

CORONARY RISK FACTORS AND PLAQUE MORPHOLOGY IN MEN WITH CORONARY DISEASE WHO DIED SUDDENLY

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ABSTRACT

Background Cigarette smoking and abnormal serum cholesterol concentrations are risk factors for acute coronary syndromes, but the underlying mechanisms are poorly understood. We studied whether cigarette smoking and abnormal cholesterol values may precipitate acute coronary thrombosis and sudden death resulting from either rupture of vulnerable coronary plaques or erosion of plaques.

Methods We examined the hearts of 113 men with coronary disease who had died suddenly and also analyzed their coronary risk factors. We found an acute coronary thrombus in each of 59 men, and severe narrowing of the coronary artery by an atherosclerotic plaque without acute thrombosis (stable plaque) in 54. Cases of acute thrombosis were divided into two groups: 41 resulting from rupture of a vulnerable plaque (a thin fibrous cap overlying a lipid-rich core), and 18 resulting from the erosion of a fibrous plaque rich in smooth-muscle cells and proteoglycans. Vulnerable plaques that had not ruptured were counted in each heart.

Results Cigarette smoking was a risk factor in 44 (75 percent) of the men with acute thrombosis, as compared with 22 (41 percent) of the men with stable plaques ($P < 0.001$). The mean (\pm SD) ratio of serum total cholesterol to high-density lipoprotein (HDL) cholesterol was markedly elevated in the men who died of acute thrombosis with plaque rupture (8.5 ± 4.0) but only mildly elevated in the men without acute thrombosis (5.5 ± 2.4 , $P < 0.001$) and in the men with thrombi overlying eroded plaques (5.0 ± 1.8 , $P < 0.001$). Multivariate analysis showed an association between an elevated ratio of serum total cholesterol to HDL cholesterol and the presence of vulnerable plaques ($P < 0.001$).

Conclusions Among men with coronary disease who die suddenly, abnormal serum cholesterol concentrations — particularly elevated ratios of total cholesterol to HDL cholesterol — predispose patients to rupture of vulnerable plaques, whereas cigarette smoking predisposes patients to acute thrombosis. (N Engl J Med 1997;336:1276-82.)

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CIGARETTE smoking and hypercholesterolemia are well-known risk factors for atherosclerotic heart disease.¹ In addition to its association with premature atherosclerosis,² cigarette smoking is a risk factor for acute myocardial infarction³ and possibly sudden death from coronary disease.⁴ Likewise, elevated serum choles-

terol concentrations and low serum high-density lipoprotein (HDL) cholesterol concentrations are associated with an increased risk of acute coronary events and premature atherosclerosis.^{2,3} Recently, it has been established that cholesterol-lowering therapy decreases the frequency of acute myocardial infarction, especially in secondary-prevention trials.⁵

Sudden death, a frequent result of severe coronary disease, is often precipitated by acute coronary thrombosis. Plaque rupture, the most frequent cause of coronary thrombosis,^{6,7} has been implicated in the episodic progression of coronary stenosis as demonstrated by sequential angiography and is often associated with unstable angina.⁸ Atherosclerotic plaques that are vulnerable to rupture have a dense infiltrate of macrophages and, to a lesser extent, lymphocytes⁸ within a fibrous cap that overlies a crescentic acellular mass of lipids. Another mechanism of coronary thrombosis, plaque erosion, has recently been identified as an important cause of sudden coronary death.⁹ Eroded plaques differ from ruptured plaques in that they have a base rich in smooth-muscle cells and proteoglycans.⁹

Antithrombotic treatment is an integral part of the prevention of recurrent coronary events,¹⁰ and both cigarette smoking¹¹ and hypercholesterolemia¹² have been linked to coronary thrombosis. Despite the evidence linking acute coronary events and coronary thrombosis to the risk factors of cigarette smoking and elevated cholesterol concentrations, autopsy studies have not yet addressed the association of the risk factors with the frequency and type of acute coronary thrombosis in men who die suddenly.

This study addressed the following questions: Are risk factors for coronary disease associated with acute thrombosis in sudden coronary death? And are those risk factors associated with one of the two major mechanisms of acute coronary thrombosis — plaque rupture and plaque erosion? The answers may help explain why cholesterol-lowering therapy and anti-thrombotic drugs prevent acute coronary events in patients with severe coronary atherosclerosis.

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METHODS

Selection of Cases

The hearts of men who died suddenly of causes that were initially unexplained were examined prospectively in consultation with the Office of the Chief Medical Examiner of the state of Maryland to establish the cause and manner of death of each of the men. Sudden death was defined as that occurring within 6 hours of the onset of symptoms (witnessed cardiac arrest) or within 24 hours of the time that the victim was last seen alive in his normal state of health. Death from coronary causes was defined as a luminal narrowing of a major epicardial coronary artery by at least 75 percent by an atherosclerotic plaque or acute thrombus when noncardiac causes of death could be ruled out by a complete forensic autopsy and the results of postmortem toxicologic testing. From an initial series of 125 cases, a total of 113 remained after cases with gross hemolysis or inadequate cells for the measurement of glycosylated hemoglobin were excluded.

Evaluation of the Hearts

All the hearts were studied under the supervision of the medical examiner; information on 26 cases has been published previously without data on risk factors other than hypertension.¹³ In every case, coronary arteries were perfusion-fixed with formalin at 100 mm Hg.¹⁴ The coronary arteries were studied by serial sectioning at 3-mm intervals after decalcification, if necessary. Any 3-mm segment that showed narrowing of more than 50 percent was submitted for histologic analysis. In every artery with luminal narrowing of more than 50 percent and a necrotic core, the mean thickness of the fibrous cap was measured by ocular micrometry.

Definitions

The culprit plaque was defined as the plaque with an acute thrombus or, in the absence of an acute thrombus, the one with the greatest degree of luminal narrowing relative to the internal elastic lamina at the narrowest segment. An acute plaque rupture consisted of a luminal platelet-fibrin thrombus continuous with an underlying lipid-rich core (Fig. 1A and 1B). The connection between the thrombus and the lipid core was through a disrupted thin fibrous cap infiltrated by macrophages. A plaque erosion (Fig. 1C and 1D) was defined as an acute thrombus in direct contact with the intimal plaque without rupture of a lipid pool, as demonstrated by serial sections. A vulnerable plaque (Fig. 2) was defined as a fibrous cap less than 65 μm thick with an infiltrate of macrophages (>25 per high-magnification [0.3-mm-diameter] field), with or without plaque rupture. The 65- μm thickness in cases without rupture was chosen as a criterion for vulnerability because in arteries with ruptured plaque, the mean (\pm SD) cap thickness was 23 ± 19 μm (95 percent of the caps measured less than 64 μm). Stable plaque was defined as cross-sectional luminal narrowing of at least 75 percent in the absence of a luminal thrombus and could be vulnerable or nonvulnerable. An infarct was defined as previously described.¹⁴

Serum and Blood Studies

Serum samples were analyzed for total cholesterol, HDL cholesterol, and thiocyanate, and blood cells were analyzed for glycosylated hemoglobin, as previously described.^{15,16} The mean postmortem interval was 19 ± 8 hours. A history of smoking was assumed if the serum thiocyanate concentration was at least 90 μmol per liter.¹⁶ Henceforth, "smoking" will denote "presumed smoking." Hypertension was determined on the basis of the history and by microscopical analysis of renal vasculature.¹³ Hypercholesterolemia was defined as a serum total cholesterol concentration of at least 210 mg per deciliter (5.46 mmol per liter) or a ratio of total cholesterol to HDL cholesterol greater than 5.0.

Statistical Analysis

We divided the 113 hearts into two groups: 59 hearts with acute thrombi and 54 hearts without acute thrombi. The effects

of smoking and race on the presence of thrombosis were assessed by using a two-by-two contingency table (Fisher's exact test), and the effects of age, serum total cholesterol concentration, serum HDL cholesterol concentration, and glycosylated hemoglobin concentration were assessed by using Student's two-tailed t-test (unpaired). For multivariate analysis, the effects of age, race, serum total cholesterol concentration, HDL cholesterol concentration, the presence or absence of hypertension, and glycosylated hemoglobin concentration on whether there was acute thrombosis were analyzed in all 113 cases by using stepwise logistic regression (significance level for removing the variable from analysis = 0.4, for entering the variable = 0.2).

We further divided the 59 hearts with acute thrombi into those with eroded plaques (18 hearts) and those with ruptured plaques (41). The two groups were compared in terms of age, the glycosylated hemoglobin value, serum total cholesterol concentration, and serum HDL cholesterol concentration by using Student's t-test, and the effect of cigarette smoking was assessed with a two-by-two contingency table (Fisher's exact test). For multivariate analysis, the effects of the risk factors on plaque rupture were evaluated by stepwise logistic regression. To evaluate the association between plaque rupture and the ratio of total to HDL cholesterol, the analysis was repeated, with total cholesterol and HDL cholesterol omitted as independent variables.

For each of the 113 hearts, we tabulated the total number of vulnerable plaques and determined a mean value. Using Student's t-test, we compared the mean number of vulnerable plaques according to cigarette-smoking status, race, the presence or absence of hypertension, and serum cholesterol concentrations; using simple regression, we related the number of vulnerable plaques to age, concentrations of total cholesterol and HDL cholesterol, the ratio of total to HDL cholesterol, and the glycosylated hemoglobin value. For multivariate analysis, we used analysis of variance to assess the effects of the risk factors age and race on the number of vulnerable plaques.

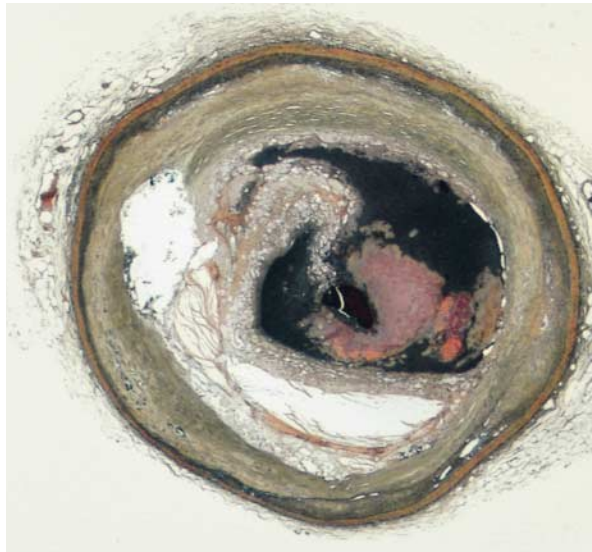
The mean heart weight among the categories of culprit plaque and the mean ages among risk-factor categories were compared by using Student's t-test.

All data are expressed as means \pm SD. For multivariate analyses, the serum total cholesterol and HDL cholesterol concentrations, the ratio of total HDL to cholesterol, and the glycosylated hemoglobin value were considered as continuous variables.

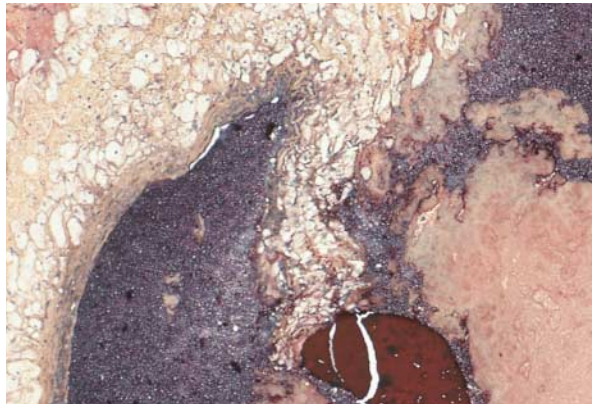
RESULTS

Descriptive Information

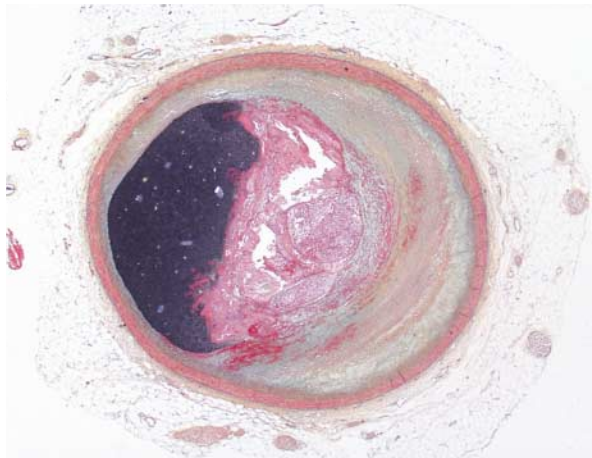
The mean age of the 113 patients at the time of death was 50 ± 10 years. There were 86 whites and 27 blacks. In 68 men (60 percent) the cardiac arrests had been witnessed, whereas 45 men (40 percent) had been found unresponsive. The mean body weight was 87.0 ± 20.7 kg. Acute coronary thrombi were present in 59 cases; of those, 41 represented plaque ruptures and 18, plaque erosions. The culprit plaques were stable in the remaining 54 cases; in 29 of these an old myocardial infarction was present. Acute myocardial infarcts were present in 8 of the 41 cases of plaque rupture, in 2 of the 18 cases of eroded plaque, and in 2 of the 54 hearts with stable plaque. The mean heart weight (normal range, 277 to 481 g for an 87-kg man)¹⁷ was 485 ± 120 g in cases of acute thrombosis and 495 ± 103 g in cases of stable plaque ($P=0.64$). In hearts with stable plaque, the mean heart weight was 522 ± 84 g in the presence of a healed infarct and 465 ± 116 g in hearts without a healed infarct ($P=0.04$). In hearts with acute throm-



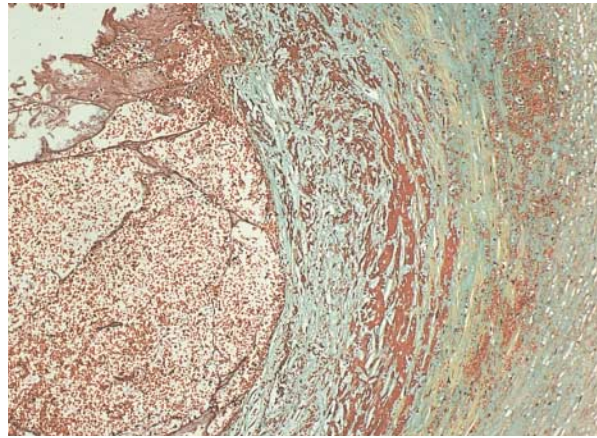
A



B



C



D

Figure 1. Acute Coronary Thrombi.

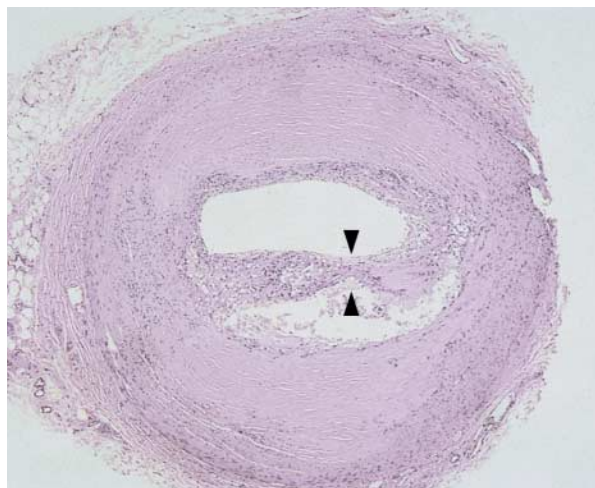
Panel A shows a cross section of the epicardial coronary artery, demonstrating a rupture of the shoulder region of the plaque with a luminal thrombus ($\times 30$). Panel B, at a higher magnification than Panel A, shows a ruptured thin cap densely infiltrated by macrophages and an adjacent fibrin-platelet thrombus (black reflects the postmortem injection of contrast material) ($\times 120$). In Panel C, showing an eroded plaque, a subocclusive luminal thrombus is visible in a cross section of the epicardial coronary artery ($\times 20$). Panel D, at a higher magnification, demonstrates a luminal thrombus (left) overlying smooth-muscle-cell fibrin-rich plaque ($\times 100$). (Movat pentachrome.)

bi, the mean heart weight was 499 ± 122 g for those with plaque ruptures and 455 ± 112 g for those with eroded plaque ($P = 0.20$).

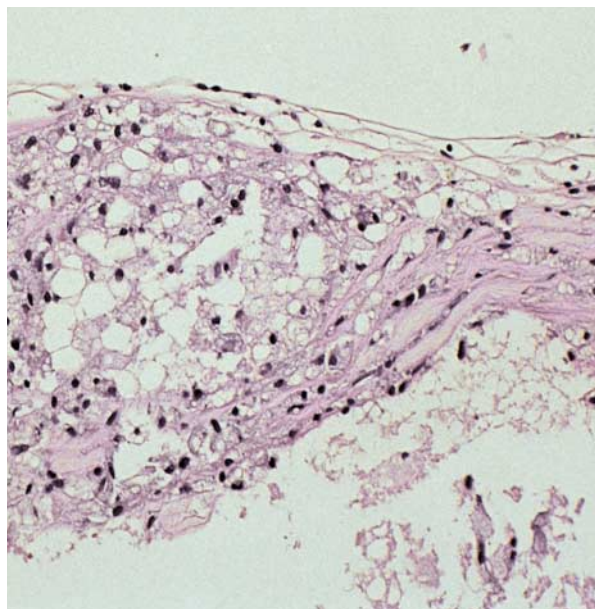
The mean age of the men who died with acute thrombi was 47 ± 9 years, as compared with 53 ± 11 years for those with stable plaque ($P = 0.005$). The mean age of the smokers was 47 ± 8 years, as compared with 54 ± 11 years for the nonsmokers ($P < 0.001$); the mean age of the men with hypertension was 55 ± 13 years, as compared with 48 ± 8 years for the normotensive men ($P < 0.001$); and the mean age of the men with elevated serum total cholesterol and an elevated ratio of total to HDL cholesterol was 48 ± 9 years, as compared with 53 ± 10 years for those without elevated values ($P = 0.05$).

Association between Risk Factors and Acute Thrombosis

The men who died with acute thrombosis were more likely to be smokers (44 of 59, or 75 percent) than the men who died with stable plaque (22 of 54, or 41 percent; $P < 0.001$) (Table 1). According to the multivariate analysis, cigarette smoking was associated with acute thrombosis (odds ratio, 3.6; $P = 0.004$). In contrast, the serum HDL cholesterol concentration (odds ratio for each additional milligram per deciliter, 1.01), hypertension (odds ratio, 0.5), age (odds ratio for each additional year, 1.0), black race (odds ratio, 0.6), glycosylated hemoglo-



A



B

Figure 2. Vulnerable Plaque.

Panel A shows a cross section of the epicardial coronary artery, demonstrating a thin fibrous cap (arrowheads) overlying a crescentic, lipid-rich core ($\times 30$). Panel B, with a higher magnification of the margin of the cap, demonstrates dense infiltration by foamy macrophages ($\times 300$). (Hematoxylin and eosin.)

bin value ($P > 0.4$), and serum total cholesterol concentration ($P > 0.4$) were not significantly associated with acute thrombosis (Table 1).

Effect of Risk Factors on the Type of Coronary Thrombus

According to the univariate analysis, plaque rupture was associated with low serum HDL cholesterol concentrations ($P = 0.008$), elevated serum total cholesterol concentrations ($P = 0.01$), and an elevated

TABLE 1. RISK FACTORS AND THE PRESENCE OF ACUTE CORONARY THROMBOSIS IN 113 MEN WHO DIED SUDDENLY WITH SEVERE CORONARY ARTERY DISEASE.*

RISK FACTOR	ACUTE THROMBOSIS (N=59)	STABLE PLAQUE (N=54)	P VALUE	
			UNI-VARIATE	MULTI-VARIATE†
Cigarette smoking — no. (%)	44 (75)	22 (41)	<0.001	0.004
Age — yr	47±9	53±11	0.005	0.24
Hypertension — no. (%)	11 (19)	23 (43)	0.008	0.22
Serum cholesterol (mg/dl)‡				
Total	249±62	222±100	0.08	>0.40§
HDL	39±15	45±18	0.10	0.16
Race			0.19	0.38
Black	11	16		
White	48	38		
Glycosylated hemoglobin — %	7.6±2.1	7.5±2.5	0.90	>0.40§

*Plus-minus values are means \pm SD.

†Stepwise logistic regression was used.

‡To convert values to millimoles per liter, multiply by 0.02586.

§This value was dropped from the analysis.

ratio of total to HDL cholesterol ($P = 0.001$) (Table 2). The mean total:HDL cholesterol ratio in the men who died of plaque rupture was 8.5 ± 4.0 , as compared with 5.5 ± 2.4 in the men who died with stable plaque ($P < 0.001$). By multivariate analysis, the serum concentrations of total cholesterol (odds ratio, 1.02) and HDL cholesterol (odds ratio, 0.92) and the ratio of total to HDL cholesterol (odds ratio, 1.78) were independently associated with plaque rupture ($P = 0.003$) (Table 2). Hypertension (odds ratio, 0.09), smoking (odds ratio, 0.28), age (odds ratio, 1.04), glycosylated hemoglobin value ($P > 0.4$), and race ($P > 0.4$) were not significantly associated with plaque rupture.

Effect of Risk Factors on Vulnerable Plaques

According to the univariate analysis, the numbers of vulnerable plaques were associated with the serum total cholesterol concentration ($r^2 = 0.08$, $P = 0.003$) and the serum HDL cholesterol concentration ($r^2 = 0.04$, $P = 0.03$), with the ratio of total to HDL cholesterol ($r^2 = 0.11$, $P < 0.001$), and with white race ($P = 0.02$); there was no association between the glycosylated hemoglobin value and the number of vulnerable plaques ($r^2 = 0.002$, $P = 0.65$). The mean numbers of vulnerable plaques were lower in the black men and higher in the men with elevated serum cholesterol concentrations (Table 3). The mean number of vulnerable plaques in the men with hypertension was 1.0 ± 1.0 , as compared

TABLE 2. RISK FACTORS AND THE TYPE OF CORONARY THROMBOSIS IN 59 CASES OF SUDDEN DEATH FROM CORONARY CAUSES WITH ACUTE THROMBOSIS.

RISK FACTOR	TYPE OF THROMBOSIS*		P VALUE	
	PLAQUE RUPTURE (N=41)	ERODED PLAQUE (N=18)	UNI-VARIATE	MULTI-VARIATE†
Serum cholesterol (mg/dl)‡				
HDL	35.8±13.5	46.9±16.1	0.008	0.003
Total	262±58	220±61	0.014	0.003
Ratio of total to HDL	8.5±4.0	5.0±1.8	0.001	0.003
Age — yr	48±9	45±9	0.16	0.30
Cigarette smoking — no. (%)	29 (71)	15 (83)	0.35	0.16
Hypertension — no. (%)	9 (22)	2 (11)	0.48	0.09
Glycosylated hemoglobin — %	7.9±2.2	6.9±1.7	0.11	>0.40§

*Plus-minus values are means ±SD.

†Stepwise logistic regression was used.

‡To convert values to millimoles per liter, multiply by 0.02586.

§This value was dropped from the analysis.

with 1.3 ± 1.6 in the normotensive men ($P = 0.33$); in the smokers, the number was 1.1 ± 1.3 , as compared with 1.4 ± 1.7 in the nonsmokers ($P = 0.33$). According to multivariate analysis, the total cholesterol concentration ($F = 19.7$, $P < 0.001$) and the HDL cholesterol concentration ($F = 7.3$, $P = 0.008$) were associated with the numbers of vulnerable plaques; there was no significant association between smoking status ($F = 4.4$, $P = 0.09$), race ($F = 1.7$, $P = 0.18$), glycosylated hemoglobin value ($F = 0.28$, $P = 0.60$), age ($F = 0.00$, $P = 0.94$), or the presence or absence of hypertension ($F = 0.02$, $P = 0.88$) and the numbers of vulnerable plaques.

DISCUSSION

Cholesterol-lowering therapy reduces the risk of acute coronary events, especially in secondary-prevention trials.^{5,18} Because the decrease in serum cholesterol is not associated with a large decrease in the luminal narrowing of coronary arteries,^{19,20} these benefits are assumed to be due to the stabilization of vulnerable plaques rather than to plaque regression. The current study demonstrates that an elevated serum cholesterol concentration is associated with the rupture of vulnerable plaques. A possible corollary is that the benefit of cholesterol-lowering therapy lies in reducing the frequency of plaque rupture. We have also demonstrated, in cases of sudden coronary death, that there is a strong correlation between serum cholesterol and the number of vulnerable plaques within the coronary tree that is independent of other risk factors.²¹⁻²⁴

A decrease in serum cholesterol may result in the stabilization of plaque by removing cholesterol from macrophage foam cells.²⁵ Lowering cholesterol may decrease the volume of soft, cholesteryl-ester-rich necrotic core, lessening the risk of plaque rupture by a "passive" mechanism involving mechanical factors.^{19,20,26} Lowering cholesterol may also reduce the risk of thrombosis by decreasing platelet reactivity¹² and endothelium-mediated vasoconstriction.²⁷ Because coronary angiography allows an in vivo diagnosis of plaque thrombosis²⁸ and thermal probes may detect vulnerable plaques,²⁹ it may be possible in the future to identify the patients who will benefit most from cholesterol-lowering strategies.

This study demonstrates that cigarette smoking in men is associated, independently of other risk factors, with coronary thrombosis in cases of sudden death from coronary causes. Cigarette smoking was associated with thrombosis regardless of the mecha-

TABLE 3. MEAN NUMBERS OF VULNERABLE PLAQUES AND SERUM CHOLESTEROL CONCENTRATIONS IN 113 MEN WHO DIED SUDDENLY WITH SEVERE CORONARY ARTERY DISEASE.*

GROUP	ALL CASES	SERUM TOTAL CHOLESTEROL CONCENTRATION†		
		≤210 mg/dl AND TOTAL:HDL RATIO ≤5	>210 mg/dl OR TOTAL:HDL RATIO >5	>210 mg/dl AND TOTAL:HDL RATIO >5
		no. of plaques (no. of men in group)		
Total	1.22±1.44	0.17±0.49 (23)	1.13±1.43 (32)	1.69±1.41 (58)‡
Whites	1.41±1.51	0.25±0.58 (16)	1.45±1.79 (20)	1.76±1.44 (50)‡
Blacks	0.65±0.98§	0.00±0 (7)	0.64±0.81 (11)	1.25±1.3 (8)¶

*Plus-minus values are means ±SD.

†To convert values to millimoles per liter, multiply by 0.02586.

‡ $P < 0.001$ for the comparison with total cholesterol ≤210 mg per deciliter and total:HDL ratio ≤5.

§ $P = 0.02$ for the comparison with whites.

¶ $P = 0.02$ for the comparison with total cholesterol ≤210 mg per deciliter and total:HDL ratio ≤5.

nism of plaque disruption (erosion or rupture) and was not associated with the number of vulnerable plaques. The mechanism of coronary thrombosis in cigarette smokers may be related to increased platelet aggregation and plasma epinephrine concentrations.¹¹ In addition to cigarette smoking, a variety of thrombotic factors have been implicated in the development of coronary-artery atherosclerosis and thrombosis, including abnormal levels of fibrinogen,³⁰ von Willebrand factor antigen,³⁰ and tissue plasminogen activator,³⁰ and the presence of anticardiolipin antibodies,³¹ cross-linked fibrin-degradation products,³² and polymorphism of a platelet glycoprotein receptor.³³

Our study demonstrates a decreased frequency of acute thrombosis in hypertension-related sudden death due to coronary events and shows that the mean age of men with hypertension who die suddenly from coronary disease is greater than that of normotensive men. The importance of left ventricular hypertrophy and microvascular disease in sudden death with hypertension, relative to epicardial coronary disease, has yet to be fully studied.¹³ The older age of the men with hypertension reflects the relatively young age of cigarette smokers, men who died with acute thrombosis, and men with hypercholesterolemia; clinical studies have shown an association between premature death from coronary disease and the risk factors of smoking and hypercholesterolemia.²

We did not find an association between glucose intolerance and sudden death with acute coronary thrombosis. In people with diabetes who have unstable angina, however, coronary thrombosis is more frequent than in those without diabetes,³⁴ indicating that in living patients with acute coronary syndromes, diabetes is strongly associated with acute thrombosis.³⁴ The absence of an association between diabetes mellitus and acute plaque disruption in our study may suggest that, as is the case with hypertensive heart disease, noncoronary mechanisms related to glucose intolerance may be factors in the precipitation of sudden death from coronary disease. The roles of renal disease, microvascular disease, and diabetic cardiomyopathy in sudden death in patients with diabetes remain to be elucidated.

The chief limitations of the current study include the inherent bias in the selection of patients for autopsy and the exclusive selection of men who died suddenly. Therefore, the results must be interpreted cautiously when applied to patients who survive acute coronary events, and may not apply to women. Because these associations corroborate clinical and experimental findings, however, we propose that among men who die suddenly, hypercholesterolemia has predisposed them to the rupture of vulnerable plaques and cigarette smoking has predisposed them to acute thrombosis. Cholesterol lowering may be particularly beneficial to patients with vulnerable plaques, and

antithrombotic therapy may be especially effective in cigarette smokers at risk for sudden death due to coronary events.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, the Department of the Air Force, or the Department of Defense.

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