Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 42, No. 2, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)00579-5

The Incidence and Risk Factors of Cholesterol Embolization Syndrome, a Complication of Cardiac Catheterization: A Prospective Study

Yoshihiro Fukumoto, MD, PHD, Hiroyuki Tsutsui, MD, PHD, Miyuki Tsuchihashi, MS, Akihiro Masumoto, MD, PHD, Akira Takeshita, MD, PHD, for the Cholesterol Embolism Study (CHEST) Investigators

Fukuoka, Japan

OBJECTIVES We sought to determine the incidence of cholesterol embolization syndrome (CES) as a complication of cardiac catheterization and to identify risk factors associated with this disease.

BACKGROUND Cholesterol embolization syndrome is a systemic disease caused by distal showering of cholesterol crystals after angiography, major vessel surgery, or thrombolysis.

METHODS We prospectively evaluated a total of 1,786 consecutive patients 40 years of age and older, who underwent left-heart catheterization at 11 participating hospitals. The diagnosis of CES was made when patients had peripheral cutaneous involvement (livedo reticularis, blue toe syndrome, and digital gangrene) or renal dysfunction.

RESULTS Twenty-five patients (1.4%) were diagnosed as having CES. Twelve patients (48%) had cutaneous signs, and 16 patients (64%) had renal insufficiency. Eosinophil counts were significantly higher in CES patients than in non-CES patients before and after cardiac catheterization. The in-hospital mortality rate was 16.0% (4 patients), which was significantly higher than that without CES (0.5%, $p < 0.01$). All four patients with CES who died after cardiac catheterization had progressive renal dysfunction. The incidence of CES increased in patients with atherosclerotic disease, hypertension, a history of smoking, and the elevation of baseline plasma C-reactive protein (CRP) by univariate analysis. The femoral approach did not increase the incidence, suggesting a possibility that the ascending aorta may be a potential embolic source. As an independent predictor of CES, multivariate regression analysis identified only the elevation of pre-procedural CRP levels (odds ratio 4.6, $p = 0.01$).

CONCLUSIONS Cholesterol embolization syndrome is a relatively rare but serious complication after cardiac catheterization. Elevated plasma levels of pre-procedural CRP are associated with subsequent CES in patients who undergo vascular procedures. (J Am Coll Cardiol 2003;42:211–6)

Cholesterol embolization syndrome (CES) is a systemic atheroembolism involving brain, eyes, kidneys, and extremities, caused by distal showering of cholesterol crystals from aortic atheromatous plaques (1). Since the 1960s, various investigators have reported cases of CES such as blue toe syndrome or acute renal failure as a complication of angiography, major vessel surgery, or thrombolytic therapy (2–11). It has been reported that eosinophil counts increase during the active phase of CES cases (12,13).

See page 217

Clinical consequences of CES vary considerably, from being completely asymptomatic to presenting acute multiorgan failure, including progressive renal failure or cutaneous involvement, with a mortality rate as high as 70% to 90% (14). However, the actual incidence of this syndrome remains uncertain. Estimates of the incidence of CES after vascular procedures have ranged from 0.15% in clinical studies (5) to 25% to 30% in pathologic series (3). Clinical studies probably underestimated the incidence because only a minority of patients can be clinically recognized. Therefore, despite the importance of this disease as a complication of percutaneous diagnostic and interventional procedures, the clinical characteristics of CES remain uncertain. Quantification of the risk factors for post-catheterization CES is critically important to both patients and physicians. However, no studies have comprehensively examined both clinical and therapeutic variables that can be applied to estimate the risk of CES in patients undergoing cardiac catheterization.

Therefore, the goals of the present study were: 1) to determine the incidence of CES after cardiac catheterization; and 2) to determine the risk factors that are independently associated with CES as complications after cardiac catheterization. For this purpose, we prospectively examined the presence of cutaneous findings, and we compared serum creatinine levels and blood eosinophil counts between pre- and post-procedure.

From the Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. A complete list of the CHEST Investigators appears in the Appendix.

Manuscript received December 9, 2002; revised manuscript received January 6, 2003, accepted January 30, 2003.

Abbreviations and Acronyms
AMI = acute myocardial infarction
CES = cholesterol embolization syndrome
CRP = C-reactive protein

METHODS

Study population. A total of 1,786 consecutive patients, 40 years old or older (mean, 65 ± 10 years; range, 40–92 years), who underwent left cardiac catheterization between June 1, 1998, and September 30, 1999, in 11 participating hospitals, were prospectively evaluated to identify CES. There were 1,169 men and 617 women. For each patient, baseline demographic, clinical, procedural, and outcome data were collected by use of a standardized data collection form by the participating hospitals. Serum creatinine levels, blood cell counts including white blood cells and eosinophils, and C-reactive proteins (CRPs) were measured before cardiac catheterization. Serum creatinine levels were measured in all patients, blood cell counts in 94% of patients, and CRP in 77% of patients. All patients provided informed consent, and the study protocol was approved by the ethical committees of participating hospitals.

Definition of CES. Cutaneous signs of CES including livedo reticularis, blue toe syndrome, and digital gangrene were recorded at the time of the initial procedure and two weeks after cardiac catheterization. Serum creatinine levels were also recorded before and two weeks following catheterization.

"Definite CES" was defined if the patients had cutaneous signs including livedo reticularis, blue toe syndrome, and digital gangrene with or without renal impairment. "Possible CES" was defined if patients had only renal dysfunction referring to a post-catheterization serum creatinine >1.3 mg/dl and an increase of creatinine level by >50% from the baseline value two weeks after the procedure without skin lesions (11,15) (Table 1). In the patients with chronic renal failure with hemodialysis, CES was diagnosed only in the presence of the peripheral cutaneous involvement. Several previous case reports have demonstrated that serum creatinine levels increase from a few days to a few months after the procedures (16–18). Therefore, although we cannot exactly exclude the possibility of the contribution of contrast nephrotoxicity, we consider that the increase of creatinine within several days is probably due to contrast nephrotoxicity, whereas the increase of creatinine at two weeks suggests possible CES.

Table 1. Diagnostic Criteria of CES

Criteria 1: Peripheral cutaneous involvement	
Livedo reticularis	
Blue toe syndrome	
Digital gangrene	
Criteria 2: Acute renal insufficiency (excluded if patients have already undergone hemodialysis)	
Increase in serum creatinine level (mg/dl)	
Before catheterization	2 weeks after catheterization
≤0.8	≥1.3
>0.9	≥50%

"Definite CES" was defined as the presence of criteria 1 with or without criteria 2. "Possible CES" was defined as the presence of only criteria 2.
CES = cholesterol embolization syndrome.

Table 2. Incidence of Definite and Possible CES

	n	(%)
Definite and possible CES	25	1.40
Skin lesion	12	0.67
Renal dysfunction	16	0.90
Both	3	0.17
Definite CES	12	0.67
Possible CES	13	0.73

Abbreviation defined in Table 1.

Data collection. Baseline demographic information (including age and gender), clinical diagnosis, comorbidities (cerebrovascular disease, aortic aneurysm, and arteriosclerosis obliterans), and atherosclerotic risk factors (hypercholesterolemia, history of smoking, hypertension, and diabetes mellitus) were recorded for each patient. History and/or vascular study documented acute coronary syndromes, cerebrovascular disease, aortic aneurysm, and arteriosclerosis obliterans. Hypercholesterolemia was defined as total cholesterol ≥220 mg/dl. Hypertension was defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg. Diabetes was defined as fasting blood sugar ≥140 mg/dl or blood sugar during a 75-g oral glucose tolerance test ≥200 mg/dl. Renal dysfunction was defined as creatinine clearance levels ≤50 ml/min/m^2 calculated by the Cockroft-Gault formula. Multivessel disease was defined as ≥75% stenosis in more than two major epicardial coronary arteries. Furthermore, left ventricular ejection fraction (LVEF) was assessed by echocardiography. Coronary interventions included all catheter-based revascularization procedures such as balloon angioplasty, stent emplacement, and directional and rotational atherectomy. All patients had 3,000 to 5,000 U heparin at the beginning of the procedure. Patients were classified as "anticoagulated" when heparin or warfarin was continued for more than 24 h after the procedures. No patient received thrombolytic agents in the present study. Death and the need for hemodialysis during hospitalization were recorded.

Statistical analysis. Continuous variables were expressed as mean ± SD. Comparisons between patients with and without CES were made by use of unpaired *t* test for continuous variables and chi-square test for categorical variables. All variables that were associated with CES with a value of $p < 0.05$ in univariate analyses were included in the multivariate models. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated based on the multiple logistic regression analysis. All statistical analyses were performed using the SPSS (SPSS Inc., Chicago, Illinois) or StatView (SAS Institute, Cary, North Carolina), and p values < 0.05 were considered statistically significant.

Table 3. Clinical Features of CES

	No CES (n = 1,761)	CES (n = 25)	p Value
Blood eosinophil count			
Baseline (/μl), mean ± SD	166 ± 152	252 ± 345	< 0.01
After (/μl), mean ± SD	200 ± 365	470 ± 496	< 0.01
Postprocedure value >500/μl, n (%)	57 (3.2)	5 (20)	< 0.01
Death, n (%)	8 (0.5)	4 (16)	< 0.01

Abbreviation defined in Table 1.

RESULTS

Clinical features of CES. Among 1,786 consecutive patients, 25 patients were diagnosed as having CES (1.4%). Twelve of 25 patients had peripheral cutaneous involvement, 16 patients had renal dysfunction, and 3 patients had both (Table 2). Therefore, 12 patients were diagnosed as definite CES and 13 patients were possible CES. The eosinophil counts after the procedure as well as at baseline were significantly higher in CES patients than in non-CES patients. The prevalence of post-procedure eosinophilia (>500/μl) was also significantly higher in patients with CES. The in-hospital mortality rate was 16.0% (4 patients) in patients with CES, which was significantly higher than in those without CES (0.5%, $p < 0.01$, Table 3). All four patients underwent coronary intervention. Three out of four patients had acute myocardial infarction (AMI), and the other patient with diabetes mellitus had silent ischemia. All four patients were treated by hemodialysis. However, one patient with AMI died of CES five months after angiography; this patient had progressive deterioration of renal function owing to CES. Two other patients died of AMI with acute renal failure seven to eight weeks after the procedure, in which CES might be attributable to the progression of renal failure. One patient with silent ischemia died of non-cardiac cause after seven months. Even though all patients had interventional procedures, none had their major complication of cardiac catheterization, including bleeding or cardiac tamponade.

Comparison of CES with and without renal dysfunction. Baseline serum creatinine concentration and eosinophil counts were comparable between CES patients with and without renal dysfunction. The mean serum creatinine concentration significantly increased, from 1.6 to 3.3 mg/dl in 16 patients with renal dysfunction (Table 4). The eosinophil counts significantly increased from 220 to 535 cells/μl in patients with renal dysfunction, whereas nine patients of CES without renal dysfunction did not show the increase (from 302 to 339 cells/μl). All four patients who died after cardiac catheterization showed progressive acute renal failure (Table 4). The remaining 21 patients were all discharged from the hospital.

Risk factors for the occurrence of CES. We performed a univariate analysis to determine the association between patient variables and the occurrence of postprocedure CES (Table 5). Acute coronary syndromes and multivessel coronary artery disease were univariate predictors of CES. Hypertension, smoking, cerebrovascular disease, and aortic aneurysm were also associated with an increased risk of a postprocedure CES. On the other hand, there were no significant differences in hypercholesterolemia and diabetes mellitus between patients with and without CES. Plasma CRP levels were significantly higher in patients with CES than in those without it (0.7 vs. 2.4 mg/dl), which means that higher CRP levels (CRP > 1.0 mg/dl) are associated with an increased risk for CES. In contrast, atrial fibrillation, the femoral artery approach, and the use of anticoagulants were not associated with an increased risk of CES.

A multiple logistic regression analysis showed that an elevated baseline CRP level was an independent predictor of CES (Table 6). There was a 4.6-fold increase in the risk of CES in those with pre-procedural increase (CRP ≥1.0 mg/dl) in plasma CRP levels. Plasma CRP level as a

Table 4. Clinical Features of Cholesterol Embolization Syndrome With and Without Renal Dysfunction

Clinical Feature	Renal Dysfunction		p Value
	Yes (n = 16)	No (n = 9)	
Serum creatinine			
Baseline (mg/dl), mean ± SD	1.6 ± 1.9	1.6 ± 2.3	NS
After (mg/dl), mean ± SD	3.3 ± 3.2*	1.6 ± 2.0	NS
Blood eosinophil count			
Baseline (/μl), mean ± SD	220 ± 272	302 ± 449	NS
After (/μl), mean ± SD	535 ± 592*	339 ± 163	NS
Postprocedure value >500/μl, n (%)	4 (25)	1 (11)	NS
Outcome			
Death, n	4	0	NS
New hemodialysis, n	4	0	NS

*$p < 0.05$ compared with "Baseline."

Table 5. Univariate Analysis of Predictors for Postprocedure CES

Variables	No CES (n = 1,761) n (%)	CES (n = 25) n (%)	p Value
Age (yrs), mean ± SD	65 ± 10	69 ± 7	NS
>75 years old	310 (18%)	4 (16%)	NS
Male gender	1,152 (65%)	17 (68%)	NS
Coronary artery disease	1,470 (83%)	20 (80%)	NS
Acute coronary syndrome	354 (20%)	10 (40%)	0.02
Multivessel coronary artery disease	503 (28.5%)	13 (52.0%)	0.01
Atrial fibrillation	68 (3.9%)	1 (4.0%)	NS
Left ventricular ejection fraction <45%	129 (7.3%)	2 (8.0%)	NS
Hypercholesterolemia	662 (38%)	7 (28%)	NS
Diabetes mellitus	550 (31%)	10 (42%)	NS
Hypertension	867 (49%)	18 (75%)	0.03
Smoking	668 (38%)	14 (70%)	0.02
Cerebrovascular disease	112 (6%)	5 (20%)	0.01
Aortic aneurysm	54 (3%)	3 (12%)	0.01
Arteriosclerosis obliterans	75 (4%)	1 (4%)	NS
Chronic renal failure with hemodialysis	46 (3%)	1 (4%)	NS
Baseline serum creatinine (mg/dl), mean ± SD	1.1 ± 1.4	1.6 ± 2.0	NS
≥2.0 mg/dl	60 (3%)	2 (8%)	NS
C-reactive protein (mg/dl), mean ± SD	0.7 ± 1.7	2.4 ± 3.0	0.01
≥1.0 mg/dl	202 (12%)	9 (36%)	0.01
Femoral approach	1,238 (70%)	20 (80%)	NS
Coronary intervention	418 (24%)	8 (32%)	NS
Anticoagulation	331 (19%)	5 (20%)	NS

Abbreviation defined in Table 1.

continuous variable was also an independent risk factor of CES ($p < 0.01$).

DISCUSSION

This is the first prospective study to assess the incidence and risk factors of CES in patients who have undergone cardiac catheterization. The incidence of CES in our patient population was 1.4%. Scolari et al. (9) retrospectively reported that 15 of 16,223 vascular procedures were complicated with CES, which was an incidence of 0.09%. In contrast, the autopsy study reported that the overall prevalence of CES was 25% to 30% of patients after cardiac catheterization (3). The prevalence in our prospective study was intermediate between clinical and autopsy studies, indicating that CES may occur in a subtle form after intravascular procedures more often than that reported by clinical manifestations (17).

Some case reports have shown a transient eosinophilia in up to 80% of patients with CES (13,19). Similarly, in our study population, the eosinophil counts were significantly higher in CES patients than in non-CES patients before and after cardiac catheterization. Furthermore, CES with renal dysfunction showed greater increase of eosinophil counts (from 220 to 535/μl) compared to those patients without renal dysfunction (from 302 to 339/μl). All patients who did not survive in the CES group had renal dysfunction after catheterization, suggesting that renal insufficiency in CES is critical. The present study showed an in-hospital mortality of 16%. Most previous case reports of CES described diffuse embolism and multiorgan failure, and hence reported a mortality of 70% to 90% (14,20). The difference between the present study and previous case series may be due to the fact that our study population included subtle cases of CES. Nonetheless, CES remained a condition associated with a high mortality.

Table 6. Multivariate Analysis of Predictors for Postprocedure CES

Variable	Odds Ratio	95% Confidence Interval	p Value
CRP >1.0 mg/dl	4.64	1.70–12.62	0.01
Aortic aneurysm	2.90	0.77–10.92	0.12
Smoking	2.67	0.99–7.22	0.08
Hypertension	2.55	0.96–6.75	0.07
Cerebrovascular disease	2.46	0.83–7.31	0.10
Multivessel coronary artery disease	1.96	0.82–4.71	0.13
Acute coronary syndrome	1.87	0.78–4.51	0.20

CES = cholesterol embolization syndrome; CRP = C-reactive protein.

This study identified independent pre-procedural predictors of CES. The syndrome occurred more frequently in patients with generalized atherosclerosis such as multiple-vessel coronary disease and cerebrovascular disease shown by univariate analysis. In particular, the variable identified as an independent predictor of CES was a higher level of plasma CRP, indicating an important association between systemic inflammation and CES. Several studies including our own have demonstrated an important role of inflammation in the initiation and progression of atherosclerosis in human and animal models (21–25). The mechanism of how inflammation leads to CES is unknown, but our present findings may extend previous observation regarding inflammation as an important cardiovascular risk factor (21–25). The vulnerable

atherosclerotic plaques contain a large amount of inflammatory cells, including macrophages (26), and such plaques can be the source of cholesterol embolization. Elevated levels of CRP may reflect enhanced immune or inflammatory activity of atherosclerotic lesions in these patients. Our findings may raise the possibility that strategies to minimize vascular inflammation can reduce the occurrence of CES in these patients. Treatment with HMG-CoA reductase inhibitors (statins) might be effective as a prophylaxis because it can reduce systemic inflammation independent of decreasing plasma cholesterol levels (27–29). Further studies are needed to investigate the usefulness of therapeutic strategies for systemic inflammation in the prevention of CES.

Several case reports have suggested that patients are more likely to develop CES when they are anticoagulated; therefore, they are recommended to discontinue anticoagulation when CES is suspected to be present (6,30). However, studies suggesting a relation between anticoagulation and CES were retrospective, and the results may have been confounded by the use of anticoagulants to treat the syndrome (31). Although anticoagulation may allow cholesterol crystals to embolize freely, the present study did not indicate any significant association between the use of anticoagulants and CES. This is in agreement with a report using transesophageal echocardiography, in which the risk of clinically apparent CES was as low as 0.7% during warfarin therapy in patients with aortic atheromas and atrial fibrillation (32).

The abdominal aorta is one of the most heavily involved areas with atherosclerotic plaques; therefore, procedures involving mechanical injury by catheters to these regions could potentially disrupt plaque material and induce CES (4). Hence, we suspect that the frequency of CES is lowered if procedures are performed via the brachial artery approach (33); however, there were no significant differences in the prevalence of the femoral approach with and without CES. Therefore, it is possible that the ascending thoracic aorta may potentially be a main embolic source of cholesterol crystals causing CES.

Study limitations. Several limitations should be acknowledged in this study. First, only the cutaneous manifestations and renal impairment were used for the diagnosis of CES, but histological confirmation was not required in this study. Even though the biopsy of characteristic cutaneous and renal lesions is helpful, less than 50% of patients show typical findings (31). Furthermore, histological presence of cholesterol embolization does not always result in clinically specific CES (31). We thus consider that biopsy is useful but not necessary to confirm the CES diagnosis.

Second, we defined renal impairment with CES as more than 50% worsening of serum creatinine levels referred from the previous study (11) and thereby we may have overestimated its true frequency. Third, we employed serum creatinine data two weeks after the procedure because previous case reports have shown that serum creatinine levels increase several days after the procedure (16–18). Furthermore, the decline in renal function immediately after the procedure may not be due to CES but, more likely, to other causes such as contrast nephrotoxicity or hypotension.

Moreover, there was no significant difference in the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) between CES and non-CES groups in our study patients. Therefore, we consider that the contribution of renal toxicity by ACEI or ARB may be excluded. However, as we could not completely exclude the possible contribution of some other causes, we diagnosed patients as possible CES if they had only renal impairment without cutaneous signs.

Finally, although there was no significant difference in the use of aspirin or statins at the time of procedure, we could not provide data concerning the duration and the dosage of aspirin or statins that were used before and after cardiac catheterization in our study patients.

Conclusions. Finally, CES often occurs after a vascular procedure in patients with systemic inflammation. It is not a rare occurrence, but it is infrequently recognized. Clinical manifestations range from mild to catastrophic. Elevated baseline CRP levels can identify patients who are at higher risk of post-catheterization CES. Better understanding and early recognition of this disease are expected to reduce patient mortality and morbidity after cardiac catheterization.

Acknowledgments

This survey could not have been carried out without the help, cooperation, and support of the cardiologists in the study hospitals. We thank the participating cardiologists for allowing us to obtain the data. We also thank Dr. Suminori Kono (Kyushu University, Fukuoka, Japan) for his helpful comments on this study.

Reprint requests and correspondence: Dr. Hiroyuki Tsutsui, Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan. E-mail: prehiro@cardiol.med.kyushu-u.ac.jp.

REFERENCES

1. Creager MA, Libby P. Peripheral arterial disease. In: Braunwald E, Zipes D, Libby P, editors. Heart Disease. 6th edition. Philadelphia, PA: Saunders, 2001:1457–84.
2. Feder W, Auerbach R. "Purple toes:" an uncommon sequela of oral coumarin drug therapy. Ann Intern Med 1961;55:911–7.
3. Ramirez G, O'Neill WM, Jr., Lambert R, Bloomer HA. Cholesterol embolization: a complication of angiography. Arch Intern Med 1978; 138:1430–2.
4. Rosansky SJ, Deschamps EG. Multiple cholesterol emboli syndrome after angiography. Am J Med Sci 1984;288:45–8.
5. Drost H, Buis B, Haan D, Hillers JA. Cholesterol embolism as a complication of left heart catheterisation. Report of seven cases. Br Heart J 1984;52:339–42.
6. Hyman BT, Landas SK, Ashman RF, Schelper RL, Robinson RA. Warfarin-related purple toes syndrome and cholesterol microembolization. Am J Med 1987;82:1233–7.

7. Shapiro LS. Cholesterol embolization after treatment with tissue plasminogen activator. N Engl J Med 1989;321:1270.
8. Bols A, Nevelsteen A, Verhaeghe R. Atheromatous embolization precipitated by oral anticoagulants. Int Angiol 1994;13:271–4.
9. Scolari F, Bracchi M, Valzorio B, et al. Cholesterol atheromatous embolism: an increasingly recognized cause of acute renal failure. Nephrol Dial Transplant 1996;11:1607–12.
10. Dressler FA, Craig WR, Castello R, Labovitz AJ. Mobile aortic atheroma and systemic emboli: efficacy of anticoagulation and influence of plaque morphology on recurrent stroke. J Am Coll Cardiol 1998;31:134–8.
11. Davila-Roman VG, Kouchoukos NT, Schechtman KB, Barzilai B. Atherosclerosis of the ascending aorta is a predictor of renal dysfunction after cardiac operations. J Thorac Cardiovasc Surg 1999;117: 111–6.
12. Cosio FG, Zager RA, Sharma HM. Atheroembolic renal disease causes hypocomplementaemia. Lancet 1985;2:118–21.
13. Kasinath BS, Corwin HL, Bidani AK, Korbet SM, Schwartz MM, Lewis EJ. Eosinophilia in the diagnosis of atheroembolic renal disease. Am J Nephrol 1987;7:173–7.
14. Blankenship JC, Butler M, Garbes A. Prospective assessment of cholesterol embolization in patients with acute myocardial infarction treated with thrombolytic vs conservative therapy. Chest 1995;107: 662–8.
15. Smith SC, Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines). J Am Coll Cardiol 2001;37:2215–39.
16. Smith MC, Ghose MK, Henry AR. The clinical spectrum of renal cholesterol embolization. Am J Med 1981;71:174–80.
17. Rosman HS, Davis TP, Reddy D, Goldstein S. Cholesterol embolization: clinical findings and implications. J Am Coll Cardiol 1990;15: 1296–9.
18. Geraets DR, Hoehns JD, Burke TG, Grover-McKay M. Thrombolytic-associated cholesterol emboli syndrome: case report and literature review. Pharmacotherapy 1995;15:441–50.
19. Wilson DM, Salazer TL, Farkouh ME. Eosinophiluria in atheroembolic renal disease. Am J Med 1991;91:186–9.
20. Fine MJ, Kapoor W, Falanga V. Cholesterol crystal embolization: a review of 221 cases in the English literature. Angiology 1987;38:769–84.
21. Libby P, Clinton SK. Cytokines as mediators of vascular pathology. Nouv Rev Fr Hematol 1992;34:S47–53.
22. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 1994;90:775–8.
23. Fukumoto Y, Shimokawa H, Kozai T, et al. Vasculoprotective role of inducible nitric oxide synthase at inflammatory coronary lesions induced by chronic treatment with interleukin-1 beta in pigs in vivo. Circulation 1997;96:3104–11.
24. Ridker PM. Intrinsic fibrinolytic capacity and systemic inflammation: novel risk factors for arterial thrombotic disease. Haemostasis 1997; 27:2–11.
25. Fukumoto Y, Libby P, Rabkin E, et al. Statins alter smooth muscle cell accumulation and collagen content in established atheroma of watanabe heritable hyperlipidemic rabbits. Circulation 2001;103:993–9.
26. Aikawa M, Libby P. Lipid lowering reduces proteolytic and prothrombotic potential in rabbit atheroma. Ann N Y Acad Sci 2000;902:140–52.
27. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) investigators. Circulation 1998;98:839–44.
28. Ridker PM, Rifai N, Lowenthal SP. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. Circulation 2001;103:1191–3.
29. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 2001;344:1959–65.
30. Bruns FJ, Segel DP, Adler S. Control of cholesterol embolization by discontinuation of anticoagulant therapy. Am J Med Sci 1978;275: 105–8.
31. Thadhani RI, Camargo CA, Jr, Xavier RJ, Fang LS, Bazari H. Atheroembolic renal failure after invasive procedures. Natural history based on 52 histologically proven cases. Medicine (Baltimore) 1995; 74:350–8.
32. Blackshear JL, Zabalgoitia M, Pennock G, et al. Warfarin safety and efficacy in patients with thoracic aortic plaque and atrial fibrillation. SPAF TEE investigators. Stroke Prevention and Atrial Fibrillation. Transesophageal Echocardiography. Am J Cardiol 1999;83:453–5.
33. Oda H, Miida T, Sato H, Higuma N. Treatment of unstable angina with cholesterol embolization as a complication of left heart catheterization. Jpn Circ J 1990;54:487–92.

APPENDIX

The following institutions/investigators participated in the "CHEST" Group: *Fukuoka Red Cross Hospital:* Tetsuji Inoh, Yoshihiro Higuchi, Nobuhiko Atsuchi; *Hamanomachi Hospital:* Yuji Maruoka; *Hiroshima Red Cross Hospital:* Shunichi Kaseda, Tomomi Yoshida; *Iizuka Hospital:* Shuichi Okamatsu, Tohru Yamawaki; *Kitakyushu Municipal Medical Center:* Yoshitoshi Urabe, Hideharu Tomita; *Kyushu Kouseinenkin Hospital:* Yutaka Kikuchi, Tsukasa Tajimi, Ryuichi Nakaike; *Kyushu University Hospital:* Yoshihiro Fukumoto, Hiroyuki Tsutsui, Miyuki Tsuchihashi, Akihiro Masumoto, Akira Takeshita; *Matsuyama Red Cross Hospital:* Takaya Fukuyama, Toshiaki Ashihara; *Saga Kouseikan Hospital:* Kiyoshi Hayasida, Masaru Takahashi, Yuji Ishibashi; *St. Mary's Hospital:* Kunihiko Yamamoto, Mitsutaka Yamamoto; *Yamaguchi Red Cross Hospital:* Kouhei Muramatsu, Takahiro Narishige.