myocardial infarction. These changes are manifest within 24 to 48 hr after the onset of acute myocardial infarction[11]. Therefore, our study included only patients in whom lipid levels were measured within 24 hr from the onset of acute myocardial infarction, which reflects the lipid profile at the onset of acute myocardial infarction. In our study, the mean TC/HDL-C ratio in group H was 7.5, similar to that in patients who had plaque rupture in previous pathological studies[3,4]. Furthermore, ulceration in the culprit lesion was more frequent in group H than in groups M and L. Maehara *et al.*[9] reported that intravascular ultrasound plaque rupture strongly correlated with angiographic ulceration. These findings suggest that plaque rupture may have played a more important role in the onset of acute myocardial infarction in patients with a high TC/HDL-C ratio than in those with a low TC/HDL-C ratio. We also found that these patients were more likely to have had a history of smoking and an elevated white blood cell count on admission. These findings are in accord with the results of a recent postmortem pathological study in 100 patients who had died of acute myocardial infarction by Kojima *et al.*[12], who found that the presence of plaque rupture was associated with smoking and greater incidences of leucocytosis.

In our study, patients with a low TC/HDL-C ratio had a lower extent index according to the criteria of Bogaty *et al*[7]. Furthermore, patients with a low TC/HDL-C ratio more frequently had angiographically visible calcification than did patients with a higher TC/HDL-C ratio. These contrasting angiographic findings are intriguing and suggest that patients with a high TC/HDL-C ratio and those with a low TC/HDL-C ratio do not have similar coronary atherosclerotic characteristics in the setting of acute myocardial infarction. In this study, we examined "severe" calcification visualized by coronary angiography without cardiac motion. Yamanaka *et al.*[13] reported that patients with stable effort angina more frequently had severe coronary calcification as assessed by cinefluoroscopy than those with acute coronary syndromes, suggesting that coronary artery calcification is associated with a slow and chronic atherosclerotic process. In our study, patients with a low TC/HDL-C ratio had a higher incidence of stable angina before acute myocardial infarction, which might be associated with a higher incidence of severe calcification, and no ulceration in the culprit lesion in the case of reperfusion spontaneously or by thrombolysis. We therefore speculated that plaques with severe angiographic calcification might be less vulnerable, *i.e.*, "hard" plaques, not prone to rupture. The precise mechanisms of acute thrombosis in these patients are not known. However, not only the vulnerability of the underlying plaque but also various factors, such as sympathetic activity, vascular reactivity, platelet aggregability, and physical or emotional stress, may precipitate acute coronary events[14–16].

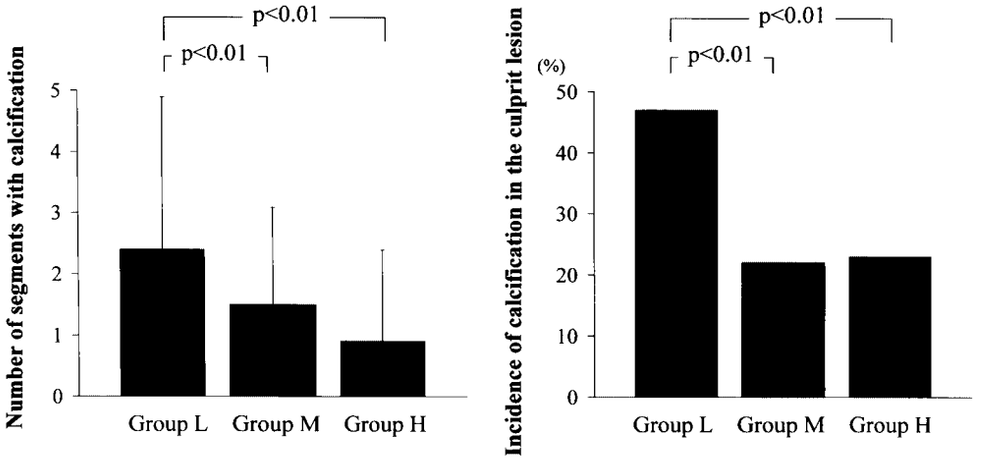

Fig. 2 Angiographic evidence of severe calcification
Bar graphs showing the comparison of severe calcification as visualized by coronary angiography without cardiac motion in the three groups. Group L had a higher incidence of severe calcification in all coronary trees as well as the culprit lesion compared with groups M and H.

Table 3 Multivariate analysis of factors associated with diffuse angiographical coronary atherosclerosis

Variable	Odds ratio (95% confidence interval)	*p* value
Age	1.04 (0.99−1.11)	0.06
Body mass index	1.28 (0.89−1.94)	0.16
TC	1.02 (0.99−1.04)	0.12
HDL-C	0.95 (0.89−1.05)	0.09
LDL-C	1.01 (0.98−1.11)	0.20
TC/HDL-C ratio	1.04 (1.01−1.09)	0.04
Triglyceride	2.00 (0.75−5.36)	0.16
Smoking	0.80 (0.32−1.57)	0.40

Abbreviations as in Table 2.

It is possible that in patients with a low TC/HDL-C ratio, these other factors except for plaque vulnerability may have played a more important role in the onset of acute myocardial infarction.

Study limitations

Our study had several limitations. First, this was a small retrospective study. Our subjects were limited to patients with a first ST-segment elevation acute myocardial infarction in whom lipid and lipoprotein levels were measured within 24 hr from symptom onset without receiving lipid-lowering therapy. However, this strict inclusion criterion enabled us to clearly demonstrate differences in clinical and angiographic features between patients with a low TC/HDL-C ratio and those with a high TC/HDL-C ratio. Second, because we evaluated coronary angiographic appearance on the basis of an extent index indicating the proportion of each coronary segment that appeared angiographically abnormal, we might have not accurately evaluated coronary atherosclerosis. Several pathological studies have demonstrated that atherosclerosis is more widespread than that predicted on the basis of angiograms[17,18]. Patients with a low TC/HDL-C ratio had a lower extent index, and we cannot rule out the possibility that diffuse intimal atherosclerosis with no discrete intraluminal protrusion may have been present. Other techniques that allow direct examination of the wall and lumen of the coronary artery, such as intravascular ultrasound, are needed to more objectively evaluate coronary atherosclerosis and provide important additional information. However, we believe that the markedly dissimilar clinical features between patients with a low TC/HDL-C ratio and those with a high TC/HDL-C ratio reflect differences in underlying pathophysiological mechanisms of acute myocardial infarction.

CONCLUSIONS

Our findings suggest that the clinical presentations and angiographic appearances differ according to the TC/HDL-C ratio in the acute phase of acute myocardial infarction.

要　約

心筋梗塞急性期の高比重リポ蛋白コレステロールに対する総コレステロールの比による臨床像および冠動脈造影所見の違い

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目　的: 病理組織学的検討では，急性冠症候群において高比重リポ蛋白コレステロール(HDL-C)に対する総コレステロール(TC)の比(TC/HDL-C)の上昇とプラーク破裂との関連が報告されている．本研究では，初回急性心筋梗塞例で急性期TC/HDL-Cと臨床像および冠動脈造影所見との関係を検討した．

方　法: 発症24時間以内に血清脂質を測定した初回急性心筋梗塞280例を対象とした．発症24時間以内のTC/HDL-Cにより4分割し，下位1/4に属する下位群70例(平均TC/HDL-C 3.0)，上位1/4に属する上位群70例(平均TC/HDL-C 7.5)，残り140例の中間群(平均TC/HDL-C 4.6)の3群に分類した．

結　果: 3群間で，性別，糖尿病，高血圧の頻度に差はなかった．下位群は中間群および上位群と比べて高齢で(66±9 vs 60±11，56±10歳，$p<0.01$)，心筋梗塞発症前の安定狭心症は有意に高率だった(26% vs 14%，10%，$p<0.05$)．3群間で病変枝数に差はなかったが，冠動脈造影上の病変の拡がりを示す指標であるextent indexは下位群が最も低く(0.7±0.5)，ついで中間群で(1.3±0.6)，上位群が最も高かった(1.7±0.6)($p<0.01$)．下位群は中間群と上位群と比べて冠動脈造影上，静止画像で認められる高度な石灰化を有する分節数，責任病変の石灰化の頻度は有意に高かった．

結　論: 初回急性心筋梗塞患者において，急性期の高比重リポ蛋白コレステロールに対する総コレステロールの比により，臨床像および冠動脈造影所見は異なることが示唆された．

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